

Care during pregnancy and early childhood for growth and development in low- and middle- income countries

Edited by

Nita Bhandari, Jai Das, Ravi Prakash Upadhyay,
Ranadip Chowdhury, Bireshwar Sinha and Sunita Taneja

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Care during pregnancy and early childhood for growth and development in low- and middle- income countries

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Nita Bhandari — Society for Applied Studies, India

Jai Das — Aga Khan University, Pakistan

Ravi Prakash Upadhyay — Center for Health Research and Development, Society for Applied Studies, India

Ranadip Chowdhury — Society for Applied Studies, India

Bireshwar Sinha — Centre for Health Research and Development Society for Applied Studies, India

Sunita Taneja — Center for Health Research and Development, Society for Applied Studies, India

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Mauro Serafini,
University of Teramo, Italy

*CORRESPONDENCE
Ranadip Chowdhury
✉ ranadip.chowdhury@sas.org.in

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Editorial: Care during pregnancy and early childhood for growth and development in low- and middle- income countries

Ranadip Chowdhury^{1*}, Ravi Prakash Upadhyay¹,
Bireswar Sinha¹, Sunita Taneja¹, Jai K. Das² and Nita Bhandari¹

¹Society for Applied Studies, New Delhi, India, ²Division of Women and Child Health, Aga Khan University, Karachi, Pakistan

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antenatal care, mental health, postnatal care, breastfeeding, complementary feeding, child stimulation, low birth weight

Editorial on the Research Topic

Care during pregnancy and early childhood for growth and development in low- and middle- income countries

Enhanced efforts have been made in recent years to improve access and utilization of optimal care practices during pregnancy and early childhood in low- and middle-income countries (LMICs) (1). Yet only around half of the pregnant women receive the minimum of the four recommended antenatal visits and this has led to a high burden of adverse pregnancy outcomes, such as babies born with low birth weight, small-for-gestational age, or preterm (2). Postnatal care and care in the first 2 years of life are also suboptimal, resulting in a high burden of undernutrition and the child's inability to achieve optimal neuro-cognitive development. There are numerous interventions for each lifecycle stage which can improve maternal and child health, and nutritional status (3).

Pregnancy care

In this supplement various important aspects of pregnancy care in low- and middle-income countries (LMICs) have been considered. The World Health Organization recommends eight antenatal care visits during pregnancy as a key strategy to promote women's health (4). Evidence from LMICs suggests that women who have had eight or more antenatal visits were more likely to have deliveries in health facilities and early postnatal care seeking (Chilot et al.).

Maternal undernutrition during pregnancy is another important issue that remains unaddressed in LMICs. A study in Ethiopia showed around half (45%) of the pregnant women were undernourished and key factors include lack of women's decision-making autonomy, household food insecurity, lack of prenatal dietary advice, poor hand washing and lack of proper sanitation (Azero). Nausea and vomiting in early pregnancy can hamper maternal food intake and impact mothers' nutritional status. A systematic review and meta-analysis included in this supplement summarizes the available evidence on efficacy of complementary and alternative medicine therapies, including acupuncture, acupressure, and ginger in comparison with first-line medications or placebo for management of nausea and vomiting during pregnancy and suggested that these interventions though showed promise but quality of evidence is low (Tan et al.).

Prenatal screening and pre-pregnancy care is of utmost importance for healthy pregnancy and the case study from Mexico discusses a care model which combines data from maternal characteristics and history, laboratory tests in early gestation (11–13 weeks) to identify patient-specific risks for pregnancy complications and fetal loss and to improve equity (Bermudez Rojas et al.).

Maternal mental health has increasingly been recognized as a vital component of antenatal care. A study from West Ethiopia, shows approximately one-fifth of women with symptoms of depression during the antenatal period and the factors include being single, unplanned pregnancy, and dissatisfactory relationship with a partner (Oljira et al.). Hence recognizing and addressing mental health concerns during antenatal care is essential for comprehensive support to expectant mothers and interventions should focus on social and emotional factors.

Child growth

The supplement offers valuable insights into the stunting determinants, postnatal growth in preterm infants, and nutrition-infection interactions during the initial 5 years of life. A study from Indonesia highlights the need for efficient and effective intervention programs targeting women's nutritional status during childbearing age and educating on child feeding practices to prevent stunting in children aged 6–23 months (Kartasurya et al.). Another study from Pakistan identified associated growth indicators at around 5 years with poverty, inappropriate complementary feeding, and infections during the first year (González-Fernández et al.). 'Catch-up growth' is identified as a potential modifier of early programming effects, especially for preterm and term SGA babies, predicting optimum neurodevelopment in later life but preterm babies in LMICs face challenges in achieving catch-up growth (5–8). A study from Indonesia reveals that preterm infants with postnatal growth failure experienced delayed full oral feeding and prolonged total parenteral nutrition (Rohsiswatmo et al.). A systematic review of probiotics suggested low to very low certainty of evidence of impact on reducing mortality and necrotizing enterocolitis (Thomas et al.).

Breastfeeding and complementary feeding practices

Optimal breastfeeding and complementary feeding practices form the foundation of child growth and development (9). The COVID-19 pandemic disrupted these practices and a study in India highlighted that separation of mothers and newborns led to disruptions in breastfeeding practices within health institutions (Maria et al.). Expressed breast milk, preferably from the biological mother, is the best alternative for premature and small for gestational age babies and a study from India demonstrated that breastfeeding counseling interventions, including expressed breastfeeding and lactation management in the first 6 months, achieved 70% exclusive breastfeeding in these vulnerable infants (Sharma et al.). A desk review and key informant interviews in seven South Asian countries revealed that integrating maternal, infant, and young child nutrition (MIYCN) counseling indicators

into the country's health information systems can positively impact behaviors related to MIYCN (Bhanot et al.).

Early child development

The supplement included rigorous original studies for factors that could potentially influence child development in the early formative years. The study from Vietnam found no association between maternal hemoglobin (Hb) concentrations during pregnancy and various child health and development outcomes (Young et al.). These findings are in contrast with previous examinations that have shown maternal Hb to be associated with infant and child neurodevelopment and brain structural development. These contradictions highlight the need for further research to understand these relations particularly in resource-poor settings (10, 11). Children exposed to environments with lack of optimal stimulation, responsive care and learning opportunities are at risk for poor cognitive and developmental outcomes (12, 13). Maternal bonding and quality of time spent with a child are considered crucial for child's development. A study from rural India indicated that mothers dedicated a significant part of their day to household chores and about one-sixth time focused on childcare during infancy and as the child grew, maternal time shifted to income-generating and leisure activities (Batura et al.). This shift poses challenges in resource-poor households, suggesting difficulties in promoting and optimal caregiving behaviors.

The Sustainable programme incorporating nutrition and games (SPRING) intervention trial was implemented through monthly home visits by community-based workers in rural India and Pakistan and aimed to enhance early child development (ECD) and growth, but there no significant effects on ECD outcomes or growth in either setting (Kirkwood et al.). The investigators attributed the lack of overall impact to implementation shortcomings, as the challenges of integrating additional tasks into community worker's workload without sufficient resources and highlighted the potential suitability of the non-governmental organization model for scale-up, emphasizing the need for robust administrative and management systems to support successful implementation.

Conclusions

This supplement sheds light on various facets of pregnancy and early childhood care, emphasizing the global need for increased efforts to enhance maternal and child health outcomes. It delves into the intricate interplay of maternal health - both physical and mental environmental factors, and the difficulties associated with implementing interventions in resource-poor settings. Notable challenges include inadequate antenatal care in LMICs, unaddressed maternal undernutrition, and limited access to intervention programs for prevention of stunting in young children. The interplay of maternal health with child development and challenges faced by mothers in resource-poor households also requires deeper exploration. Implementation challenges, as highlighted by the SPRING trial, call for enhanced field supervision, skill development, and workload management. Bridging these gaps requires concerted efforts, from improving antenatal care and

maternal nutrition to addressing issues related to access to quality childhood nutrition and care related interventions.

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RC: Writing—original draft, Writing—review & editing. RU: Writing—original draft, Writing—review & editing. BS: Writing—original draft, Writing—review & editing. ST: Writing—original draft, Writing—review & editing. JD: Writing—original draft, Writing—review & editing. NB: Writing—original draft, Writing—review & editing.

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EDITED BY

Nita Bhandari,
Center for Health Research and
Development, Society for Applied
Studies, India

REVIEWED BY

Jeanette Mary Andrade,
University of Florida, United States
Azam Doustmohammadian,
Iran University of Medical
Sciences, Iran

*CORRESPONDENCE

Arti Maria
artimaria@gmail.com
Archisman Mohapatra
archisman.m@thegridcouncil.org

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Barriers and enablers of breastfeeding in mother–newborn dyads in institutional settings during the COVID-19 pandemic: A qualitative study across seven government hospitals of Delhi, India

Arti Maria^{1*}, Ritika Mukherjee², Swati Upadhyay¹,
Kumari Pratima¹, Tapas Bandyopadhyay¹, Rachita Gupta³,
Bhawna Dubey¹, Abhinav Sharma¹, Pranaya Kumar Mall¹,
Manaswinee Sahoo¹, Keshav Kumar Pathak¹, Priyanka Pawar²
and Archisman Mohapatra^{2*}

¹Department of Neonatology, Atal Bihari Vajpayee Institute of Medical Sciences and Dr. Ram Manohar Lohia Hospital, New Delhi, India, ²Generating Research Insights for Development (GRID) Council, Executive Office, Noida, Uttar Pradesh, India, ³WHO Country Office for India, Nutrition, R.K. Khanna Stadium, Safdarjung Enclave, New Delhi, India

Introduction: The COVID-19 pandemic disrupted newborn care and breastfeeding practices across most healthcare facilities. We undertook this study to explore the barriers and enablers for newborn care and breastfeeding practices in hospitals in Delhi, India for recently delivered mother (RDM)–newborn dyads during the first wave of the COVID-19 pandemic (2020) and inductively design a “pathway of impactation” for informing mitigatory initiatives during the current and future pandemics, at least in the initial months.

Materials and methods: We used an exploratory descriptive design (qualitative research method) and collected information from seven leading public health facilities in Delhi, India. We conducted separate interviews with the head and senior faculty from the Departments of Pediatrics/Neonatology ($n = 12$) and Obstetrics ($n = 7$), resident doctors ($n = 14$), nurses (labor room/maternity ward; $n = 13$), and RDMs ($n = 45$) across three profiles: (a) COVID-19-negative RDM with healthy newborn ($n = 18$), (b) COVID-19-positive RDM with healthy newborn ($n = 19$), and (c) COVID-19 positive RDM with sick newborn needing intensive care ($n = 8$) along with their care-giving family members ($n = 39$). We analyzed the data using grounded theory as the method and phenomenology as the philosophy of our research.

Results: Anxiety among clients and providers, evolving evidence and advisories, separation of the COVID-positive RDM from her newborn at birth, providers’ tendency to minimize contact duration and frequency

with COVID-positive mothers, compromised counseling on breastfeeding, logistic difficulties in expression and transportation of COVID-positive mother's milk to her baby in the nursery, COVID restrictions, staff shortage and unavailable family support in wards and nursery, and inadequate infrastructure were identified as major barriers. Keeping the RDM–newborn together, harmonization of standard operating procedures between professional associations and within and between departments, strategic mobilization of resources, optimization of human resources, strengthening client–provider interaction, risk triaging, leveraging technology, and leadership-in-crisis-situations were notable enablers.

Conclusion: The separation of the RDM and newborn led to a cascade of disruptions to newborn care and breastfeeding practices in the study institutions. Separating the newborn from the mother should be avoided during public health emergencies unless there is robust evidence favoring the same; routine institutional practices should be family centered.

KEYWORDS

breastfeeding, newborn care, India, COVID-19, hospital, isolation, baby friendly hospital initiative, family centered care

Introduction

Feeding mother's own milk (MOM) is advantageous for the recently delivered mother (RDM)–newborn dyad (1–6). Governments worldwide, care providers and breastfeeding support groups, the WHO, and several other stakeholders have been working toward its universalization. It is recommended that mothers should initiate breastfeeding immediately after birth, provide exclusive breastfeeding for up to 6 months, and continue breastfeeding along with complementary for at least up to 2 years. However, ensuring optimal breastfeeding practices among the population at large has been an uphill task for countries, especially low- and middle-income countries (LMICs). Institutional practices around birth and immediately thereafter, e.g., early-uninterrupted skin-to-skin contact, early initiation of breastfeeding, rooming-in, involving families in care of RDM–newborns, help in establishing and sustaining optimal newborn care, and breastfeeding practices (7–9). The increasing rate of institutional deliveries across the world provides an opportunity to ensure that optimal newborn care and breastfeeding practices are reinforced for mother–newborn dyads before their discharge. Unfortunately, the COVID-19 pandemic has challenged health systems worldwide leading to the disruption of routine healthcare services. Anticipating the pandemic's disruptive effect on RDM–newborn care services and optimal breastfeeding practices (10–13), the WHO released

mitigatory advisories in early 2020 (14–16). Professional associations and institutional authorities also made efforts to mitigate the disruptions. Still, breastfeeding practices got compromised even in the most advanced healthcare setups (17, 18). Studies published later into the pandemic, i.e., in 2021 and 2022 indicate that breastfeeding practices got compromised in newborns during the pandemic due to a gamut of reasons including lack of high-quality professional services, peer-to-peer support, and social vulnerability and ignorance amidst challenges posed by the mass movement restrictions (19–21).

India has the world's largest annual birth cohort (~25 million) (22). Nevertheless, it continues to struggle in ensuring exclusive breastfeeding (EBF) in infants (as per the latest Demographic and Health Survey in India (NFHS-5), EBF rates were only about 63.7%) India promotes breastfeeding for improving newborn survival and development (23–25). Hence, India prioritizes institutional deliveries and baby-friendly hospital initiatives (BFHI) and has witnessed appreciable improvement in institutional practices for maternal and newborn care. In the initial months of the pandemic, India had to suspend non-essential healthcare services, e.g., outpatient consultations and elective procedures so that health care resources could be mobilized and redirected to pandemic combat (26). Teaching medical institutions (the front-leaders of optimal evidence-based practices) also had to reposition their resources to meet surge demands (27). During these initial months, India also witnessed a dip in institutional deliveries, duration of stay in the hospital post-delivery, and post-partum follow-up (both for the mother and the newborn) (28). To mitigate the potential disruption caused by the pandemic on

Abbreviations: HCP, Healthcare Provider; HOD, Head of Department; IPC, Infection prevention and control; PPE, Personal Protective Equipment; RDM, Recently delivered mothers.

institutional care of mother–newborn dyads and to standardize practices across India, the Federation of Obstetric and Gynecological Societies of India (FOGSI), National Neonatology Forum of India (NNF), and Indian Academy of Pediatrics released a joint statement in April 2020 (29). Nevertheless, newborn care and optimal breastfeeding practices likely got affected adversely during the pandemic. While there was an inadequate understanding of the “pathways” through which the COVID-19 pandemic impacted newborn care and optimal breastfeeding practices in institutional settings in India during the initial months of the pandemic, there was a gap in knowledge on how these could have been best salvaged. As with the guidance documents of WHO, even the joint statement needed contextual adaptation for implementation across healthcare facilities which most premier health care facilities would have likely undertaken. Thus, there was a need to explore, identify, and learn from experiences and practices across institutions. In the wake of the impediments caused by the COVID-19 pandemic, there was also a window of opportunity to examine institutional practices for newborn care and breastfeeding for critical learnings for building resilient “BFHI” systems. Consequently, we undertook this study to explore the barriers and enablers for newborn care and breastfeeding practices in hospitals in Delhi, India, for recently delivered mother (RDM)–newborn dyads during the first wave of the COVID-19 pandemic (2020) and inductively design a “pathway of impactation” for informing mitigatory initiatives during the current and future pandemics, at least in the initial months. Thus, in this study, we explored how newborn care and breastfeeding practices got impacted in institutionalized mother–newborn dyads in the major teaching medical institutions in Delhi, India in the initial months of the pandemic. We also explored what challenges these institutions faced in their effort to mitigate risk and sustain services and what innovations/enablers they identified in the process that could help inform ongoing practices and also develop standard protocols for future disasters. We believe that policy and program managers and healthcare providers engaged in mother-and-baby care and breastfeeding promotion efforts will find the findings useful for evidence-based action.

Methods

Study design and setting

We used an exploratory descriptive qualitative design and conducted in-depth interviews (IDIs) with participants from seven medical institutions in Delhi; six of these were premier teaching medical schools in India. Two of the institutions were operating as ‘exclusive COVID-care facilities’ at the time of data collection. Delhi had been one of the first and worst affected states and union territories in India during the COVID-19 pandemic (30). It also has some

of the premier teaching medical institutions that not only provide state-of-the-art health services to a huge population but also actively engage in innovating and designing case management protocols that are adapted/followed by institutions nation-wide. Exploration of the impact of the COVID-19 pandemic on newborn care and breastfeeding practices in these institutions and how these managed mitigatory efforts held the promise of identifying not only the factors and pathways of impactation but also the potential nodes for intervention. These health facilities are spread across Delhi and cater to a diverse range of clientele across socio-economic strata from the Delhi National Capital Region as well as referral patients from across India with variegated newborn care and feeding practices.

Participants

In the study, we considered the “newborn” as the central focus (though it would have been ideal to center around mother–newborn dyads, it was operationally difficult at that point in time). We prepared a list of the stakeholders involved in newborn care and feeding in institutional settings by preparing a “pathway of care” schematic (described below in Study instruments). To start with, we decided to interview the head and the second-senior-most faculty in the departments of neonatology or pediatrics (if the institution did not have a department of neonatology) of the selected institutions. However, we also felt that we needed to get inputs from the head of the department of obstetrics at these institutions in order to triangulate information comprehensively and in line with our phenomenological philosophy. Consequently, we interacted with seven head obstetricians from the institutions studied. Neonatologists and obstetricians were responsible for the care of the newborn and the RDM, respectively, in maternity wards, isolation wards, nurseries, and newborn intensive care units. We considered these HCPs as a common group for triangulating information from “administrative leadership” perspective. Having three such HCPs from an institution added up to a total of 21 respondents in this category and were deemed adequate to saturate information. However, our team also appreciated that most of the maternal–newborn care, and especially that related to breastfeeding, in these institutions was delivered through resident doctors and nurses posted in the labor room and maternity wards. Hence, we requested the neonatology/pediatrics heads to nominate two residents and two nurses from their teams who had been posted in the care of RDM newborns for the longest duration and among the ones most actively involved in caregiving to this clientele among their colleagues. We requested to identify those residents and nurses who had been working in the institution before the pandemic hit, i.e., before February 2020. Thus, at each center, we selected these participants purposively. At that point, we assumed that

with as many resident and nurse participants, we would most likely hit information saturation for each (31).

At each center, we included RDMs across each of the three profiles: (a) COVID-19-negative RDM with a healthy newborn, (b) COVID-19-positive RDMs with healthy newborns, and (c) COVID-19-positive RDMs with sick newborns. We did not intend to stratify our results according to the RDM–newborn profile since we aimed at characterizing the “phenomenon” at the institutional level; having the three profiles of RDM–newborn dyads allowed for capturing nuanced experiences and insights. We aimed at interviewing as many participants in each profile till we hit information saturation. These participants were selected purposively with the help of the neonatology residents while balancing data saturation requirements, operational feasibility, participation from the seven healthcare institutions studied, and other socio-demographic characteristics (the socio-economic class, literacy, religion, parity of the RDM, and gender of the newborn). We chose RDMs who had delivered beyond 7 days preceding the date of the interview to a maximum of up to 10 days before. We kept this day-range in order to capture institutional experiences. We also undertook non-formal interactions (NFIs) with the RDMs’ escorting family members (1 per RDM) at the hospital.

We interacted with all participants with prior informed consent and appointment. We did not have any refusal to participate.

The participant profiles are shown in Table 1.

Study instruments

For identifying the items of inquiry, we convened a meeting of the unit head and four faculty members (Neonatology), one lactation counselor, one obstetrics resident, and two extramural public health researchers with experience in qualitative methods. We prepared a “pathway of care” schematic for a pregnant woman reporting to a typical hospital in Delhi for delivery during the pandemic until her and her baby’s discharge from the hospital. The pathway was reviewed with the three prototype RDM–newborn dyads (mentioned above) in mind. We anecdotally plotted the possible disruptions in pre-pandemic institutional practices at pre-delivery, at time of delivery, immediately post-delivery, during stay in the hospital, at discharge, and during follow-up. We reviewed relevant literature and designed interview guides for each participant category, pretested, and finalized them. We developed separate instruments for each participant category. Some of the items of inquiry were, however, retained across two or more tools. Supplementary Box 1 provides the tool development process. Box 1 illustrates the topics covered in the interviews and the number of items in each tool for the respective participant category. A checklist was prepared for NFI with the RDMs’ escorts.

BOX 1 Topics discussed in the interviews with Unit Heads, Resident Doctors, Lactation Counselors/Nurses, and Recently Delivered Mothers (RDMs).

Interviews with Unit Heads

- Overall effect of COVID-19 on breastfeeding promotive approaches
- Modifications made to accommodate IPC protocols in care of newborn
- Practices around testing of RDMs for COVID-19
- Challenges in implementing guidelines for breastfeeding and mitigating strategies
- Best practices for promoting optimal breastfeeding according to COVID-19 status
- Practices to reinforce optimal breastfeeding in RDMs after discharge
- Impact of COVID-19-related anxiety and stigma in care of RDM–newborn dyads
- Requirement for further skill building of staff
- Challenges in staff allocation for COVID duty
- Mitigation strategies for staff shortage
- Ways to ensure inter-departmental coordination while managing RDM–newborn dyads
- Suggestions for improving policies and practices

Interviews with Resident Doctors

- Adaptation of practices for newborn care immediately after delivering a baby
- Adaptation of routine in-patient services for RDM–newborn dyads
- Challenges experienced in advising for expression and feeding of breastmilk during COVID-19*
- Impact of COVID-19 on practices for optimal breastfeeding among RDMs*
- Challenges to breastfeeding during the pandemic and its impact on counseling strategies
- Receptivity of RDMs to breastfeeding advice during COVID-19 and its determining factors*
- Strategies adopted for managing babies born to COVID-19-positive mothers as compared to those COVID-19 negative and its effectiveness
- Challenges to decision-making with regard to breastfeeding practices
- Self-reflection on individual performance in ensuring optimal breastfeeding practices in RDMs*

Interviews with Lactation Counselors/Nurses

- Effect of COVID-19 in usual way of counseling of RDMs
- Challenges to effective lactational counseling during the pandemic and mitigating strategies
- Adaptation of newborn care practices for COVID-19 negative mothers
- Most effective strategies for reinforcing optimal newborn feeding practices

Interviews with Recently Delivered Mothers

- Experience regarding care and feeding of your newborn in the hospital
- Advice received on newborn feeding from hospital and family members during hospital stay and its impact
- Challenges experienced in feeding newborns during hospital stay and ways to address them
- Support received from the hospital that have helped her in feeding her newborn
- Support expected from hospital staff in feeding newborns during hospital stay
- Support expected for optimal feeding after discharge and in follow up

*Also discussed with Lactation Counselors/Nurses

IPC-Infection prevention and control; RDM- Recently delivered mother, COVID- Coronavirus disease

TABLE 1 Distribution of participants from the study sites ($n = 7$).

Participant profile		Medical institution (study site) [^]							Total
		A	B*	C	D*	E	F	G	
Health care workers	Head/ Senior faculty, (Neonat./Peds.)	02	02	02	01	02	01	02	12
	Head (Obstetrics)	01	01	01	01	01	01	01	07
	Resident doctor (Neonat./Peds.)	02	02	02	02	02	02	02	14
	Nurse	02	02	02	02	02	02	01	13
	Total	07	07	07	06	07	06	06	46
Recently delivered mothers (RDMs)	COVID-negative mother with healthy baby	01	0	09	0	0	05	03	18
	COVID-positive mother with Healthy newborn	03	03	02	05	03	01	02	19
	Sick newborn	01	04	03	0	0	0	0	08
	Total	05	07	14	05	03	06	05	45
	Husband	03	03	12	04	02	08	02	34
Attendants	Other family members	0	01	01	0	02	0	01	05
	Total	03	04	13	04	04	08	03	39

[^]A: Maulana Azad Medical College and GB Pant Institute of Post Graduate Medical Education and Research (MAMC and GB Pant PGIMER), B: University College of Medical Sciences and Guru Teg Bahadur Hospital (UCMS and GTB), C: Atal Bihari Vajpayee Institute of Medical Sciences and Dr. Ram Manohar Lohia Hospital (ABVIMS and Dr RML), D: Deep Chand Bandhu Hospital (DCBH), E: Vardhman Mahavir Medical College and Safdarjung Hospital (VMMC and SJ), F: Lady Hardinge Medical College and Kalawati Sharan Hospital (LHMC and KSH), and G: All India Institute of Medical Sciences (AIIMS), New Delhi.

*Designated COVID-hospitals.

Data collection

Six interviewers collected data—two qualitative researchers [AMo (male, MD) and RM (female, PhD)] and four neonatology faculty members [two females (SU and KP) and two males (SK and TB)], trained in interviewing techniques. The team interacted with participants over video meetings (Google Meet and WhatsApp) since physical meetings were restricted during the pandemic (32).

Data management and analysis

IDIs with the doctors were analyzed using English transcripts. Responses from nurses, RDMs, and their escorts were directly analyzed from the audio (“tape analysis”) to allow for the comprehension of responses that were in mixed language (Hindi and Indian English) and often emotional (33, 34). Analysis was done using NVIVO (35). Responses were free-listed and coded thematically using the grounded theory approach by RM, AMo, and PP (female, MPH), in consensus (36). We achieved data saturation for each participant category (31). The code frequencies were grouped as follows: “None” (0%); “Few” (below 25%); “Some” (25–49%); “Many” (50–74%);

“Most” (75–99%); and “All” (100%) (37). “Quotable quotes” were identified from the responses.

We improvised the “pathway to care” schematic as an inductive framework enumerating the disruptions to breastfeeding practices in institutionalized RDM–newborn dyads. For this, we (RM, AMo, PP, AMa, SU, KP, and TB) triangulated narratives across stakeholder categories and incorporated feedback from the larger team of authors between November 2020 and February 2021 through an iterative process. The findings were deemed consistent with the data.

Quantitative information was summarized as frequency and proportion using MS Excel (MS Office 365).

Quality assurance

The RDMs and their escorts were interviewed at the hospital/home between the 7th and 10th day of delivery as per their convenience. We conducted and audio-recorded each interaction with a prior appointment and informed verbal consent for participation in the interview and for audio-recording, which was also recorded prior to the initiation of the interview. Written consent was difficult to obtain due to the COVID-19 physical access restrictions in the

isolation wards and healthcare facilities. The interactions were done in the participant's preferred language. The HCPs were interviewed in the office. The IDIs were limited to 45-to-75 min, while the NFIs were for about 10–15 min each to manage respondent burden and sustain engagement. Trained interviewers administered the interview items verbatim using structured interview guides. The responses were audio-recorded on multiple devices to protect against data loss. Transcripts were matched with the recordings for accuracy and completeness before analysis; we did tape analysis to capture the “sentiments” of the respondents. Findings were reported using the CONSolidated criteria for REporting Qualitative research (COREQ) checklist.

Results

Participant profile

The age of the senior HCPs (neonatologists, pediatricians, and obstetricians) was 58.1 ± 3.4 years, the residents 29.3 ± 3.1 years, and nurses 43.2 ± 5.6 years. The age of the RDMs was 23.8 ± 3.2 years; 44.4% ($n = 20$) of these were first-time mothers, 82.2% ($n = 37$) were Hindus, 15.6% ($n = 7$) had 0–5 years of formal education, 8.9% ($n = 4$) were from economically weaker section, 51.1% ($n = 23$) had delivered through cesarean section. Of the newborns, 44.4% ($n = 20$) were female. We have provided the details of the RDMs' profiles and newborn care and feeding practices in [Supplementary Table 1](#).

Perceived barriers to optimal breastfeeding and newborn care practices

Here, we have narrated the key barriers across RDM–newborn profiles ([Table 2](#)); these were most prominent in the initial months of the pandemic.

Anxiety related to COVID-19

Providers as well as clients were anxious that they might contract and/or transmit SARS-CoV-2 with fatal outcomes. Staff anxiety was attributable to inadequate availability and knowledge of using personal protective equipment (PPE), and unavoidable interactions with patients and escorts who often lacked COVID-appropriate behavior. Several staff members got exposed inadvertently, especially during posting in COVID-suspect wards, and had to undergo quarantine; this heightened anxiety and reluctance among colleagues.

“Reluctance was from seniors, including me. But residents and sisters were always prompt and discharged their duties sincerely, not putting senior people at risk of infection for work which may be handled (over phone) without going (physically).” (HOD, Neonatology)

During the initial months of the pandemic, institutional isolation had been made mandatory for all individuals testing positive for SARS-CoV-2. The RDMs, especially those asymptomatic, found such isolation extremely distressful. They were often not convinced that they were infected and did not want to co-isolate with those with symptomatic infection.

“I did not have fever or cold. I had no symptoms, not even breathlessness. I had absolutely no problems. Even then I was told that I am corona positive. This is my exact problem here. How can they do that? I still have no symptoms and no ailments. No cough, no cold, no fever. Yet, they say I am corona positive.” (-RDM, COVID-19 positive with healthy baby)

There were instances when RDMs, including those negative for COVID-19, resisted rooming-in and/or breastfeeding, fearing transmission of infection to their newborns. There were also instances when RDMs were more willing to breastfeed than to express and transport; they felt that storage may lead to an increased risk of infection. Clients feared that they and/or the newborn may get infected during the hospital stay. At times, family members did not want to accompany the RDM to the hospital for fear of getting infected. The RDMs and family members would often insist on discharge immediately after delivery. Family members also resisted rooming-in, breastfeeding, and transportation of expressed milk citing the risk of transmission of infection.

“I still feel that my baby became COVID positive because I breastfed. I hope I did not infect him, but I feel so because I breastfed him. So, I do not want to take any further risks. I do not want to breastfeed him again.” (-RDM, COVID-19 positive with sick baby)

Logistics and operations challenge

As separate wards had to be created for risk stratification, resources often fell short. Procurement of new equipment had to be expedited and prudently distributed between the wards. PPEs, being in short supply, had to be used frugally. There was a lack of space for expansion. In most places, the isolation ward for the RDM was relatively far off from the nursery making transportation of expressed milk difficult. There were times when suspected COVID-19 patients and non-COVID-19 patients had to be kept in the same area, leading to increased anxiety among the RDMs and those accompanying them.

TABLE 2 List of core themes and sub-themes for optimal breastfeeding practices emerging from inductive data analysis and their code prevalence according to the different groups of recently delivered mothers.

Core theme	Sub-themes	Code prevalence*			Total (N = 45)
		Healthy (COVID-19 -ve) RDM with healthy newborn (N = 18)	RDM with COVID-19 and Healthy newborn (N = 19)	Sick newborn (N = 8)	
Perceived barriers	Compromised newborn care	Many	Most	All	Most
	Anxiety related to COVID-19	Many	Many	Some	Many
	Difficulty in breastfeeding or expressing breastmilk	Many	Many	Many	Many
	Inadequate counseling on IPC for newborn care	Many	Few	Some	Some
	Inadequate knowledge on breastfeeding	Some	Few	Many	Some
	Management and logistic issues	Some	Some	Many	Some
	Delayed or unsatisfactory inpatient care services	Some	Some	Some	Some
	Rooming in avoided	Few	Some	All	Some
	Mother and newborn were discharged separately	Few	Some	Few	Few
	RDMs lacked support as attendants entry into the wards was restricted	Few	Many	Some	Some
	Problems faced during admission for delivery	Few	None		Few
	Inadequate/ lack of support with follow-up care	Few	Few		Few
	Lack of privacy for RDMs		Few		Few
	Referral transfer between hospitals for COVID		Some	Many	Few
Perceived enablers	Counseling on breastfeeding	Most	Many	Most	Many
	Counseling on COVID-19 to allay fear	Few	Many	Some	Some
	Optimizing time for discharge from hospital for mother–newborn dyads	Few	Few	Few	Few
	Infrastructural modifications and “zoning” during COVID	Few	Some	Few	Some
	Additional measures were undertaken for control of infection and anxiety among patients and providers	Many	Few	Some	Some
	No help required to the RDM in feeding the newborn	Many	Some	Many	Some
	Support from family for follow-up care	Some	Some	Some	Some
	Support from family members during hospital stay	Some	Some	None	Some
	Support from hospital and doctor for follow-up treatment	Some	Some	Many	Some
	Support received in inpatient care	Many	Most	Most	Most
	Received comprehensive advice on newborn care & infection control practices	Many	Most	Most	Many
	Family members advised RDM to breastfeed		Few	Many	Few
	Infrastructural modifications for better support		Some		Few
	Support to RDMs during isolation		Some	Many	Some
	Support from the hospital staff with feeding of the baby		Some	Most	Some
	No help with follow-up care required			Few	Few
	Prompt care of the newborn received			Many	Few

*Percentages grouped as: “None (0%); Few (below 25%); Some (25–49%); Many (50–74%); Most (74–99%); All (100%)”.

HOD, heads of department/unit of Neonatology, Pediatrics, Obstetrics; RDM, Recently Delivered Mother, COVID, Coronavirus disease.

Distancing between beds and rooming-in was challenging, and privacy could not be ensured for the RDMs to breastfeed or express milk.

Inconsistencies in evolving guidelines

As evidence was evolving fast, hospital and departmental protocols had to be updated frequently. The staff faced difficulty in adapting to the frequent change in the hospital protocols. Providers reported that obstetricians and neonatologists differed in respective departmental protocols for skin-to-skin contact, rooming-in, breastfeeding, and discharge. Initially, there was a lack of clarity on responsibilities and coordination between the departments.

“Problem is about the mindset and overcoming these resistances with our own *[name of department]* colleagues. I am strong minded, I get it implemented if these recommendations are strong, I still want to do it, but probably it's not all in my hands. I will definitely work on it, we as a team will try to do something and definitely, we will make it happen.” (- HOD, Department anonymized)

Inadequate staffing

Given the surge in adult patients due to COVID-19, staff from the neonatology as well as obstetric departments was diverted toward adult wards, leading to acute staff shortage therein. The raging pandemic, quarantine protocols, and a few staff resignations accentuate the shortage. At times, to meet surge preparedness and/or meet gaps in staff strength, personnel from other specialties who had little/no experience in maternal–newborn care were posted in nurseries and maternity wards.

“Mother-baby dyads are being handled by health care providers who are usually not taking care of the newborn or mothers. So definitely we are trying to educate more and more.” (-HOD, Neonatologist)

Delays in test results for the RDMs led to prolonged stay of the newborn in the nursery, thus overburdening the inadequate staff therein. PPEs also reduced the staff's efficiency.

“Repeated counseling, getting expressed breast milk, looking at babies frequently, that all needs manpower, and time and manpower, get doubled when you are working with PPE.” (-HOD, Neonatologist)

Entry restrictions

Due to infection prevention and control (IPC) protocols, RDM's escorts were disallowed in delivery rooms and maternity wards. RDMs, especially those who were primiparous or had

delivered by cesarean section, needed support for self-care and expression of breastmilk and faced many difficulties; escorts were anguished.

“Because of COVID, mother and baby were completely isolated. I or any other family member was not allowed inside. But this is not right, especially because she had C-section and someone should have been allowed to take care and help her.” (- Family member of RDM)

Separation of mother and newborn

In the initial months of the pandemic, providers were unsure if breastfeeding was safe during COVID-19. If the RDM was COVID-19 positive or suspect, her newborn was separated immediately after the birth and started on artificial milk till the dyad tested negative for SARS-CoV-2. At times, a mother delivering at a non-COVID hospital was referred to a designated COVID hospital on being detected positive, while her baby was retained at the hospital of delivery. The separation was quite distressing for the RDMs and their families.

“I was not allowed to breastfeed or send expressed breastmilk to my baby. My baby was not given my milk. (-RDM, COVID-19 Positive with healthy baby)

“I did not even see my baby since birth, how could I have possibly breastfed her?”

(-RDM, COVID-19 Positive with healthy baby)

“I have to go to the other building to get the milk. I do it about 7-8 times a day. It is difficult as I have arthritis, but I have to do it because if I won't, who else (would do it)!” (- Mother-in-law of a COVID-19 positive RDM)

Compromised provider–patient interaction

Interaction between the doctor, RDMs, and family members got compromised due to fear and limited visitations in face of staff shortage. The gap for counseling services was most glaring at places where these were most needed.

“When I had my first child, I was advised well about the breastfeeding. However, this time they explained nothing to me. They did not discuss or advised anything. Since delivery, the doctor has not even visited once to check on me.” (-RDM, COVID-19 negative)

Repeated donning and doffing of PPEs were inconvenient. Furthermore, conversations with masks on their face compromised both the duration and quality of interaction. Massages for newborn care and breastfeeding could not be provided consistently due to various reasons, e.g., reallocated staff often lacked standardized skills and motivation to counsel, specialties differed in their opinions, etc. All these factors

adversely affected the opportunities for counseling in the early postnatal period for establishing optimal breastfeeding. Pandemic restrictions had separated the RDM from the family. Thus, the two had to be counseled separately. This not only increased the workload of the staff but was also deemed as less efficient than counseling both together.

Some of the RDMs and family members also reported being unaware of the newborn's care and wellbeing, indicating a gap in communication.

Discharging RDM and newborn separately

For instances where the RDM was COVID-positive, the family resisted rooming-in of the baby and rather preferred to take the baby home. In some cases when the mother was COVID-negative and the baby required nursery care, even obstetricians as well as families preferred that the mother be discharged to minimize risk exposure. Discharging the RDM and her newborn at different time points disrupted breastfeeding practices. Families also reported difficulty in managing the newborn at home without the mother.

"I am troubled that they are not discharging my wife. I am staying with the baby alone in the house. It's difficult for me to manage. Yesterday they asked me to come at 10 am today and they would discharge, now they are saying they will not" (- Family member of RDM)

Inadequate follow-up care

Most hospitals had suspended post-partum as well as neonatal follow-up clinics and had moved on to patient-initiated telephonic follow-up. However, with frequently changing staff, it was difficult for an RDM to contact the staff that had tended to her and her newborn when in the hospital. Also, hospitals at times did not have phone numbers of the RDMs or their families to contact after discharge. The providers were unsure if optimal breastfeeding practices were sustained once discharged from the hospital.

Client dissatisfaction

While most patients were satisfied, some complained of inadequate communication during their hospital stay. Family members at times reported facing stigmatized behavior and inadequate help from the hospital support staff. The RDM in the isolation ward as well as family members felt under-informed; they reported a gap in communication with the nursery staff. As entry into the nursery was restricted, they questioned the quality of care for the newborn.

While most clients appreciated improved hygiene and IPC at the hospital, others expressed dissatisfaction. They complained about unclean wards, walkways, toilets,

cumbersome administrative processes, uncomfortable beds (no backrest to support breastfeeding mothers), and lack of privacy and comfort. Family members accompanying RDMs reported overcrowding, lack of chairs in waiting areas, and lack of adequate, clean, and separate toilets for men and women.

"Hygiene was very bad. 2 maternity rooms 1 room had 12 – 15 beds while the other room had 3 beds. At one point 10 – 12 patients were there who were all using one common toilet. The toilet was being cleaned only once in 24 hrs. (There were) cockroaches in the room" (- Family member of RDM)

The clients complained that stringent IPC practices coupled with conflicting information from different health personnel led to avoidable delays in services. Family members had to arrange their own personal protective provisions adding to their out-of-pocket expenditures.

"We reached emergency at 2 am and then the report was not accepted, she was not given the private ward... These were not good. The Gynae doctor said we can do the test from outside but emergency doctor refused... Took too much of time in admission" (- Family member of RDM)

Overcoming barriers to optimal breastfeeding and newborn care practices

We noticed temporal trends in the providers' and participants' attitudes to COVID-19 after the initial months; practices and innovations emerged as enablers (Tables 3, 4) in response to disruptions caused by the pandemic.

Change in attitude of patients and healthcare providers with time

Toward August 2020, evidence was emerging that breastfeeding was safe during the pandemic. The COVID-19 wave in Delhi was also receding. HCPs were more confident and RDMs and family members were more receptive toward breastfeeding and rooming-in-related advice. The workload in hospitals was easing-off. The availability of PPEs had improved. Concurrently, COVID anxiety had also started waning. Provider–patient interactions improved.

Efficiency of counter-measures increased with time

Hospital processes had become more "COVID-adaptive" over time. Operational innovations minimized the risk of cross-infection and optimized IPC practices and the use of

TABLE 3 List of core themes and sub-themes for optimal breastfeeding practices emerging from inductive data analysis and their code prevalence according to the healthcare providers.

Core theme	Sub-themes	Code prevalence*		
		HOD	Resident doctors	Nurses
Perceived barriers	Anxiety related to COVID-19	All	Most	Most
	Reduced quality of provider–patient interaction	Most	Many	All
	RDMs lacked support as attendants' (family members) entry into the wards was restricted	Most	Most	Many
	Mother and newborn were discharged separately	Some	Some	
	Inadequate/ lack of support with follow-up care	Few	Some	Few
	Inadequate staff capacity	Most	Most	Many
	Separation of mother and newborn immediately after birth and its prolongation	Most	Most	Most
	Inconsistent and evolving guidelines	Most	Some	
	Inadequate infrastructure and logistics	Many	Most	Most
Perceived enablers	Additional measures were undertaken for control of infection and anxiety among patients and providers	All	Most	Many
	Optimizing time for discharge from hospital for mother–newborn dyads	Most	Many	Few
	Infrastructural modifications and “zoning” during COVID	Most	All	Most
	Guidelines coming up after initial months and their sharing and adherence by staff	Few	Some	Few
	Evolution of existing practices for newborn care and breastfeeding during COVID	Most	Most	Most
	Change in attitude of patients and healthcare workers with time	Many	Some	Many
	Leadership in promoting breastfeeding in newborn	Some	None	Few
	Good coordination and teamwork between Obstetrics and Neonatology	Most	Some	Few
	Innovation of follow-up practices	Many	Many	Some
	Staff deployment	Most	Some	
	Promotion of optimal breastfeeding in the COVID-19 pandemic	Most	Most	
	Support (physical) provided to RDMs during the isolation	Some	Few	
	Regular testing for COVID	Some		
	Able to follow newborn care practices because case load of deliveries during COVID is low	Some		
	Willingness of the RDMs to be counseled		Some	
	Choice given to the family to decide rooming in if mother is positive		Few	
	Positive receptivity of breastfeeding counseling by RDMs			Most

*Percentages grouped as: “None (0%); Few (below 25%); Some (25–49%); Many (50–74%); Most (74–99%); All (100%)”.

HOD, heads of department/ unit of Neonatology, Pediatrics, Obstetrics; RDM, Recently delivered mother, COVID, Coronavirus disease.

resources. For example, doctors scheduled clinical rounds of COVID wards after that in non-COVID wards and did the case notes documentation in the duty room instead of bedside, thus, minimizing the demand for PPEs. Staff allocation rosters were rationalized according to risk exposure and client load. Simultaneously, sensitization training and hand-holding support were also provided to the staff rotated from other specialties to the nursery and maternity wards. Crowd management practices became more efficient.

Suspension of elective services, mass movement restrictions (lock-down), and having designated COVID facilities helped in optimizing workload and improving institutional efficiency. As referral chains for transferring COVID-19 cases to designated facilities strengthened, case load on non-COVID facilities decreased. Institutional designations as exclusive COVID/non-COVID facilities made the implementation of SOPs easier, safer, and more efficient.

TABLE 4 Barriers experienced, and counter measures undertaken to ensure optimal breastfeeding among institutionalized mothers during COVID-19 pandemic.

Perceived barriers	Examples of counter measures/innovations undertaken
* Inadequate client-provider interaction	Nursery staff were made more easily accessible to RDMs
* Anxiety related to COVID-19 (Hesitancy of mother/ family members; Hesitancy of HCWs)	- Centralized facility of audio and video for the family members to connect with the RDMs; mobile and video calling facility in the nursery for communication between doctor and RDM Strategies and content for counseling of RDMs was modified in the context of COVID-19 to increase its effectiveness - Shared picture of mothers breastfeeding with masks; counseling done individually and/or in smaller groups; other breastfeeding mothers involved in counseling of the RDMs to motivate for breastfeeding; senior doctors counseled mothers who were extremely depressed and resisted breastfeeding Repeated counseling of family members - Counseled to do away with anxiety and agree to breastfeeding by RDM; family members encouraged and involved in decision-making.
* Mother-baby discharged early/ separately	Optimizing time for discharge from hospital for mother-newborn dyads
* Reduced post-discharge follow-up	Ensured seamless follow-up of RDMs and newborns after discharge
	Dedicated teams/ personnel and phone lines for telephonic and video calls assigned; developing robust checklist for scheduled calls for follow up
* Deployment of staff not trained in pandemic-appropriate skills	Staff management optimized for non-disruption of services while maintaining staff motivation and protection.
* Staff shortage	Rotational duties followed by quarantine; staff sensitization and training up-scaled for sustained motivation and skill enhancement; active involvement of senior staff and department leadership in the COVID ward to set an example; accommodation for HCWs with dedicated conveyance was arranged
* Logistic constraints	Infrastructural changes to meet improved IPC requirement, need for risk triaging, and for maximizing efficiency
* Frugal use of PPE	Reassigning and redesigning of resources to facilitate and promote optimal breastfeeding; curtains and screens were put between beds for privacy to the RDM for breastfeeding/ expression; documentation of the patients done in the duty room and not along the bedside; created antenatal OPD for COVID cases only; installation of camera in the wards/ rooms for remote monitoring of patients
* Need to harmonize Neonatology-Obstetric SOPs for Maternal-Newborn Care	Zoning according to risk for minimizing risk of exposure
* Infection prevention protocols in hospitals	- Zoning of nursery and maternity wards depending on the COVID status; separate red/ green zone depending on patient movement and location of wards Special IPC measures for crowd management - Screening of accompanying family members for COVID-19 symptoms before allowing entry; sanitizer dispensers were installed at places; crowd management SOPs were developed Support mobilized for RDMs – both logistic and emotional - Attendants allowed and arrangements were made for attendants to help mother with all IPC measures; RDM were asked to make notes of queries that were addressed

COVID, Coronavirus disease; RDM, Recently delivered mother; PPE, Personal Protection Equipment; SOP, Standard Operating Procedure; IPC, Infection prevention and control; OPD, Outpatient department; HCW, Healthcare workers.

“Through these past 6 months, whole system has evolved so much! Initially we didn’t know what to do. When we got COVID positive mother, the first question was, what to do with the baby if the baby is well. Now we have a separate step-down unit... we have COVID positive step-down nursery, we have COVID positive ward. So initially we did not have the whole setup and we used to lack on those aspects, and we have built ourselves around it.”
(-Resident Doctor)

As testing capacity increased, all RDMs were tested for SARS-CoV-2. This increased confidence in the staff. The RDMs and families appreciated that the hospitals were strict with norms of social distancing and IPC and had made testing

mandatory for all patients seeking admission. The RDMs, newborns, and HCPs were also monitored for COVID-19 symptoms. Symptomatic HCPs were tested and isolated, if positive. Hospitals had arranged separate accommodation, travel, and quarantine facilities for the staff on COVID-19 duty. This improved staff availability while minimizing the exposure of their families to SARS-CoV-2.

Making services family-centered

With time, the staff had adopted effective ways to counsel clients. HCPs had increased their availability and access for RDMs and family members. Departments now laid greater emphasis on counseling for skin-to-skin contact, breastfeeding,

and rooming-in during pre-labor, labor, and at discharge to the RDMs and families. Providing detailed information on breastfeeding and newborn care as well as engagement of family members in the decision-making process led to better compliance with breastfeeding practices and overall satisfaction among the clients. Regular telephonic or video call-based updates about RDMs and their babies to the family members were initiated in two study hospitals. Reports were also shared with the family through WhatsApp messages. Several RDMs reported receiving prompt and timely treatment. The staff was also reported to be more patient, caring, and addressing their queries. Even the capacity of the support staff (e.g., guards and workers) for facilitating patients improved with experience.

“We get to talk to the doctor every day and get updates on the patient...they gave their number and they called twice in a day too! Once in the morning and once in the evening. They made two video clips and sent it to us, so that we can see the baby” (-Family member of a COVID-positive RDM)

“People say bad things about Government hospitals but my experience was very good. The doctors patiently heard and advised every patient, and we could ask them anything and they would always provide a solution for that.” (-Family member of a COVID-positive RDM)

Optimizing and coordinating discharge for mother–newborn dyads

Over the months, most facilities realized that if the RDM and her newborn were discharged on different days, it impeded breastfeeding. Consequently, they made efforts to align their discharge dates, i.e., only after both had completed mandatory days of institutional isolation or had tested negative for SARS-CoV-2. If rooming-in was possible, they were discharged after establishing breastfeeding.

Support to the RDM during hospital stay and during follow-up

One of the study hospitals had started allowing one family member per RDM to visit her in-hospital but with PPE on and within strict visiting hours. A few institutions had allowed family members into the nursery and involved them in the care of the newborn. This had improved care as well as feeding of expressed breastmilk.

As routine health services were impaired in the community, the institutions ensured that vaccination of the newborn was up to date and that the RDMs and family members had been adequately counseled for exclusive breastfeeding and after-care at home, at the time of discharge. They prioritized follow-up calls to RDM–newborn dyads that were in the high-risk category.

The use of video-calling services was a major technological innovation that one of the institutions had adopted. With funding from the Government, the institution had received hand-held electronic tablets with an internet connection—these were used by the staff in the nursery to interact with the RDMs under isolation. The RDMs in the said institution hailed this as a major enabler that allayed their anxiety as they could interact with the nursery staff as well as watch their babies being cared for in the nursery.

Infrastructural modifications and “zoning”

Gradually, the hospitals were able to install exhaust fans, cameras, and devices for remote monitoring and counseling of patients. Separate passages, lifts, and “red-green-yellow” zoning were done based on infection status for positive, negative, and suspected cases, respectively. Donning and doffing areas were separately ear-marked. Equipment was also procured for each zone to ensure IPC. Separate labor rooms and neonatal intensive care units (NICUs) were accordingly zoned and equipped expeditiously.

Guidelines coming up after initial months and their sharing and adherence by staff

The Federation of Obstetric and Gynecological Societies of India (FOGSI), National Neonatology Forum of India (NNF), and Indian Academy of Pediatrics (IAP) had come up with a joint statement titled “clinical practice guidelines for perinatal-neonatal management of COVID-19 infection” on 26th March 2020 (38); an updated second version was released on 7th May 2020 (39). Simultaneously, the Indian Council of Medical Research (ICMR) also actively updated its advisories. Availability and wider dissemination of these guidelines facilitated the adoption and standardization of practices by providers who were now more confident in taking decisions and counseling the patients and their family members. Departmental standard operating protocols (SOPs) were revised in view of the guidelines after internal and interdepartmental meetings. Sharing literature on social media groups, e.g., closed WhatsApp groups, webinars, and training (physically provided in small groups or through virtual platforms) improved staff confidence for coordinated care.

Interdepartmental coordination

The pandemic demanded efficient coordination and active engagement between Obstetric, Neonatology/Pediatric departments for optimal care of RDM–newborn dyads. As structured management protocols were evolving, coordination between these departments became dynamically adaptive. We noted that the departments that already had a smooth consensus-driven work culture could tide over the coordination

challenges effectively. Day-to-day coordination was often through non-formal (not written down) understanding and accomplished over WhatsApp groups.

“...there are some coordinators in OBG team and neonatal team. Initiating breastfeeding is more of a joint effort.” (-HOD, Neonatology)

Leadership in promoting breastfeeding in newborns

Departmental leadership played a very critical role as an enabler (“leadership in crisis”). Active engagement in surge preparedness for IPC and pandemic combat (“leading from front”) was deemed as a major leadership trait by the participants. These “leaders” advocated for the sustenance of pre-existing quality of maternal and newborn care practices even in the COVID wards, had active involvement in updating and contextual adaptation of the SOPs, and were at the forefront of patient care and administration. They kept abreast with the fast-evolving evidence and this instilled confidence among peers and staff. Alongside, they organized frequent sessions of counseling with staff and patients and motivated them constantly, exercised high levels of emotional intelligence, and demonstrated empathy for the overworked and often anxious staff and distressed patients.

“...our practices in terms of ensuring that the baby gets 1st drop of milk and every drop of her own mother’s milk, is something that we ensure from the point that the lady is in the labor room... We have (a practice that) for the mother and her baby, breastfeeding has to be established... So, we ensure it happens here.” (-HOD, Neonatology).

Analytic framework depicting the pathways of impaction of optimal breastfeeding practices in institutionalized RDM-newborn dyads during the COVID-19 pandemic

Figure 1 shows the factors (in white and yellow boxes) influencing breastfeeding practices and their interactions (arrow heads) in institutionalized RDM-newborn dyads during the COVID-19 pandemic. The red colored boxes suggest the endpoints. Various barriers are depicted in the white and yellow boxes. The barriers highlighted in yellow are those that the institutions could intervene and overcome, at least partially.

Table 5 summarizes the suggestions for improvement coming from all participants of the study.

Discussion

We observed that the pandemic disrupted newborn care and breastfeeding practices across RDM-newborn profiles at the study institutions through complex interrelated pathways. We identified RDM-newborn separation at birth as an important barrier that institutions largely failed to overcome in the initial months of the pandemic. In the initial months of the pandemic, there was considerable confusion and stress for healthcare providers (HCPs) and breastfeeding mothers regarding the safety of breastfeeding in RDMs with SARS-CoV-2 infection. Furthermore, the high delivery case load (~40–50 deliveries/day) at the participating facilities and lack of space precluded the possibility of rooming-in of so many suspect mothers and baby dyads in isolation wards. Institutions tried to stratify the laboring mothers by the status of SARS-CoV-2 test reports. The institutions kept the RDM baby separated until the test was reported negative. Since test results were invariably delayed, this resulted in the separation of the RDM and her newborn. Once separated, rooming-in and establishing breastfeeding became challenging. For a baby who was admitted to the nursery away from the mother, transportation of expressed breastmilk from the isolation ward to the nursery was another major barrier in our study. As a mother’s visitation to the nursery to be involved in the care of her baby was limited for the fear of spreading COVID-19, there was considerable anxiety and stress among mothers that was counterproductive for their uninterrupted milk supply. We also noted that formula feeding and early discharge of the baby with alternative caregivers while the mother was still admitted in the COVID-ward became common practices.

Findings similar to ours have been reported from other countries too. In a global online survey involving 62 LMICs to provide insights on disruptions to coverage and quality of small and sick newborn care, it was found that preparedness for COVID-19 was suboptimal in terms of guidelines and availability of personal protective equipment and that the guidelines for testing of mother and newborn changed frequently. More than 85% of health personnel feared for their own health and 89% had increased stress (21). Newborn care practices were disrupted both due to reduced care-seeking and compromised and inexperienced staffing in the COVID wards. More than half reported that standard practices for small neonates such as kangaroo mother care were either discontinued or discouraged. Separation of the mother-baby dyad was reported for both COVID-positive mothers (50%) and those with unknown status (16%). Follow-up care was disrupted primarily due to families’ fear of visiting hospitals (~73%). COVID-19 has also been reported to have also compromised the quality of counseling and the extent of social support to RDMs; we have also observed the same in this study (40).

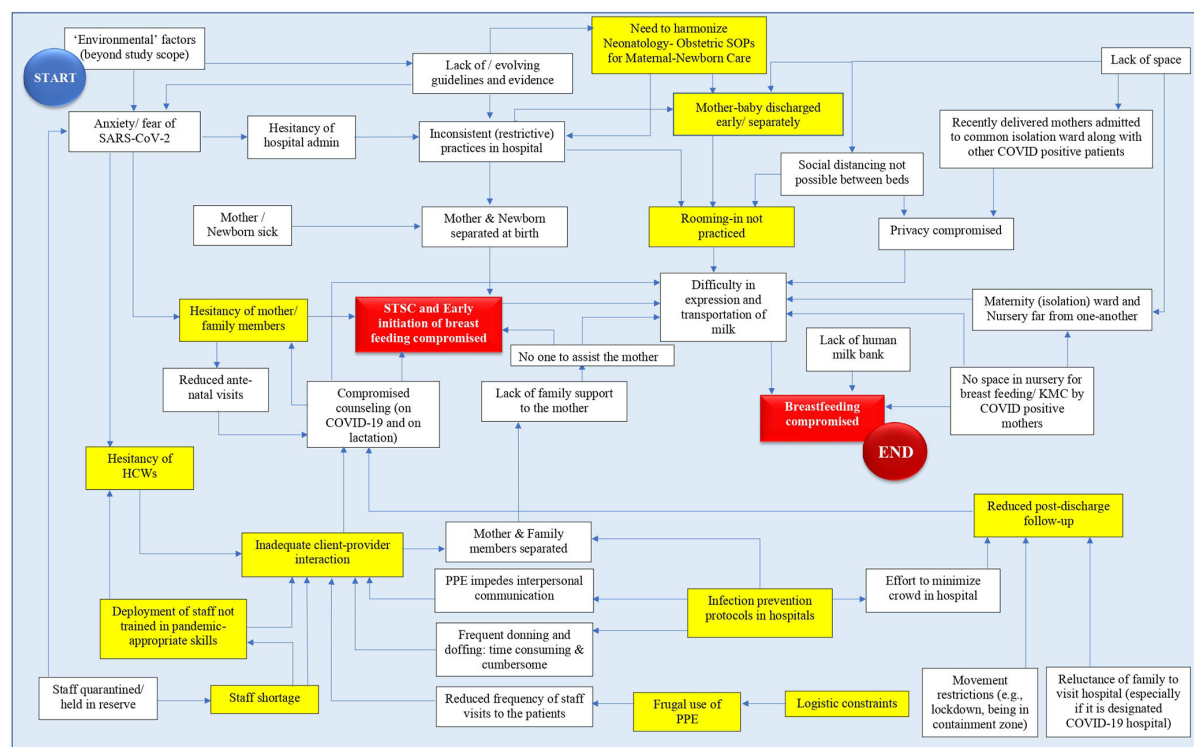


FIGURE 1

Analytic framework depicting the pathways of impact of optimal breastfeeding practices in institutionalized mother-newborn dyads during the COVID-19 pandemic. The various barriers are depicted in the white boxes – the ones targeted by the study institution for mitigation have been highlighted in yellow. Boxes highlighted in red represent end-points; HCW, Health Care Worker; KMC, Kangaroo Mother Care; PPE, Personal Protection Equipment; STSC, Skin-To-Skin Contact; SARS-CoV-2, severe acute respiratory syndrome coronavirus 2; COVID, Coronavirus disease; SOP, Standard Operating Procedure.

Despite clear and comprehensive guidance from the WHO regarding exclusive breastfeeding, during the beginning of the pandemic (14), newborns were often separated from the mother at birth. Even professional associations, e.g., in the Philippines, Thailand, Malaysia, and the United States of America (USA) released guidelines supporting the separation (41). The separation affected breastfeeding (41–43). Some places allowed only screened donated breastmilk from COVID-19-negative mothers (44, 45). The disharmony between guidelines from the professional associations and that from the WHO was evident in the high-income countries as well. In a study (46) comparing the initial recommendations of the professional obstetrical and gynecological societies of five high-income countries, namely Australia, New Zealand (NZ), Canada, the United Kingdom (UK), and the USA, with that from the WHO (14, 16, 47), none of these aligned perfectly. Discordant guidelines impeded confident decision-making and the families received conflicting information. First-time mothers who were COVID-19 negative also reflected fear, anxiety, and doubts and often made a personal choice of not wanting to breastfeed their newborn for fear of unknowingly transmitting COVID-19 infection (test results were at times considered to be

unreliable) (48). Inadequate provider–patient interaction both during hospital stay and during follow-up was another barrier to successful breastfeeding, during the COVID-19 pandemic. Nevertheless, mitigatory efforts were also responsive to the evolving evidence on the low risk of transmission of the virus through breastfeeding (49–55). For example, in April 2020, the American Association of Pediatrics recommended separating infected mothers from newborns but in July 2020, it retracted the advice (56, 57).

In the present study, the use of video-calling services was a major technological innovation that one of the institutions had adopted. This innovation was found to be a major enabler that allayed the anxiety of the mothers. Family-centered care (FCC) in the NICU focuses on building trust, reducing anxiety, partnering, and integrating families into the care of their infants. Many newborns in NICU have critical health issues causing anxiety and feelings of fear to parents and families. Separation, especially in life-threatening conditions, causes worry and apprehension among families. Providing a means for families to view live videos of their infants, any time of the day or night, and while away from the unit, can help alleviate this stress. Virtual visitation of caregivers has been used in a few NICUs

TABLE 5 Suggestions for improvement from the participants.

Neonatologists/pediatricians

Need for comprehensive guidelines	85	Most
Update and adapt practices quickly according to evolving guidelines	46	Some
Design guidelines that are feasible for ground-level implementation	46	Some
All stakeholders and subject experts should come together for formulation	15	Few
Clarity of guidelines	23	Few
Need for protocols on attendants	8	Few
Better logistics and staff management required	54	Many
Need for more dedicated staff	38	Some
Logistic supply chain needs to be strengthened	8	Few
Need for more dedicated space	15	Few
Make staff deployment more efficient	15	Few
Facilitate breastfeeding and newborn practices	54	Many
Create dedicated lactation teams	46	Some
Arrange for allowing birth companions to help mothers	8	Few
Create mechanisms to reinforce exclusive breastfeeding for 6 months	8	Few
Newborn care must be practiced	8	Few
Need for effective counseling of patients	46	Some
Ensure skilled counseling for mothers	31	Some
Improve communication with the patients and providers for better implementation	15	Few
Training of staff	38	Some
Training needed for waste disposal	15	Few
Staff needs training upon return to duty from posting elsewhere	8	Few
Staff training for kangaroo mother care required	8	Few
Need to train rotated staff for newborn care	8	Few
Joint training with clear role rationalization for neonatology and obstetric staff	8	Few
Training on infection control measures and on handling patients with COVID	8	Few
Improving inter-departmental support	15	Few
Need to improve interdepartmental coordination	15	Few
Departments need to sensitize one another about their SOPs	8	Few
Motivating and empowering healthcare workers	23	Few
Identifying and complementing champions	15	Few
Need for motivational endeavors for staff	23	Few
Prioritizing and promoting BF practices in newborn	23	Few
Prioritize health care budget	8	Few
Promotion of breastfeeding on primetime channels by professionals and ministries	8	Few
Technological innovation	8	Few
Obstetricians	33	Some
Training of staff		
Improve communication with the patients and providers for better implementation	17	Few
Training on infection control measures or how to handle COVID	17	Few
Facilitate better BF and newborn practices	17	Few
Newborn care must be sustained irrespective of pandemic situation	17	Few
Need for comprehensive guidelines	17	Few
Provide clear guidelines	17	Few
Need for effective counseling of patients	17	Few
Strengthen counseling skills of staff through training	17	Few
Prioritize effective counseling of RDMs	17	Few

(Continued)

TABLE 5 (Continued)

Neonatologists/pediatricians

Residents	50	Many
Requirement for better logistics and increase in staff capacity		
Increase availability of staff for better monitoring	7	Few
Allocate more space for mother and baby to room together	36	Some
Create designated team for COVID mothers for better care	7	Few
Ensure adequate availability of equipment	7	Few
Need for effective counseling of patients	50	Many
Start counseling and communication even before the delivery	14	Few
Work toward improving quality of counseling	36	Some
Intensify counseling for patients with COVID	14	Few
Staff training on effective counseling of mothers	14	Few
Need for comprehensive guidelines on optimal breastfeeding practices	29	Some
Create robust (stable) guidelines	21	Few
Need to involve ground-level staff to formulate guidelines contextually	7	Few
Prioritizing and promoting breastfeeding practices in newborn	29	Some
Need for availability of group support	7	Few
Allocate dedicated specialist nurse for newborn care	7	Few
Explore options for early discharge without compromising breastfeeding practices	7	Few
Provide privacy for breastfeeding	14	Few
Improve staff orientation to guidelines	7	Few
Nurses	54	Many
Facilitate optimal breastfeeding and newborn practices		
Infection prevention and control protocol must ‘accommodate’ rooming-in	23	Few
Have an allocated room with staff for Kangaroo mother care and breastfeeding	15	Few
Discharge and let them be in-home quarantine so that they get some help	8	Few
Allow mother to see her baby being cared at least from a distance	8	Few
Have a meeting area where the mothers could meet their family and newborn	8	Few
Facilitate transportation of expressed breastmilk from mothers to newborn	8	Few
Need to focus more on practical practice of breastfeeding than documentation	8	Few
Practice early initiation of breastfeeding and rooming-in	8	Few
Better logistics required	31	Some
Need for a better diet as attendants or visitors are not being allowed	8	Few
Need for more manpower	8	Few
Need for personal protective equipment kit	8	Few
Need for setup of NICU adjacent to ward with a glass wall, so that mothers can see the baby anytime they want	8	Few
Need to have more staff to help us with our work	8	Few
Postnatal ward and nursery should be near each other	8	Few
Improve staff skills	31	Some
Need for more detailed training on counseling during COVID	8	Few
Need for routine sensitization of healthcare workers to allay fear	15	Few
Training needed for all staff irrespective of COVID duties	8	Few
Need for effective counseling of patients	31	Some
Need for dedicated lactation counselors for better breastfeeding	15	Few
Need for more effective counseling especially for positive mothers	15	Few
Need for patient education for establishing breastfeeding	8	Few
The neonatologist should take a leading role in media to spread awareness	8	Few

(Continued)

TABLE 5 (Continued)

Neonatologists/pediatricians

Healthy mother and newborn	6	Few
Counsel all first-time mothers beforehand		
Counsel on how to clean the breasts to avoid infecting the newborn	6	Few
Provide information on alternatives to breastmilk for feeding the newborn	6	Few
Identify a person exclusively for addressing all in-patient queries	6	Few
Staff should be available to resolve queries during follow up	6	Few
Provide information on infection prevention and control practices	6	Few
Mother with COVID-19 and healthy newborn	11	Few
Improve treatment and behavior toward infected patients		
Provide physical support to the mother (especially if a cesarean section)	11	Few
Facilitate rooming-in	5	Few
Improve crowd management in queues for testing for SARS-CoV-2	5	Few
Provide further guidance and advice on feeding expressed milk to baby	5	Few
Provide more information related to COVID-19	5	Few
Mother with COVID-19 and sick newborn	13	Few
Staff needs to be more empathetic		
Provide help for expressing milk (especially, if delivered by cesarean section)	13	Few
Improve the quality of food supplied in the hospital	13	Few
Provide more information on feeding baby before discharging	13	Few
Provide daily updates on the health status of the newborn	13	Few

SOP, Standard Operating Procedure; COVID, Coronavirus disease, SARS-CoV-2, severe acute respiratory syndrome coronavirus 2.

in the USA and UK even before the COVID-19 pandemic (58–61). The NICVIEW is a web-based camera system (WBCS) that streams real-time video of the baby around the clock. In a questionnaire survey conducted in a Canadian hospital, following the implementation of NICVIEW for virtual visitation of caregivers during the COVID-19 pandemic due to the strict implementation of the policy of restricted entries found that 98.0% of parents felt very connected with their baby, and almost 90.0% of parents reported having the WBCS helped reduce their anxiety and stress levels to a great extent. An accepting attitude from HCPs, especially the nursing staff, is of paramount importance in improving the successful implementation of WBCS in the NICU.

While family centrality is important, HCP centrality was also critical during the early days of the pandemic, since it kept the HCPs confident and motivated. In a large hospital-based prospective cohort study from India with high patient load and resource limitations, a dynamic policy using a low-cost paperless communication system with mobile devices was reported to reduce the risk of HCP infection, improve their motivation, and re-deployment in the COVID wards (62). There are reports that leadership skills were useful during the pandemic for delivering essential facilities and services rapidly and with empathy during the pandemic (63–65). In the present study, we recorded leadership-in-crisis skills as helpful

in mounting up a coherent response within the healthcare institutions, e.g., in motivating the staff, by rapidly delegating authority to organizational management, framing and updating standard operation procedures as per changing guidelines for the management of pregnant women and their neonates with suspected or proven COVID-19 infection, allaying anxiety of patients and providers, by innovating for improving neonatal and follow up care, and interdepartmental coordination, besides facilitating the mobilization of resources. This guiding coalition had an overriding vision to contain the infectious disease throughout the pandemic, while simultaneously catering to patients with and without COVID-19 infection. In the present study, other enablers which played a critical role in improving neonatal care and breastfeeding rates have conducive attitudes and neonatal care practices with the passage of time. Certain systemic interventions were also helpful e.g., designating some facilities exclusively for COVID-19 care, strengthening referral pathways, and release of joint statements by FOGSI-NNF-IAP. FOGSI-NNF-IAP Joint Statement greatly helped practitioners take confident decisions related to sustaining routine pre-pandemic practices for breastfeeding and newborn care (29). We infer that in case of a public health crisis, national health agencies and professional associations must ensure that coherent guidelines are released at the earliest and disseminated widely along with strategies to counter misinformation.

Strengths and limitations

We pooled information from clients and providers across seven premier institutions in Delhi, which had pre-existing systems for evidence-based optimal newborn care practices. This gave us an opportunity to identify deviations from the “near-ideal.” However, we acknowledge that each institution had its own unique strengths and weaknesses, and our aggregated analysis does not delve deeper into these. To address the influence of temporal change, we requested the participants to respond with the initial 6 months of the pandemic (March–August 2020) as the reference period. We could not explore post-discharge breastfeeding practices.

Conclusion

We recommend against separating the mother and the newborn during public health emergencies without robust evidence favoring the same. We call for making routine RDM–newborn care practices family-centered at all times. We encourage the practice of early release of joint statements by professional associations and authorities during public health emergencies. Leveraging social media and video conferencing technology, having dedicated lactation teams, investing in improved hospital architectural planning, and having an in-campus human milk bank could provide an advantage against potential disruption and merit further research.

The learning of this study should help in building institution-based newborn care services more resilient against disruptions by public health emergencies.

Data availability statement

The raw data supporting the conclusions of this article will be made available by the authors, without undue reservation.

Ethics statement

The Institutional Ethics Committee of ABVIMS and Dr. Ram Manohar Lohia Hospital, New Delhi reviewed and approved the study protocol. Administrative approval was provided by the Ministry of Health and Family Welfare. Written informed consent for participation was not required for this study in accordance with the national legislation and the institutional requirements.

Author contributions

AMa: concepts, design, definition of intellectual content, tool development, manuscript editing, manuscript review,

and guarantor. RM: tool development, literature search, data acquisition, data analysis, manuscript preparation, and manuscript editing. SU, KPr, and TB: data acquisition, manuscript editing, and manuscript review. RG, BD, AS, PM, MS, and KP: manuscript review. PP: tool development, literature search, data acquisition, and manuscript review. AMo: concepts, design, definition of intellectual content, tool development, data acquisition, data analysis, manuscript preparation, manuscript editing, and guarantor. All authors contributed to the article and approved the submitted version.

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Conflict of interest

The authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

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Supplementary material

The Supplementary Material for this article can be found online at: <https://www.frontiersin.org/articles/10.3389/fnut.2022.1052340/full#supplementary-material>

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EDITED BY

Diego Augusto Santos Silva,
Federal University of Santa Catarina,
Brazil

REVIEWED BY

Samer Abuzerr,
Ministry of Health, Palestine
Misganaw Melesse,
Debre Markos University, Ethiopia

*CORRESPONDENCE

Godana Arero
garero2015@gmail.com

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Undernutrition and associated factors among pregnant women in East Borena Zone, Liban District, Oromia regional state, Ethiopia

Godana Arero *

Oromia Regional Health Bureau, Addis Ababa, Ethiopia

Background: Undernutrition is cellular imbalance between supply of nutrients, energy and body's demand to ensure growth, maintenance, and specific function. However, there was no study conducted earlier on this topic in East Borena Zone.

Objective: To assess the prevalence of undernutrition and associated factors among pregnant women in East Borena Zone, Liban District.

Method: A community-based cross-sectional study was conducted on 420 study participants from November 20 to December 2021. The systematic sampling technique and simple random sampling methods were used to select study participants. Data were double entered into Epi-info software version 7 and SPSS version 21 software for analysis. Descriptive statistics were used to describe the characteristics of study participants. Bivariate and multivariable logistic regressions were carried out to identify the association between independent and dependent variables by measuring the adjusted odds ratio and 95% confidence interval. P-values less than 0.05 were considered statistically significant.

Results: Prevalence of undernutrition among pregnant women was about (44.9%) of family monthly income [AOR = 8.72 (4.80, 15.83)], women's decision-making autonomy [AOR = 0.40 (0.19, 0.82)], skipping meal [AOR = 2.62 (1.41, 4.89)], substance use [AOR = 2.01 (1.07, 3.77)], household food insecurity [AOR = 2.01 (1.06, 3.80)], lack of prenatal dietary advice [AOR = 2.73 (1.53, 4.89)], absence of household latrine [AOR = 9.23 (3.48, 24.46)], not participating health development army's meeting at village level [AOR = 3.01 (1.57, 5.72)] and hand washing habit [AOR = 6.55 (3.02, 14.20)] had shown statistically significant association with undernutrition.

Conclusion: The prevalence of undernutrition among pregnant women was high income. Women's decision-making autonomy, skipping meals,

substances use, household food insecurity, lack of prenatal dietary advice, poor hand washing habit, lack household of latrine, and not participation in health development army's meeting were found to be predictors of the undernutrition.

KEYWORDS

undernutrition, wasting, stunting, underweight, anthropometric, MUAC, FFQ

Introduction

Globally, undernutrition is an important health concern, predominantly in under-five children and pregnant women. The World Health Organization (WHO) classifies undernutrition as the greatest threat to public health (1) and every country is facing a serious challenge from undernutrition (2, 3). In spite of extensive global economic growth in recent decades, maternal undernutrition is highly prevalent in most countries in south-central and south-eastern Asia and Sub-Saharan Africa (4–6).

Ethiopia is one of the countries with a high burden of maternal and child undernutrition. Though maternal undernutrition has declined over the past 16 years, from 30% in 2000 to 22% in 2016, Ethiopia is still among the countries with a high burden of maternal undernutrition (7). Specifically, two institution-based cross-sectional studies conducted in the Amhara region reported a prevalence rate of undernutrition ranging from 16 to 29.8% (7).

Maternal undernutrition in low and middle-income countries is an underlining cause of 3.5 million mothers' deaths and disabilities due to the physical and mental effects of poor dietary intake in the earliest months of life (8, 9). Previous studies have established that undernourished pregnant women suffer from a combination of chronic energy deficiency that leads them to have a low birth weight (LBW), and preterm and unsuccessful birth outcomes (10–12). Regardless of significant gains and signs of progress in the last decade, maternal undernutrition still remains a major public health problem in Ethiopia (13). The government of Ethiopia has developed a revised national nutrition program in 2016 to address the double burden of undernutrition in pregnant and lactating women

(14). Even though the progress of this program implementation needs to be supported with a piece of continuous evidence through research, limited institution-based studies that lack an important variable crucial for prioritizing, designing, and initiating intervention programs have been conducted (15, 16).

Maternal undernutrition is highly prevalent in low and middle-income countries (17) and Ethiopia as one of these countries has been significantly affected by the burden of undernutrition. Many African women consume less than the recommended daily caloric intake and 5–20% are underweight. Pregnant women in industrialized countries gain on average twice as much as pregnant women in Africa. In 12/17 African countries, 10% or more of babies are born with low birth weight. Inadequate micronutrient intake, particularly of iron, vitamin A, zinc, folic acid, riboflavin, iodine, and vitamin E (18). Socio-demographic, economic, reproductive, medical, behavioral, healthcare, environmental, and dietary factors are associated with a pregnant mother's nutritional status. Associated factors should be included in this research on page 18. A comparative study on maternal nutritional status in 16 of the 18 DHS-conducted countries and a study in the Oromia regional state showed that rural women are more likely to suffer from chronic energy deficiency than women in urban areas (17, 19). Dietary characteristics of the study participants such as (Minimum Dietary Diversity of Women, household food insecurity, improved dietary feeding, skipping meals/snacks, and eating additional meals were considered as associated with the nutritional status of pregnant mothers (20). The nutritional status of women before and during pregnancy can be determined by maternal knowledge, attitudes, and perceptions toward certain foods (21). Pregnancy is the most crucial nutritionally demanding period of every woman's life. Appropriate nutrient intake during this period has a critical role in fetal development (22). Failure to receive necessary micro and macronutrient during this period will result in undernutrition and adverse pregnancy outcome (6). Undernutrition during pregnancy yields both short and long-term effect on the health of an infant by programming the infant's development, increases the risk of non-communicable diseases, and is intimately related to the survival of both mothers and their babies (23). Hence, nutrition interventions such as nutrition education in different villages, health centres, health posts, and women's

Abbreviations: AHMC, Adama Hospital Medical College; AOR, adjusted odds ratio; COR, crude odds ratio; CI, confidence interval; CED, chronic energy deficiency; DHS, demographic and health survey; EDHS, Ethiopia demographic and health survey; FANTA, Food and Nutrition Technical Assistance; FANC, focused antenatal care; GDP, gross domestic product; GA, gestational age; HFIAS, Household Food Insecurity Access Scale; IFA, iron folic acid; IUGR, intra-uterine growth restriction; LBW, low birth weight; MDD, minimum dietary diversity; MDDW, minimum dietary diversity-women; MUAC, mid-upper arm circumference; NCD, non-communicable disease; SD, standard deviation; WDDS, women dietary diversity score; WRA, women in reproductive age.

organizations should be given to the community particularly for pregnant mothers concerning nutrition during pregnancy in the study area (24). At the national level, unmarried women were about 1.9 times more likely to be undernourished than currently married women, and the difference was statistically significant (25). Household economic status is one of the most important determinants of nutritional status in Ethiopian women. The study shows that, as compared with women residing in medium/higher economic status households, the risk of being undernourished for women in very poor or poor households was significant. This finding is consistent with other studies and the UNICEF conceptual framework (26, 27).

Women's employment status is also another important socioeconomic variable explaining nutritional status. According to the findings of this study, unemployment or unpaid (cash) employment of women is a significant factor for chronic energy deficiency (CED) in these women as compared with women employed for cash. Women's paid employment could provide an additional income source that can improve the food security of the household and raise the status of women by allowing them to have more control over resources. Some evidence also indicates that the nutritional impact of increased household income is a function of the income earner and the kind of income (10). It was also found that unemployed women were at high risk of undernutrition, even in households with a relatively better socioeconomic status (28). The objective of this study was, therefore, to assess the magnitude of undernutrition at the community level by including an important variables among pregnant women living in East Borena Zone.

The conceptual framework used for this study was adopted and modified from UNICEF's conceptual framework on the determinants of malnutrition (UNICEF (29). Maternal health status is greatly influenced by the dietary diversity and morbidity/physiological status of the mother which are the immediate causes (Figure 1). When the dietary diversity is poor it affects the woman's morbidity status as there is reduced immunity and increased chances of developing infections. On the other hand, morbidity status in pregnancy affects dietary diversity either due to poor appetite which leads to only likable foods being selected, or some practices such as pica which affect nutrient intake.

Materials and methods

Study setting

The study was conducted in the East Borena Zone, Liban District, Oromia regional state in Ethiopia from November 20 to December 2021. The 2007 national census reported that the total population for this district was 138,813, of which 70,130 were men and 68,683 were women; 1,385 or 1% of that population were urban dwellers. During the study period, there were 22,081.

Study period

It was conducted from November 20 to December 2021. Study design a community-based cross-sectional study design was conducted.

Population

Source population

All pregnant women in the Liban District living in east Borena Zone for more than 6 months.

Study population

All randomly selected pregnant women living in the district during the study period.

Inclusion and exclusion criteria

All pregnant women who lived in the district for more than 6 months, if chosen, were not included in the study, as were non-pregnant women who were severely ill.

Sample size calculation and sampling techniques

The sample size was estimated using a single population proportion formula, considering 46.5% of the prevalence of undernutrition among pregnant women from a study conducted in Jimma Town (15).

Other parameters considered were 5% margin of error, 95%CI, and 10%, non-response rate.

$$n = \frac{3.84 \times 0.465(1-0.535)}{2} = 382$$

$$d^2 = (0.05 * 0.05)$$

Where n = sample size $Z_a = Z$, value corresponding to a 95% level of significance = 1.96.

p = expected proportion of practices of mothers on nutrition during pregnancy = 50% = 0.5.

d = absolute precision (5%). Therefore, from the above, the sample size is = 382.

$$n = 382_{10\% \text{ none-response rate}} = 38, n = 382 + 38 = 420.$$

Sample size determination for the second objective

The sample size for the second objective was calculated using the double population proportion formula using the Stat-calc of Epi-Info Statistical Software Version 7.0 with the

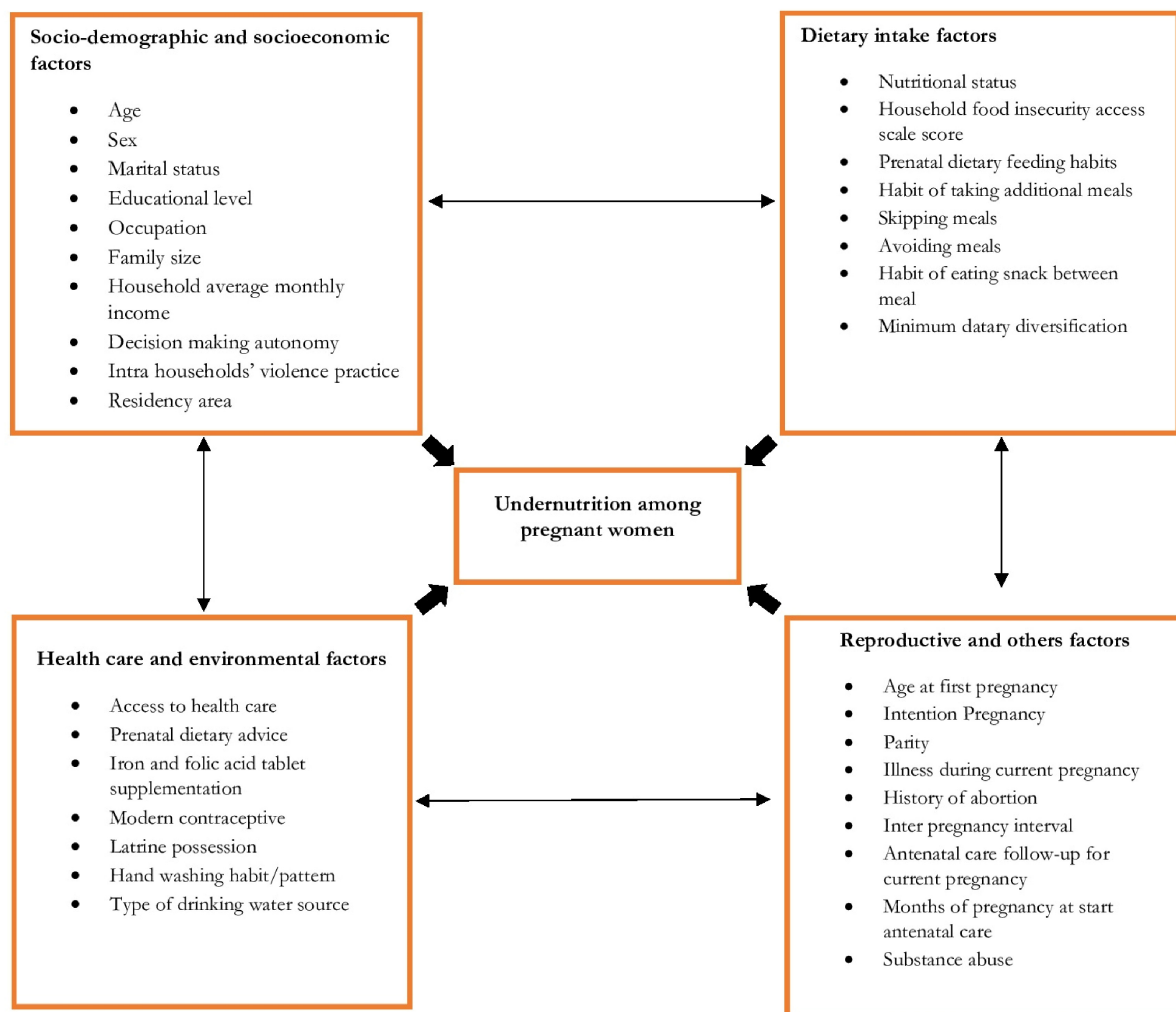


FIGURE 1

Conceptual framework assessing nutritional status among pregnant women in East Borena Zone, Liban District.

following assumptions: Confidence level = 95%, power = 80%. The maximum sample size that was obtained from the general/first objective was 420. This sample was the larger sample size than the sample size calculated from the second specific objective. As a result, the final sample size decided for this study was 420, as determined by the first objective (Table 1).

Sampling procedures

First, Kebeles (the lowest governmental administrative structure in Ethiopia) were stratified into urban and rural areas. The sample size was proportionally allocated for each stratum and then, representative pregnant women were randomly selected. A random sampling technique was utilized to select 10 Kebeles out of 35 total Kebeles. Finally, 420 samples were allocated proportionally to each selected Kebeles based on their

total number of pregnant mothers. The calculated sample size of 420 study participants was proportionally allocated to randomly selected five health post out of 20 health post in the Liban District and two health centers out of five based on the number of clients attending antenatal care at health post and health center. Then, at each antenatal care unit, every seven pregnant women who were registered were included in the study until the desired sample size was reached.

The dependent variable of this study was the nutritional status of pregnant women. Independent variables were socio-demographic characteristics of the pregnant women included age, marital status, education, religion, ethnicity, residence area, family size, income, women's decision-making, autonomy, intra-households violence, and polygamy. Reproductive, medical, and behavioral characteristics of the study participants like age at first marriage/pregnancy, trimester of pregnancy, pregnancy intention, gravidity, parity, abortion, inter-pregnancy

TABLE 1 Sample size calculation for the second specific objective.

Variables	Magnitude		Power CI level	AOR	Sample size	References
	Exposed	Non exposed				
Average monthly income of HH	15.83%	4.8%	80%, 95%	8.72	73	(11)
Decision making autonomy of pregnant women	11.09%	1.81%	80%, 95%	2.7	160	(24)
Work load on women	28.8%	6.3%	80%, 95%	13.6	46	(24)
Frequent hand washing habits	14.20%	3.02%	80%, 95%	6.55	68	(11)
Educational status	2.91	0.77	80%, 95%	1.50	131	(7, 10)

interval, and recent illness in the past 15 days and substance abuse were independent variables considered in this study. Others were healthcare, and environmental characteristics such as accessibility to healthcare, prenatal dietary advice, antenatal care follow-up, drinking water source, and latrine possession. Dietary characteristics of the study participants such as minimum dietary diversity of women, household food insecurity, improved dietary feeding, skipping meals/snacks, and eating an additional meal are also independent variables included in the study.

Data collection tools

During data collection, face-to-face interview, observation, anthropometric measurements, and standard structure questionnaires were used to collect data from pregnant women after the interviewers explained the purpose of the study and obtained the participant's verbal consent to participate in the study. In this study, minimum dietary diversity for women (MDD-W) was measured by the Food and Agriculture Organization (FAO) (30) standard questionnaire developed for this purpose which is recommended for 24-h dietary recall.

Household food insecurity was measured by the Food and Nutrition Technical Assistance [FANTA (31)] standard tool that has nine questions each comprising three responses, 27-score-based Household Food Insecurity Access Scale (HFIAS) scale. The mid-upper arm circumference was used to assess malnutrition. MUAC [in cm] on their left arm at the midpoint between the tip of the shoulder (olecranon process) and the tip of the elbow (acromion process), and the insertion type of MUAC tape was benonelastic and non-stretchable to take with correct tension (not too loose/tight) with nearest 0.1 cm reading.

Age at pregnancy and afterbirth time were estimated using local memorable events. The participants were asked to recall and describe all the food and drink consumed in the previous 24 h from waking to sleeping. A recall interview contains 28 min to complete. In addition, anthropometric assessment mid-upper arm circumference (MUAC) measurement was involved. A structured questionnaire was developed and adopted from the Ethiopia Mini Demographic and Health Survey (EMDHS) (32) (EMDHS), the food frequency questionnaire, and the WHO

standard. All the variables to be assessed were incorporated (Figure 1).

Data quality assurance

For data quality control, study instruments were translated into local languages (by native speakers and then back translated to English by two other competent persons. Six interviewers and two supervisors were recruited for the survey and were trained on the overall data collection process. The six data collectors were BSC midwives and the supervisors were senior public health experts with Master's degrees in local languages. Completeness and consistency of the data were assured through direct and daily supervision by the supervisors and principal investigator. Interviewers re-administered the questionnaires to the respondent under supervision by the supervisor. To ensure the quality of data, data collectors and supervisors were trained, and the questionnaire was translated into respondents' native language to aid comprehension. In addition to written documentation of responses from study participants, tape recordings were done after obtaining verbal consent to ensure that all feedback were captured for analysis. Data collectors and supervisors were selected based on their educational background (particularly those who have received training on essential nutrition actions), work position, and experience in data collection. Supervisors and data collectors were trained on the objectives, methods, and data collection techniques of the study. Daily discussions and check-ups of data completeness were made with supervisors and the principal investigator. The data cleaning and entry were conducted exclusively by the principal investigator. The questionnaire was pretested among 5% of the total sample size to assess its clarity, length, completeness, and consistency. After the pretest was conducted, adjustments were done according to enhance the reliability and validity of the tool. The structured questionnaire was then rephrased in light of the responses. Test-retest reliability was established by examining the consistency of pretest responses using, and the three main components of the test-retest method are as follows: test-retest reliability of the research instrument was established during pretesting. Pretesting was done on two occasions but on the same

respondents, on Monday and Friday: assume there is no change in the underlying condition (or trait you were trying to measure) between test 1 and test 2. Finally, compute the correlation between the two separate measurements; if test 1 and test 2 become consistent, the questionnaire was considered reliable.

Statistical analysis

The collected data were checked for incompleteness and inconsistency. Data were entered into Epi-Info version 7.2 software and then exported to SPSS version 21 for analysis.

Prior to running for analysis, data were cleaned, composite indexes were computed and recorded over missing values, and extreme values were identified and trimmed. Descriptive statistics were used to describe the sample accordingly. Bivariate logistic regression was carried out to assess the association of each independent variable with acute undernutrition and those with *p*-values less than 0.25 remained in the final model (multivariate logistic regression). Odds ratios (ORs) were generated for each variable and the independence of any association was controlled by entering all variables into the model using the backward stepwise method. The magnitude of the association between the independent variables in relation to acute undernutrition was measured using adjusted odds ratios (AORs) and 95% confidence interval (CI) and *p*-values below 0.05 were considered statistically significant. Descriptive statistics were used to show socio-demographic characteristics and the prevalence of nutritional status. Logistic regression analysis was used to identify the association between factors, and the nutritional status of pregnant mothers and multivariate logistic regressions were performed to determine independent predictors of the nutritional status of pregnant mothers. A *p*-value < 0.05 was declared as statistically significant. The VIF and tolerance were checked for the presence of multicollinearity among the independent variables. The stepwise model building strategy with *p*-value = 0.05 was applied to identify independent predictors of nutritional status, and the Hosmer–Lemeshow test of goodness-of-fit was used to test how well the model explains the data. Adjusted odds ratios and their 95% confidence intervals were reported. Additionally, tables and figures were used to present the findings.

Results

A total number of 420 pregnant women were interviewed making a response rate of 97.3%. The median ages of the mothers were (18.0 ± 1.2) years. The majority of the respondents were married (96.2%), housewives (75.5%), and residents of rural (78.8%). The overall prevalence of undernutrition among pregnant women was 44.9% [95%CI: (41.5, 50.1)] (Table 2).

TABLE 2 Socio-demographic, and socio-economic characteristics of study participants (*n* = 420), 2021.

Characteristics	Categories	Frequency	Percentage (%)
Residence area	Rural	309	78.8
	Urban	83	21.2
Age category in years	±25	109	27.8
	26–29	96	24.5
	30–33	102	26.0
	≥34	85	21.7
Current marital status	Single	3	0.8
	Married	377	96.2
	Widowed	10	2.6
	Other	2	0.5
Educational level	No formal education	110	28.1
	Primary education	144	36.7
	Secondary education	91	23.2
	Diploma and above	47	12.0
Occupation	Employee	11	2.8
	Private business	15	3.8
	Daily labourer	70	17.9
	Housewife	296	75.5
Family size	≤3	127	32.4
	4–6	189	48.2
	≥7	76	19.4
Household average monthly income	≤2,000	126	32.1
	2,001–2,300	78	19.9
	2,301–3,000	117	29.8
	≥3,001	71	18.1
Decision making autonomy	Low	19	4.8
	Medium	166	42.3
	High	207	52.8
	Media	392	100.0
Intra households' violence practice	No	342	87.2
	Yes	50	12.8

Reproductive, medical, and behavioral characteristics of respondents

About 90% of pregnancies of women were planned and wanted. Around 85% of women do not have a history of illness, 93% had a history of abortion, 79% worked all household jobs alone, and 94.1% had substance abuse. Dietary characteristics of respondents The prevalence of undernutrition among pregnant women was (44.9%) and the rest were normal nutritional status. The household food security score indicates that 103 (26.5%) households were food insecure and 288 (73.5%) were food insecure. Out of the 391 respondents, 272 (69.4%) consumed six or more diets in the past 24 h, indicating that they had good

TABLE 3 Reproductive, medical, and behavioral characteristics of pregnant women in Liban District (*n* = 420), 2021.

Characteristics	Categories	Frequency	Percentage (%)
Age at first pregnancy (in year)	≤18	98	25.0
	19–20	155	39.5
	≥21	139	35.5
Intention pregnancy	Not planned and wanted	40	10.2
	Planned and wanted	352	89.8
Parity	≤2	214	54.6
	3–4	124	31.6
	≥5	54	13.8
Any illness during current pregnancy	Yes	59	15.1
	No	333	84.9
History abortion any type	No	365	93.1
	Yes	27	6.9
Inter pregnancy interval	≤18	119	30.4
	19–24	125	31.9
	25–28	60	15.3
	≥29	88	22.4
Antenatal care follow-up for current pregnancy	No	127	32.4
	Yes	265	67.6
Months of pregnancy at start antenatal care	≤4	239	61.0
	≥5	153	39.0
Working all household duties alone	No	310	79.1
	Yes	58	14.8
Substance abuse	Substance abused	22	5.6
	No substance abuse	369	94.1

minimum dietary diversification. More than three-quarters of pregnant women, 312 (79.6%), had a habit of taking additional meals, and 298 (76%) did not skip meals on a regular basis. Of the 420 study participants, 372 (98.2%) had consumed cereals in the previous 24 h. The main cereal consumed was teff in the form of injera/a staple food for Ethiopians made up of teff and certain barley and maize in the area. Vegetables held an integral part of the main meal for the majority of the study participants. More than 171 (43%) consumed vegetables, 123 (84.8%) consumed dark green leafy vegetables, and 124 (32.7%) consumed other vegetables. Oil and fat consumption was reported by 300 (76.5%) of the study participants. The white tubers and roots were consumed by 58 (14.8%; [Table 3](#)).

Dietary characteristics of respondents

The prevalence of undernutrition among pregnant women was (44.9%) and the rest were normal nutritional status.

TABLE 4 Dietary characteristics of pregnant women living in Liban District (*n* = 420), 2021.

Characteristics	Categories	Frequency	Percentage (%)
Nutritional status	Under-nourished	30	7.7
	Normal	361	92.3
HFIAS score	Food insecure (<5)	103	26.5
	Food secure (≥5)	288	73.5
Prenatal dietary feeding habits	Unimproved	283	72.2
	Improved	109	27.8
Habit of taking additional meals	Yes	312	79.6
	No	79	20.2
Do you ever skip meals during this pregnancy	No	298	76.0
	Yes	94	24.0
Avoiding any food	No	256	65.3
	Yes	111	28.3
Habit of eating snack between meal	No	320	81.6
	Yes	33	8.4
Minimum dietary diversification for women	≥6	272	69.4
	<6	120	30.6

The household food security score indicates that 103 (26.5%) households were food insecure and 288 (73.5%) were food secure. Out of the 391 respondents, 272 (69.4%) consumed six or more diets in the past 24 h, indicating that they had good minimum dietary diversification. More than three-quarters of pregnant women, 312 (79.6%), had a habit of taking additional meals, and 298 (76%) did not skip meals on a regular basis. Of the 420 study participants, 372 (98.2%) had consumed cereals in the previous 24 h. The main cereal consumed was teff in the form of injera/a staple food for Ethiopians made up of teff and certain barley and maize in the area. Vegetables held an integral part of the main meal for the majority of the study participants. More than 171 (43%) consumed vegetables, 123 (84.8%) consumed dark green leafy vegetables, and 124 (32.7%) consumed other vegetables. Oil and fat consumption was reported by 300 (76.5%) of the study participants. The white tubers and roots were consumed by 58 (14.8%; [Table 4](#)).

A total of 98.2 present (*n* = 372) of the study population had consumed cereals in the previous 24 h which is predominant. The main cereal consumed was teffs in the form of Injeras which is a made of teff and certain barley and maze in the area. Vegetables form an integral part of the main meal for majority of the population generally. Over 43% (*n* = 171) consume vegetables; with 84.8% (*n* = 123) consuming dark green leafy vegetables and 32.7% (*n* = 124) consuming other vegetables. Oils and fats consumption was reported by 76.5% (*n* = 300) of the population. White tubers and roots were consumed by 14.8%

($n = 58$; [Table 4](#)). During the women affirmed that: “Most people consume cereal. This is what is easily available but those who have money may eat some meat but it depends on an individual’s economic ability.”

Healthcare and environmental characteristics of respondents

Around 375 (95.7%) pregnant women had access to healthcare services traveling on foot for less than 1 h pregnant women 143 (79%) were supplied with iron–folic acid tablets during the second and third trimesters of pregnancy. About 270 (70.7%) had a history of using modern contraceptives for at least 1 year. There were 219 (55.9%) pregnant women who used latrines and washed their hands frequently ([Table 5](#)).

Nutritional status and associated factors

The binary logistic regression analysis was performed for each variable written in the conceptual framework. Accordingly, average monthly income, decision-making autonomy, intrahousehold violence practice, history of any type of abortion, antenatal follow-up, current pregnancy intention, any illness during the current pregnancy, substance use (1 of these substances), household food security status, and type of latrine possessed were negatively associated with undernutrition. After binary logistic regression analysis, predictors with statistical significance and a p -value less than 0.25 were used in multivariable logistic regression analyses. In a multiple logistic regression analysis, those who had a gestational age between 25 and 28 months were 5.51 times more likely to be normal nutritional status compared to those who had gestational age above 33 months (AOR = 5.51, 95% CI: 1.27–23.96) and, those respondents who had been following antenatal care were six times more likely to be in normal nutritional status compared to those who had not been following ANC [AOR = 5.95, 95% CI: (1.49–23.82)] (see [Table 6](#)).

Discussion

The study showed that (92.3%) of the women had normal nutrition status, while (44.9%) were undernourished. This finding is different from a study conducted in Nigeria which revealed the proportion of undernutrition among pregnant women was 11% (33). This might be because of socioeconomic status as Nigeria is richer than Ethiopia and the availability of infrastructure is better than health care delivery in our country. The finding of the present study is also higher than study conducted in Wolayita Sodo Town, high land of Ethiopia

TABLE 5 Health care and environmental factors of pregnant women in Liban District ($n = 420$), 2021.

Characteristics	Categories	Frequency	Percentage (%)
Access to health care	No	17	4.3
	Yes	375	95.7
Prenatal dietary advice	No	356	90.8
	Yes	36	9.2
Iron and folic acid tablet supplementation	No	38	21
	Yes	143	79
Modern contraceptive	No	121	25.8
	Yes	270	70.7
Latrine possession	No	105	25.5
	Yes	287	71.7
Hand washing habit/Pattern	Not frequently	173	44.1
	Frequently	219	55.9
Type of drinking water source	Unprotected	85	21.7
	Protected	303	77.3

which showed overall, undernutrition status was 39.94% (95% CI: 34.7–45.2%), of which the majority (60%) had moderate anemia (33, 34). The reason behind the difference might be the present study was conducted in the most marginalized pastoralist area of the country where –frequent attacks of drought, shortage of rain, and above all conflict are more prevalent than in the highland area of the country. The majority of predictor factors of the present study like monthly income, decision-making autonomy, intra-household violence practice, history of any type of abortion, antenatal care follow-up, current pregnancy intention, any illness during the current pregnancy, substance use, food security, and type of latrine possessed were associated with undernutrition whereas in previous study family size > 5 (AOR:7.74, 95%CI:4.15–16.47), multigravida (AOR:2.66, 95%CI:1.131–4.53), having a low income (AOR:5.81, 95%CI:2.93–14.11), current clinical illness (AOR: 6.38, 95%CI:3.13–13.00), intestinal parasitic infection (AOR:2.41, 95%CI:1.08–5.81), no history of contraceptive usage (AOR:5.02 95%CI:2.21–11.47), being in third trimesters (AOR:11.37, 95%CI:4.56–24.82, low body mass index (AOR:9.44, 95%CI:7.79–22.18) were identified as independent predictors of anemia among pregnant women (33, 34).

The prevalence of undernutrition in the present study is (44.9%) which was higher than a similar study conducted in Yemen, maternal under-nutrition was 11.4% (95% CI 3.8–35.2), maternal anemia (OR 5.3, 95% CI 1.5–18.6) and rural residents (OR 0.2, 95% CI 0.1–0.7) (35). This might be because of differences in socioeconomic status.

TABLE 6 Multivariate analysis test for nutritional status of pregnant women.

Characteristics	Nutritional status		P-value	Odds ratio (95%CI)	
	Under-nutrition (MUAC < 23 cm)	Normal (MUAC ≥ 23 cm)		COR	AOR
Household average monthly income in ETB					
≤2,000	18 (14.3%)	108 (85.7%)	0.00	1	1
2,001–2,300	2 (2.6%)	76 (97.4%)	0.02	0.17 (0.04–0.77)*	0.30 (0.06–1.62)
2,301–3,000	8 (6.8%)	109 (93.2%)	0.92	1.10 (0.15–8.03)	2.96 (0.31–28.18)
≥3,001	2 (2.8%)	69 (97.2%)	0.25	0.39 (0.08–1.91)	0.26 (0.05–1.55)
Intra household violence practice					
Yes	17 (34.0%)	33 (66.0%)	0.00	1	1
No	13 (3.8%)	329 (96.2%)	0.001	13.4 (5.82–29.19)**	18.81 (6.34–55.8)**
Decision making autonomy					
Low	4 (21.1%)	15 (78.9%)	0.04	1	1
Medium	13 (7.8%)	153 (92.2%)	0.03	0.25 (0.07–0.87)*	0.29 (0.05–1.82)
High	13 (6.3%)	194 (93.7%)	0.56	0.79 (0.36–1.75)	1.92 (0.62–5.95)
Ant type of abortion					
Yes	5 (18.5%)	22 (81.5%)	0.003	1	1
No	25 (6.8%)	340 (93.2%)	0.036	3.09 (1.08–8.86)*	4.30 (1.08–17.17)*
This pregnancy intention					
Planned	9 (22.5%)	31 (77.5%)	0.001	0.22 (0.09–0.52)**	0.29 (0.10–0.90)*
Unplanned	21 (6.0%)	331 (94%)	0.000	1	1
Any illness during current pregnancy					
Yes	9 (15.3%)	50 (84.7%)	0.000	1	1
No	21 (6.3%)	312 (93.7%)	0.021	0.37 (0.16–0.86)*	0.34 (0.10–1.09)
Substance use (≥1 of these substances)					
Yes	7 (31.8%)	15 (68.2%)	0.000	1	1
No	22 (6.0%)	347 (94%)	0.001	0.14 (0.05–0.37)**	0.16 (0.04–0.64)*
Household food security status (HFIAS score)					
Food secure	17 (5.9%)	271 (94.1%)	0.034	0.44 (0.21–0.94)*	0.65 (0.22–1.91)
Food insecure	13 (12.5%)	91 (87.5%)	0.000	1	1
ANC follow up					
Yes	26 (9.8%)	239 (90.2%)	0.012	3.35 (1.14–9.80)*	5.95 (1.49–23.82)*
No	4 (3.1%)	123 (96.9%)	0.0	1	1
Type of latrine possessed					
Improved	3 (2.8%)	105 (97.2%)	0.04	0.27 (0.08–0.92)*	0.22 (0.05–0.90)*
Unimproved	26 (9.5%)	246 (90.5%)	0.00	1	1
Gestational age					
≤24 months	4 (4.0%)	96 (96.0%)	0.53	1	1
25–28 months	9 (14.0%)	55 (56.0%)	0.02	1.92 (0.60–6.13)	5.51 (1.27–23.96)*
29–32 months	5 (7.60%)	61 (92.4%)	0.82	0.49 (0.20–1.22)	1.16 (0.32–4.41)
≥33 months	12 (7.4%)	150 (92.6%)	0.13	0.98 (0.33–2.88)	2.96 (0.74–11.78)

*Statistically significant at P value < 0.05. **Statistically significant at P value < 0.01. COR, crude odds ratio; AOR, adjusted odds ratio.

It is also higher than a study conducted in eastern Ethiopia which showed on average, 19.06% of subjects were malnourished, while 23.3% of study participants were underweight (body mass index < 19.8 kg m⁻²). In the final adjusted analysis, the risk of malnutrition was more than twofold higher in pregnant women with low (adjusted odds ratio = 2.47, 95% confidence interval = 1.41–4.34) and medium

(adjusted odds ratio = 2.74, 95% confidence interval = 1.40–5.35) (23).

The present study finding is dissimilar from a study conducted in Shashemenne District, West Arsi Zone, South Ethiopia which revealed that 34.0% (95%CI: 29.5 and 38.4% of the women were undernourished (24). The possible reason as commonly mentioned the present study was conducted in a very

low land area where agricultural production is very low and the food system always deteriorates by drought when compared to the previous study central Oromia.

The findings from present study were also highest when compare with different previous studies findings: For instance, study conducted among pregnant women visited Antenatal Care clinics in Silte zone, Southern Ethiopia showed: 21.8% (36); the study conducted in Southern Ethiopia among contextual risk factors for maternal malnutrition in a food-insecure zone revealed that 28.1% of the women were malnourished (BMI < 18.5) (37); study conducted among women in Addis Ababa, Ethiopia on The burden of underweight and overweight was 21% (22); the study conducted in Konso district, Southern Ethiopia was the overall prevalence of undernutrition was 43.1% (95% CI 38.7–47.5%) (38); the prevalence of undernutrition among pregnant women in Gambella town was 28.6% (25); similar study conducted in Tigray Region Northern Ethiopia among pregnant women, revealed that the prevalence of undernutrition was found to be 40.6% with 95% confidence interval (38.93% and 42.27%) (39); the study conducted in Western Ethiopia showed that the magnitude of undernutrition among pregnant women was 39.2% (95%CI: 35.7, 42.6%) (40); the study conducted in Eastern Ethiopia showed that the prevalence of undernutrition was 43.8% (95% confidence interval: 40.8, 47.0) (41); the study conducted in Gondar town, Northwest Ethiopia among pregnant mothers indicated that the prevalence of undernutrition was 14.4% (95%CI: 12.3–16.7) (42); the study conducted in Bench-Sheko and Kaffa zone, southwest Ethiopia among pregnant women showed that the prevalence of undernutrition was 23.7% (95% CI: 20.1, 27.4) (43); the study done in Nairobi, Kenya revealed that the prevalence of undernutrition among the pregnant women was 27% (44); the study conducted in Gedeo Zone, southern Ethiopia showed the prevalence of undernutrition among pregnant women was 21% (95% CI: 20.8–21.2) (45); the study done in Eastern Ethiopia revealed that the prevalence of undernutrition among pregnant was 43.8% (41). The study conducted in Uganda showed that the prevalence of underweight and stunting was 6.9% (318/4640) (46); the study conducted in Somali Region, East Ethiopia among pregnant women showed that the prevalence of undernutrition was 16.4% (47); the study done Somali region, Eastern Ethiopia revealed the prevalence of undernutrition was 35 (9%; 95%CI (30.8%, 40.2%) (48); the study conducted at Mettu Karl Referral Hospital, Southwest Ethiopia showed that the prevalence of undernutrition among pregnant was 17.5%. Family size > 5 [AOR = 8.2, 95%CI: 12.383, 46.217] (49).

The possible reasons for the difference might be in the Borena pastoralist zone shortages of rain, drought, and malnutrition are common epidemic problems. The Borena communities' are many marginalized people in terms of primary health care delivery, safe drinking water, education, and the like. There is no almost food system people rely on for their daily

energy intake. Livestock death is common because of drought. For this reason prevalence of malnutrition is expected to be higher than in other parts of the country.

The prevalence of the present study was lower than the study conducted in Ethiopia at large scale households among women's malnutrition determinants which showed 59% was underweight (posterior odds ratio [OR] = 1.59; 95% credible interval [CrI]: 1.32–1.90). The possible reason might be the previous study used strong methods and Bayesian multilevel analysis. Furthermore, it was large-scale households along with a larger sample size compared to the present study (50).

The finding from the present study is slightly lower than (the 44.9%) study conducted in Ziway Dugda district, central Oromia 48.6% and 48.7% among pregnant women residing the in the Keserwan District in the Middle East (51, 52), respectively. The possible reason might be because of knowledge regarding utilization as the place where production is higher people use for commercial purposes rather than utilization at households and individual level and also health food eating is an issue to be considered.

The finding from the present study is lower than (44.9%), of a study conducted in Kacha Birra District, Southern Ethiopia which revealed (52.6%) of pregnant women were undernourished (53). The possible reason might be an epidemic outbreak (severe acute malnutrition) in Kacha Birra District increasing the proportion in the study area. However, it was higher than the study conducted in the same district Kacha Birra which showed the prevalence of anaemia among pregnant women was 29% (95% CI:1.18–5.84) (54) and also higher than the study conducted in Africa which indicated 23.5% (95%CI: 17.72–29.32; I2 = 98.5%) pregnant women were undernourished (7) and, also present study finding is higher than (44.9%), a study conducted in Mieso Health Centre in South Ethiopia among pregnant women indicated 30.3% was undernourished (55) and also study conducted in the pastoral communities of Afar Regional State in northeast Ethiopia was 30.9% [95% CI 26.5, 35.8%]. The possible reasons might be climate conditions, drought, and malnutrition in Borana Zone are more risk area than any part of Ethiopia.

The finding from the present study is higher than (44.9%), study conducted in Sudanese, Khartoum women who were underweight 4.4%, 95 (28.1%), 127 (37.6) reported (28). The possible reason might be the diagnostic method in the previous study was depend on blood peripheral and Haemoglobin tests which are preferable to simple MUAC, and BMI assessment methods.

Conclusion

In this study, the prevalence of undernutrition among pregnant women was higher (44.9%) than in other similar studies. Average family income of households of the

respondents, decision-making autonomy of pregnant women at the household level, Using Substance, household food insecurity, household average monthly income, women decision-making autonomy, intra-household violence practice during the current pregnancy, history of any type of abortion, gestational age, pregnancy intention, of any illness during current pregnancy and substance use, household food security status, pregnant women FANC attendant and household possessing improved type latrine were found to be independent predictors of pregnant mother nutritional status.

Data availability statement

The original contributions presented in this study are included in the article/**Supplementary material**, further inquiries can be directed to the corresponding author.

Ethics statement

The ethical approval was obtained from Oromia Regional Health Bureau Institutional review Board (IRB) depending on Helsinki ethical principles Ref. No. ORHB/1560/2021. Oral consent form was obtained from study participants.

Author contributions

GA: conceptualization, proposal development, methodology, data collection, analysis, write-up, project administration, advising, consultation, revision, and edition.

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Conflict of interest

The author declares that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

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Supplementary material

The Supplementary Material for this article can be found online at: <https://www.frontiersin.org/articles/10.3389/fnut.2022.1008701/full#supplementary-material>

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EDITED BY

Jai Das,
The Aga Khan University, Pakistan

REVIEWED BY

Tsinuel Girma Nigatu,
Jimma University, Ethiopia
Elaine Ferguson,
University of London, United Kingdom

*CORRESPONDENCE

Melissa F. Young
✉ melissa.young@emory.edu

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Maternal hemoglobin concentrations across pregnancy and child health and development from birth through 6–7 years

Melissa F. Young^{1,2*}, Phuong Nguyen³, Lan Mai Tran^{1,2},
Long Quynh Khuong⁴, Sonia Tandon^{1,2}, Reynaldo Martorell^{1,2} and
Usha Ramakrishnan^{1,2}

¹Hubert Department of Global Health, Emory University, Atlanta, GA, United States, ²Doctoral Program in Nutrition and Health Sciences, Laney Graduate School, Emory University, Atlanta, GA, United States, ³Poverty, Health and Nutrition Division, International Food Policy Research Institute (IFPRI), Washington, DC, United States, ⁴Hanoi School of Public Health, Hanoi, Vietnam

Background: The role of changes in maternal hemoglobin (Hb) across pregnancy on child health and development (CHD) remains unclear.

Objective: We examined the association between maternal Hb trajectories and CHD outcomes: (a) birth outcomes (birth weight, length, gestational age, preterm, and small for gestational age); (b) child Hb at 3, 6, 12, and 24 months; and (c) motor and mental development at 12 and 24 months and cognitive functioning at age 6–7 years.

Methods: We used data from a randomized controlled trial (PRECONCEPT) conducted in Vietnam ($N = 1,175$ women enrolled during preconception with offspring follow-up through 6–7 years). Maternal Hb trajectories were developed using latent class analysis with Hb data at preconception, early (≤ 20 weeks), mid (21–29 weeks), and late (≥ 30 weeks) pregnancy. Multivariable linear and logistic regression models were used to assess the association between maternal Hb trajectories on CHD outcomes, adjusting for confounding variables at the maternal, child and household levels.

Results: Four distinct maternal Hb trajectories were identified. Track 1 (low initial Hb-decline) was associated with lower child Hb at 3 months (β [95% CI] -0.52 [-0.87 , -0.16]), 6 months (-0.36 [-0.68 , -0.05]), 12 months (-0.46 [-0.79 , -0.13]), and 24 months (-0.44 [-0.72 , -0.15]) and motor development at 12 months (-3.58 [-6.76 , -0.40]) compared to track 4 (high initial Hb-decline). After adjustment for multiple testing, relationships remained robust with the exception of associations with child Hb at 6 months and motor development at 12 months. Track 2 (low initial Hb-improve) was the only Hb trajectory to increase across pregnancy; however, it was insufficiently powered. Track 3 (mid Hb-decline) was associated with lower child Hb at 12 months (-0.27 [-0.44 , -0.10]) and 24 months (-0.20 [-0.34 , -0.05]) compared to track 4 (high initial Hb-decline). Maternal Hb trajectories were not associated with birth outcomes or child development at 24 months or 6–7 years.

Conclusion: Maternal Hb trajectories during pregnancy are associated with child Hb concentrations across the first 1,000 days, but not with birth outcomes or later cognitive functioning. More work is needed to better understand and interpret changes in Hb levels during pregnancy especially in resource poor settings.

KEYWORDS

hemoglobin, pregnant women, child development, anemia, nutrition

Introduction

Maternal anemia during pregnancy is a pressing global health problem impacting 32 million women (1). Anemia during pregnancy is associated with increased risk of maternal and neonatal mortality, preterm births (PTB) and small for gestational age (SGA), and impaired child health and development (2–5). The prevention and control of anemia is an important public health priority for meeting the Sustainable Development Goals on nutrition, health and wellbeing, and the WHO 2025 global targets of reducing maternal anemia by 50% (4, 6).

Despite the widespread acknowledgment of the importance of preventing anemia during pregnancy to improve maternal and child health outcomes (7, 8), many questions remain. A systematic review by Young et al. (5), identified several limitations of existing literature in response to a special call by the WHO to review global guidelines for anemia. First, although prior research suggests a differential impact of maternal hemoglobin (Hb) concentrations during pregnancy on birth outcomes depending on timing of measurement (i.e., gestational age), there are few longitudinal studies with serial measurements of maternal Hb over the course of pregnancy and/or reliable estimates of gestational age (5, 9). Defining anemia during pregnancy is further complicated by the dramatic increases in plasma volume expansion (10). Early in pregnancy, maternal hemoglobin may play a key role in placental development and function as well as nutrient availability for fetal growth and development, whereas mid pregnancy is a critical time period of rapid fetal growth and late pregnancy is a time period of greatest placental iron transfer to fetus and completion of organ development (11–14). Second, most studies do not use valid methods to evaluate the independent and time-specific relative contributions of Hb levels, which tend to be highly correlated across pregnancy and early childhood. Third, few prospective cohorts examine the relationship between maternal Hb and long-term child development outcomes. Despite decades of research, the relationship between maternal Hb concentrations and long-term child development remains unclear (5, 15). Furthermore, there is limited data that has examined these associations in contexts with a high prevalence of anemia but low prevalence of iron deficiency anemia.

In order to address these important research gaps, we leveraged secondary data from a large micronutrient supplementation trial conducted in Vietnam (PRECONCEPT, NCT01665378) (16). Over 5,000 non-pregnant women who were intending to get pregnant were enrolled and those who conceived were carefully monitored throughout pregnancy and their offspring were followed from birth through age 6–7 years. Our objective was to examine the association between maternal Hb trajectories during pregnancy and child health and development outcomes: (a) birth outcomes (birth weight, length, gestational age, preterm, and small for gestational age); (b) child Hb at 3 months,

6 months, 12 months, and 24 months; and (c) motor and mental development at 12 months and 24 months and cognitive functioning at age 6–7 years.

Materials and methods

Study design, participants, and setting

Children in this study are offspring of women who participated in a randomized controlled trial that was originally designed to evaluate the effects of preconception micronutrient supplementation on maternal and child health outcomes in Vietnam (PRECONCEPT study; NCT: 01665378). Details of the PRECONCEPT study have been published previously (16). Briefly, the study included 5,011 women of reproductive age who were randomly assigned to receive weekly supplements containing either 2,800 µg folic acid (FA), 60 mg iron and 2,800 µg FA (IFA), or multiple micronutrients (MM) containing the same amount of IFA, from baseline until conception, followed by daily prenatal supplements containing 60 mg iron and 400 µg FA until delivery. Women were followed prospectively to identify pregnancies and evaluate child outcomes from delivery through 6–7 years. We included women with singleton, live births and data on birth weight, gestational age as well as maternal Hb data during preconception and three time points during pregnancy.

Outcome measures

The key outcomes of interest include: (1) birth outcomes; (2) offspring Hb during the first 1,000 days; and (3) child development at 12 months, 24 months and 6–7 years described in brief below and in further depth in prior publications (16–19).

Birth outcomes

Birth weight was measured as early as possible within 7 days after birth using standard procedures and highly trained research assistants (20) using electronic weighing scales precise to 10 g. Birth length was measured with collapsible length boards, which were precise to 1 mm. Gestational age was calculated as the number of days between the first day of the last menstrual period (obtained prospectively by village health workers during their biweekly home visits) and the day of delivery. Prior work has reported on accuracy and validity of estimates compared to ultrasound measurements in this study (21). A pre-term birth was defined as a birth occurring before 37 completed weeks of pregnancy. Small for gestational age (SGA) was defined as a birth weight below the 10th percentile for gestational age and sex (22).

Offspring Hb during the first 1,000 days

Offspring Hb was measured from finger prick capillary blood samples at 3 months, 6 months, 12 months, and 24 months of age using a portable HemoCue 301 Analyzer (23). Child anemia was defined as a Hb value < 11 g/dL (24). All research assistants were highly trained with close supervision on standard protocols (16, 19).

Child development

Child development at 12 and 24 months of age was assessed using the Bayley Scales of Infant Development (BSID) III (25) which includes cognitive, language, and motor subscales. The BSID-III has been translated and adapted in Vietnam using standardized methods and has been used in previous studies (26–28). The raw summary scores for each of the domains were then transformed to standardized composite scores (approximately mean $\pm$ SD: 100 ± 15) to facilitate comparisons across domains. The BSID-III was administered in a quiet room at community health centers by well-trained researchers. Data quality was assessed based on weekly field-based supervision and monthly staff meetings. Site visits were also carried out regularly by study investigators, and refresher training sessions were conducted every 6 months after the initial training to ensure testing was conducted in a standardized manner.

Child intellectual development at 6–7 years was assessed using the Wechsler Intelligence Scale for Children®—Fourth Edition (WISC-IV) (29). The WISC-IV consists of four specific cognitive domains (Verbal Comprehension Index–VCI, Perceptual Reasoning Index–PRI, Working Memory Index–WMI, and Processing Speed Index–PSI) and the Full-Scale Intelligence Quotient (FSIQ). The WISC-IV has been translated, adapted, and validated to be a standardized test in Vietnam (30). The WISC-IV was assessed by pediatricians or researchers with master's degrees in public health. Quality control were conducted with field-based supervision, monthly staff meetings, and refresher training (18).

Exposure variables

The primary exposure variables are Hb at preconception, early (≤ 20 weeks), mid (21–29 weeks), and late (≥ 30 weeks) pregnancy that were measured by Hemocue™ 301 from a capillary blood sample obtained by finger-prick (23) using standardized training protocols (19).

Confounders

Confounding variables were considered at child, maternal, and household levels. These included child sex, maternal age, maternal education, maternal depression, and intervention group. Maternal education was categorized into four groups: primary school (completed 1–5 years), secondary school (6–9 years), high school (10–12 years), and college or higher. Maternal depression was measured at baseline using the Center for Epidemiologic Studies Depression Scale (CES-D) (31). The intervention group included the FA, IFA, and MM groups. At household level, the quality of the learning environment at home was measured using the Infant/Toddler HOME inventory at 12 months of age (32); the HOME assesses the quality and quantity of the social, emotional, and cognitive support available to a child in the home environment.

Household socio-economic status (SES) index was calculated using a principal components analysis of housing quality and assets that were assessed at baseline; the first component derived from component scores was used to divide household SES into tertiles (33, 34).

Statistical analysis

The Kolmogorov–Smirnov test was used for testing the normality of the continuous outcome variables. Descriptive statistics were used to report characteristics of the study population, with frequencies and percentages to describe categorical variables, means, and standard deviations to describe quantitative variables.

We used Latent Class Growth Analysis (LCGA) to identify different maternal Hb latent classes with qualitatively distinct trajectories. Trajectories of maternal Hb was created using censored normal model which was most appropriate for the ordinal nature of the indicator variables, Hb level at preconception early (≤ 20 weeks), mid (21–29 weeks), and late (≥ 30 weeks) pregnancy in order to allow for us to maximize sample size and equally distribute available data over critical periods across pregnancy. We selected best fitting model in identifying the tracks by fitting different models with the increasing numbers of trajectories. The final number of trajectories were determined based on the information criteria (AIC: Akaike's Information Criterion; BIC: Bayesian Information Criterion) and the interpretability of the class membership. The LCGA categorized women into four Hb trajectories, in which no additional variation in the estimated trajectory within class, just random error.

Multivariable linear regressions (for continuous outcomes) and logistic regression (for binary outcomes) were used to assess the association between maternal Hb trajectories and birth outcomes, offspring Hb during the first 1,000 days, and child development at 12 months, 24 months and 6–7 years. Associations with birth outcomes and offspring Hb during the first 1,000 days were examined in two models: (1) unadjusted model; and (2) adjusted for maternal age, ethnicity, education, SES, infant sex, and age and intervention group. Similar analyses were conducted to examine associations with child development at 12 months and 24 months and child intellectual development at 6–7 years with additional adjustment for home environment, mother IQ, and depression. All analyses were conducted using Stata v17 (StataCorp, College Station, TX, USA). An initial significance level of 0.05 was used for all statistical tests and adjusted for multiple testing using the Bonferroni Approach for each domain outcome.

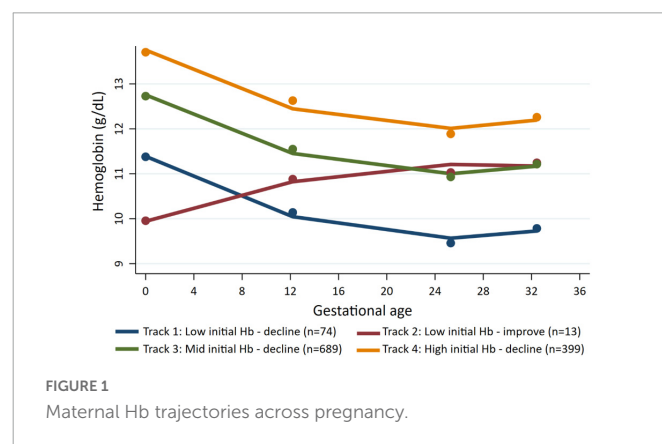


TABLE 1 Baseline characteristics of participants at preconception enrollment, by maternal Hb trajectories¹.

Variable	All women (n = 1,175)	Track 1 (n = 74)	Track 2 (n = 13)	Track 3 (n = 689)	Track 4 (n = 399)
Age (years)	26.0 ± 4.3	26.5 ± 4.8	27.8 ± 3.4	25.8 ± 4.4	26.1 ± 4.1
Minority ethnic, % ²	577 (49.2)	46 (62.2)	6 (46.2)	359 (52.2)	166 (41.7)
Work as farmers, % ²	938 (79.9)	61 (82.4)	10 (76.9)	575 (83.5)	292 (73.4)
Number of children ≥1, %	927 (94.2)	62 (96.9)	10 (100.0)	546 (94.6)	309 (92.8)
Time to pregnancy	33.8 ± 24.3	33.6 ± 25.9	29.0 ± 28.9	34.3 ± 24.4	33.1 ± 23.7
Education level, %					
Primary school	88 (7.5)	4 (5.4)	2 (15.4)	52 (7.5)	30 (7.5)
Secondary school	636 (54.2)	39 (52.7)	7 (53.8)	396 (57.5)	194 (48.7)
High school	305 (26.0)	23 (31.1)	3 (23.1)	169 (24.5)	110 (27.6)
College or higher	145 (12.4)	8 (10.8)	1 (7.7)	72 (10.4)	64 (16.1)
Socio-economic status, %					
Low	385 (32.8)	31 (41.9)	3 (23.1)	228 (33.1)	123 (30.9)
Average	393 (33.5)	24 (32.4)	4 (30.8)	239 (34.7)	126 (31.7)
High	396 (33.7)	19 (25.7)	6 (46.2)	222 (32.2)	149 (37.4)
Preconception nutritional status					
Weight (kg)	45.7 ± 5.3	45.3 ± 4.9	44.1 ± 5.2	45.6 ± 5.1	46.1 ± 5.8
Height (cm)	152.6 ± 5.0	152.9 ± 5.0	153.7 ± 5.7	152.3 ± 5.0	153.0 ± 5.0
BMI (kg/m ²)	19.6 ± 2.0	19.4 ± 1.9	18.7 ± 2.2	19.6 ± 1.8	19.7 ± 2.2
Low BMI (<18.5), %	359 (30.6)	22 (29.7)	9 (69.2)	201 (29.2)	127 (32.0)
Preconception Hb (g/dL) ²	12.9 ± 1.3	11.1 ± 1.0	9.5 ± 1.2	12.7 ± 1.0	13.9 ± 1.1
Anemia, % (Hb < 12 g/dL) ²	236 (20.1)	58 (78.4)	12 (92.3)	151 (21.9)	15 (3.8)
Mild (11 < Hb < 12 g/dL)	164 (14.0)	29 (39.2)	0 (0.0)	121 (17.6)	14 (3.5)
Moderate/severe (Hb < 11 g/dL)	72 (6.1)	29 (39.2)	12 (92.3)	30 (4.4)	1 (0.3)

¹Values are means ± SDs or n (%). BMI, body mass index; FA, folic acid; Hb, Hb; IFA, iron and folic acid; MM, multiple micronutrient; SGA, small for gestational age.

²Significant differences across the four Hb groups, $p < 0.05$.

Ethical approval

The study was approved by the Ethical Committee of Institute of Social and Medicine Studies in Vietnam and Emory University's Institutional Review Board, Atlanta, Georgia, USA. The trial was registered in the US Clinical Trials registry (identification number NCT01665378). Written informed consent was obtained from all study participants.

Results

We identified four distinct maternal Hb trajectories (**Figure 1** and **Supplementary Table 1**). Track 1 (named *low initial Hb-decline*) included women with low initial mean Hb (11.1 ± 1.0 g/dL) at preconception and declined (mean Hb between 9.3–9.6 g/dL) during pregnancy ($n = 74$, 7.5%). Track 2 (named *low initial Hb-improve*) included women with the lowest initial mean Hb (9.5 ± 1.2 g/dL) at preconception; however, Hb recovered early in pregnancy and remained between 10.6–11.5 g/dL throughout pregnancy ($n = 13$, 1.7%). Track 3 (named *mid initial Hb-decline*) included women with an initial mean Hb of 12.7 ± 1.0 and remained between 10.9–11.5 g/dL ($n = 689$, 55%). Track 4 (named *high initial Hb-decline*) include women with high preconception Hb

(13.9 ± 1.1 g/dL) and remained between 12.0–12.8 g/dL ($n = 399$, 36%).

Preconception baseline characteristics of the women by the different Hb trajectories are described in **Table 1**. Maternal age and education were similar across the four groups with an average age around 26 year and over half of the women completed secondary school. Maternal BMI was likewise similar across groups with 30% of women having low BMI; the exception was Track 2 (*low initial Hb-improve*) where almost 70% of women had a low BMI. Track 1 (*low initial Hb-decline*) and Track 3 (*mid initial Hb-decline*) had a greater prevalence of minority women and employment in farming. Child characteristics are described in **Table 2**. Overall, 8.5% of infants were born preterm, 4.4% were born low birth weight and 15.5% were born SGA. Child anemia was high with over 60% anemia at 3 months, 53% at 12 months, and 40% at 24 months. Basic maternal and child characteristics were also similar for the final analytic sample of 1,175 mother-child pairs (**Supplementary Figure 1**) when compared to those who were excluded due to missing data (**Supplementary Tables 2, 3**).

Maternal Hb trajectories were not significantly associated with birth weight, birth length, gestational age, preterm and SGA (**Table 3**). Maternal Hb trajectories were significantly associated with offspring Hb during the first 1,000 days (**Table 4**). Offspring of women in Track 1 (*low initial Hb-decline*) had lower Hb at ages

TABLE 2 Child characteristics at birth, Hb through 1st 1,000 days and child development through 6–7 years¹.

Variable	<i>n</i> = 1,175
Child characteristics	
Female, %	584 (49.7)
Gestational age (week)	39.3 ± 1.9
Preterm, %	100 (8.5)
Birth weight (gr)	3,094.4 ± 439.7
Low birth weight, %	52 (4.4)
SGA, %	172 (15.5)
Birth length (cm)	48.9 ± 3.1
Child Hb	
Hb at 3 months (g/dl)	10.6 ± 1.3
Anemia, % (Hb <11 g/dL)	615 (61.0)
Hb at 12 months (g/dl)	10.8 ± 1.2
Anemia, % (Hb <11 g/dL)	486 (52.7)
Hb at 24 months (g/dl)	11.2 ± 1.2
Anemia, % (Hb <11 g/dL)	209 (39.9)
Bayley scales for infant development at 12 months	
Cognitive	112.2 ± 10.3
Language	97.8 ± 11.0
Motor	102.9 ± 11.7
Bayley scales (overall)	104.3 ± 8.7
Bayley scales for infant development at 24 months	
Cognitive	99.3 ± 9.8
Language	102.2 ± 11.0
Motor	105.8 ± 12.1
Bayley scales (overall)	102.9 ± 8.9
Wechsler scale global intelligence, performance and verbal scores at 6–7 years	
Verbal comprehension index (VCI)	82.0 ± 12.4
Perceptual reasoning index (PRI)	93.5 ± 14.2
Working memory index (WMI)	101.8 ± 11.6
Processing speed index (PSI)	89.6 ± 12.4
Full scale IQ (FSIQ)	88.6 ± 12.2

¹Values are means (SDs) or *n* (%).

BMI, body mass index; FA, folic acid; Hb, Hb; IFA, iron and folic acid; MM, multiple micronutrient; SGA, small for gestational age.

3 months (β [95% CI] -0.52 [-0.87 , -0.16]), 6 months (-0.36 [-0.68 , -0.05]), 12 months (-0.46 [-0.79 , -0.13]), and 24 months (-0.44 [-0.72 , -0.15]) compared to those born to women in track 4 (*high initial Hb-decline*). Children born to women in Track 3 (*mid initial Hb-decline*) also had lower Hb at 12 months (-0.27 [-0.44 , -0.10]) and 24 months (-0.20 [-0.34 , -0.05]) compared to those born to women in track 4. These results remained significant after applying a more stringent *p*-value of 0.01 to account for multiple testing with the exception for associations with child Hb at 6 months which became non-significant.

Offspring born to women in Track 1 (*low initial Hb-decline*) had lower motor development scores at 12 months (-3.58 [-6.76 , -0.40]) when compared to track 4 (*high initial Hb-decline*) (Table 5).

However, this association was no longer significant after adjusting for multiple comparisons ($0.05 > p > 0.017$) and was not observed at 24 months. Maternal Hb trajectories were also not associated with child cognition or language at 12 or 24 months or with child cognition at 6–7 years in adjusted models (Table 6).

Discussion

In this cohort from Vietnam, we identified four unique maternal Hb trajectories across pregnancy which were not a significant predictor of birth outcomes, but were associated with child Hb across the first 1,000 days of life. Maternal Hb trajectories were not associated with long-term child development or cognition at age 6–7 years.

The lack of association between maternal Hb trajectories during pregnancy and birth outcomes are in contrast to prior research demonstrating the importance of maternal Hb concentrations on adverse birth outcomes (5, 9). There are several factors that may contribute to our findings. First, 80% of women entering pregnancy were non-anemic and most of those who were anemic had mild anemia. However, there was divergence in Hb concentrations patterns across pregnancy and although we had hypothesized that track 1 (*low initial Hb-decline*) would have the highest risk of adverse birth outcomes, this was not the case. This could likewise be due in part to the nature of anemia in our cohort and low prevalence of iron deficiency anemia (19, 35). However, it remains unclear how the etiology of anemia may impact birth outcomes (5). Furthermore, all the women in our study were randomized to receive weekly supplements containing IFA, MM or FA preconception, followed by daily IFA supplementation during pregnancy. Compliance was high with nearly 80% of women consuming more than 80% of the preconception and prenatal tablets (36). While preconception supplementation with IFA and MM was not associated with improvements in birth outcomes or anemia reduction in this cohort, modest improvements in maternal and infant iron status were noted (17, 19). In addition, IFA supplementation during pregnancy is a well-established public health intervention associated with lowered risk of maternal anemia and improved birth outcomes (7, 37). It is possible the high overall uptake of an evidence-based intervention among all participants may have decreased the likelihood of demonstrating associations with maternal Hb on birth outcomes. High maternal Hb during pregnancy likewise has been associated with adverse birth outcomes (5, 9); potentially driven by inadequate plasma volume expansion (38) or excess iron (39–41). Among women in track 4 (*high initial Hb-decline*), nearly 40% had Hb values greater than 13 g/dL in early pregnancy and nearly 25% in late pregnancy. However, this track was not associated with increased risk of adverse birth outcomes. Further research examining the etiology of anemia and high Hb throughout pregnancy is needed to better understand the underlying mechanisms. Furthermore, other nutritional and non-nutritional risk factors should be explored to help guide future programs and improve birth outcomes in this context.

Maternal Hb trajectories were associated with child Hb across the first 1,000 days of life. In particular, for offspring born to women in track 1 (*low initial Hb-decline*) of which over 90% were anemic throughout pregnancy, had lower Hb concentrations at 3, 6, 12, and 24 months compared to those born to women in track 4 (*high initial Hb-decline*). The largest effect sizes were noted at 3 months

TABLE 3 Maternal Hb trajectories and association with birth outcomes¹.

Variable	Birth weight (β)		Birth length (β)		GA (β)		Preterm (OR)		SGA (OR)	
	Unadjusted	Adjusted	Unadjusted	Adjusted	Unadjusted	Adjusted	Unadjusted	Adjusted	Unadjusted	Adjusted
Track 1 (low initial Hb-decline)	-94.10 ⁺ [-203.22, 15.02]	-86.17 [-195.42, 23.08]	0.44 [-0.38, 1.26]	0.42 [-0.40, 1.25]	0.26 [-0.20, 0.72]	0.16 [-0.30, 0.62]	0.89 [0.36, 2.19]	1.03 [0.41, 2.58]	1.57 [0.84, 2.93]	1.62 [0.86, 3.06]
Track 2 (low initial Hb-improve)	-107.60 [-350.59, 135.39]	-127.01 [-369.20, 115.18]	-1.15 [-2.96, 0.66]	-1.25 [-3.06, 0.57]	-0.11 [-1.13, 0.92]	-0.12 [-1.14, 0.90]	0.84 [0.11, 6.65]	0.79 [0.10, 6.45]	1.68 [0.45, 6.28]	2.04 [0.53, 7.81]
Track 3 (mid initial Hb-decline)	9.83 [-44.41, 64.07]	15.56 [-39.03, 70.14]	0.30 [-0.11, 0.71]	0.31 [-0.10, 0.73]	0.04 [-0.19, 0.27]	-0.03 [-0.26, 0.20]	0.91 [0.59, 1.41]	0.98 [0.62, 1.53]	0.98 [0.68, 1.39]	1.00 [0.69, 1.43]
N	1,175	1,172	1,072	1,070	1,175	1,172	1,175	1,172	1,108	1,105

¹Track 4 (high initial Hb-decline) is the reference category; Values are (β [95% CI]) or (OR [95% CI]).

Models adjusted for maternal ethnicity, age, education, SES, infant sex, intervention group. GA, gestational age, SGA, small for gestational age.

(β [95% CI] -0.52 [-0.87, -0.16]), but remained high even at 24 months (-0.44 [-0.72, -0.15]), and remained significant even after adjustment for multiple testing with the exception of the 6-months measurement. This could be due to the greater variability in diet and other risk factors during the transition to complementary foods. For women in track 3 (*mid Hb-decline*), associations between maternal and child Hb were significant only at 12 and 24 months. The rationale for the delayed associations is unclear, though this could be associated with the underlying etiology of anemia. While up to 50% of maternal anemia is often attributed to iron deficiency, this can vary widely across different contexts (4, 42). Prior research has suggested a potentially stronger correlation between maternal iron deficiency anemia with child anemia compared to maternal non-iron deficiency anemia (43). Maternal iron deficiency anemia is associated with decreased iron endowment at birth and thus greater risk of early infant anemia (44). However, in our cohort, preconception iron deficiency was very low (<5%) and maternal anemia may be more driven by other factors such as hookworm infections (19, 35). Shared dietary, genetic (hemoglobinopathies) or environmental factors could contribute to delayed as well as continued associations across early childhood. The role of other micronutrient deficiencies, such as vitamins A and B₁₂, during pregnancy and their potential influence on infant hemoglobin likewise remains unclear. A better understanding of the etiology of maternal anemia and impact on child hematologic and micronutrient profiles is needed. Furthermore, few studies have examined how the strength of association between maternal and child Hb may vary by timing of assessment. In a recent 2020 systematic review among 32 studies, there was a negligible association between maternal Hb and offspring Hb within the first 48 h of life (0.15: 95% CI 0.10, 0.20) (45). The authors note the heterogeneous and weak associations may be due to varying anemia etiology across included studies (45).

We had expected that maternal Hb trajectories would be associated with child development; however, we found only modest associations with motor development at 12 months and no long-term associations at 6–7 years. In the literature, few studies have examined the long-term impact of maternal anemia on functional outcomes such as offspring IQ or school readiness (46, 47). A recent study of a Danish cohort of over 500,000 children showed that anemia in early pregnancy was associated with over a twofold increased risk of development of intellectual disability in the offspring between the ages of 6–29 years, but much weaker associations were seen for anemia in late pregnancy (48). In a prospective multicenter cohort study among 12 university hospitals in the US, maternal hematocrit during pregnancy was associated with offspring IQ at 4 and 7 years of age (46). The lack of long-term impact in our cohort of maternal Hb trajectories on child development could be due to similar reasons as discussed for birth outcomes: low prevalence of iron deficiency anemia early in pregnancy and primarily mild anemia, etiology of anemia, strong adherence to prenatal supplementation, or other unknown factors. Further replication of our findings in contexts with a higher burden of anemia and micronutrient deficiencies may be merited.

A key strength of our study is the use of prospectively collected data with low loss to follow up that allowed us to comprehensively examine changes in maternal and child Hb across the continuum of preconception and pregnancy through early childhood at 6–7 years. This is an advantage over prior research that has often examined associations focusing on women of reproductive age, pregnancy, or childhood in isolation. Our study had over 95% power, at an alpha

TABLE 4 Association between maternal Hb trajectories and offspring Hb during the first 1,000 days¹.

Variable	Hb 3 months		Hb 6 months		Hb 12 months		Hb 24 months	
	Unadjusted	Adjusted	Unadjusted	Adjusted	Unadjusted	Adjusted	Unadjusted	Adjusted
Track 1 (low initial Hb-decline)	−0.49 [−0.85, −0.14]	−0.52 [−0.87, −0.16]	−0.35 [−0.67, −0.04]	−0.36 [−0.68, −0.05]	−0.51 [−0.84, −0.18]	−0.46 [−0.79, −0.13]	−0.48 [−0.76, −0.19]	−0.44 [−0.72, −0.15]
Track 2 (low initial Hb-improve)	−0.25 [−1.00, 0.51]	−0.32 [−1.08, 0.43]	−0.08 [−0.76, 0.60]	0.01 [−0.66, 0.69]	−0.37 [−1.10, 0.35]	−0.37 [−1.08, 0.34]	0.23 [−0.37, 0.84]	0.22 [−0.38, 0.83]
Track 3 (mid initial Hb-decline)	−0.10 [−0.27, 0.08]	−0.10 [−0.28, 0.07]	−0.14 [−0.30, 0.01]	−0.12 [−0.28, 0.03]	−0.31 [−0.48, −0.15]	−0.27 [−0.44, −0.10]	−0.22 [−0.37, −0.08]	−0.20 [−0.34, −0.05]
N	1,007	1,005	960	960	943	943	1,031	1,030

¹Track 4 (*high initial Hb-decline*) is the reference category; Values are (β [95% CI]).

Models adjusted for maternal ethnicity, age, education, SES, infant age and sex, intervention group. Hb, hemoglobin.

TABLE 5 Association between maternal Hb trajectories and child development at 12 and 24 months¹.

Variable	Child development–12 months					
	Cognition–12 months		Language–12 months		Motor 12 months	
	Unadjusted	Adjusted	Unadjusted	Adjusted	Unadjusted	Adjusted
Track 1 (low initial Hb-decline)	−1.63 [−4.45, 1.18]	−1.25 [−4.09, 1.58]	−0.54 [−3.54, 2.47]	−0.67 [−3.68, 2.35]	−3.75 [−6.95, −0.55]	−3.58 [−6.76, −0.40]
Track 2 (low initial Hb-improve)	2.30 [−3.65, 8.25]	2.25 [−3.66, 8.16]	−0.82 [−7.17, 5.53]	−1.14 [−7.44, 5.15]	−0.60 [−7.35, 6.16]	−0.66 [−7.29, 5.98]
Track 3 (mid initial Hb-decline)	−0.69 [−2.06, 0.69]	−0.29 [−1.69, 1.12]	−0.89 [−2.35, 0.58]	−0.77 [−2.27, 0.73]	−0.99 [−2.56, 0.57]	−0.72 [−2.30, 0.86]
N	1,008	969	1,009	970	1,008	969
Variable	Child development–24 months					
	Cognition–24 months		Language–24 months		Motor 24 months	
	Unadjusted	Adjusted	Unadjusted	Adjusted	Unadjusted	Adjusted
Track 1 (low initial Hb-decline)	−0.56 [−3.05, 1.93]	−0.17 [−2.63, 2.30]	0.13 [−2.69, 2.94]	0.40 [−2.37, 3.17]	1.58 [−1.52, 4.68]	1.93 [−1.16, 5.02]
Track 2 (low initial Hb-improve)	4.87 ⁺ [−0.54, 10.28]	4.73 ⁺ [−0.60, 10.05]	0.76 [−5.32, 6.84]	0.79 [−5.16, 6.75]	0.31 [−6.39, 7.01]	−0.47 [−7.12, 6.18]
Track 3 (mid initial Hb-decline)	−0.08 [−1.34, 1.18]	0.32 [−0.93, 1.58]	−0.64 [−2.06, 0.78]	−0.20 [−1.60, 1.20]	−0.79 [−2.35, 0.77]	−0.54 [−2.10, 1.03]
N	1,084	1,080	1,082	1,077	1,081	1,076

¹Track 4 (*high initial Hb-decline*) is the reference category; Values are (β [95% CI]).

Models adjusted for maternal ethnicity, age, education, SES, infant age and sex, intervention group, home environment, maternal IQ, depression.

of 5%, to detect biologically relevant associations between maternal Hb and child health and development indicators. Another important strength is the availability of repeated measurements of maternal Hb before and during pregnancy and accurate assessment of gestational age (16), which is rare yet essential for current analysis given the effects of plasma volume expansion during pregnancy. Another key strength was our trajectory analytic approach that allows us to leverage multiple highly correlated Hb measures across pregnancy and examine associations with CHD.

While our study provides rich prospective data on child health and development, a limitation of this work is insufficient data on maternal health outcomes. Prior work using a similar Hb trajectory approach, reported that women with low Hb across pregnancy or who had a progressively decreasing Hb trajectory were at a higher risk of transfusion (49). On the other hand, in this cohort high maternal Hb trajectories were associated with increased risk of preterm birth and SGA (49). Thus, demonstrating a need for future work to have dual focus on both maternal and child outcomes as well consideration of low and high Hb levels. Another limitation is that while we had

a relatively large overall sample size of women, track 2 (*low initial Hb-improve*) was underpowered and no conclusions can be drawn on this trajectory. We ran sensitivity analyses excluding the women in this track and it does not impact our key findings (data not shown). While we cannot draw conclusions on the association of track 2 Hb trajectories and CHD, we opted to retain all data in the manuscript to show the full picture. For all trajectories, other than track 2, preconception Hb values set the stage for pregnancy and then concentrations decreased throughout pregnancy. Track 2 was the only trajectory to increase during the course of pregnancy. Our study also used capillary blood samples rather than venous blood samples for assessing hemoglobin and this may increase measurement error (50). Another limitation of this work is a lack of data on the etiology of anemia during pregnancy. Further research on the complex and context specific nutritional and non-nutritional risk factors is needed to better understand key findings as well plan appropriate public health interventions. Our findings from a south-eastern Asian population on the four Hb trajectories identified may not be generalizable to other contexts with lower IFA compliance or a

TABLE 6 Association between maternal Hb trajectories and child cognition at 6–7 years¹.

Variable	VCI		PRI		WMI		PSI		FSIQ	
	Unadjusted	Adjusted	Unadjusted	Adjusted	Unadjusted	Adjusted	Unadjusted	Adjusted	Unadjusted	Adjusted
Track 1 (low initial Hb-decline)	−1.70 [−5.12, 1.72]	−0.85 [−4.27, 2.57]	−2.01 [−5.93, 1.91]	−0.20 [−4.08, 3.68]	−0.76 [−3.96, 2.44]	−0.64 [−3.86, 2.58]	−1.79 [−5.20, 1.62]	−1.32 [−4.73, 2.09]	−2.13 [−5.49, 1.23]	−0.94 [−4.24, 2.35]
Track 2 (low initial Hb-improve)	1.21 [−6.25, 8.68]	0.75 [−6.59, 8.10]	−6.23 [−14.79, 2.34]	−6.50 [−14.83, 1.82]	−1.80 [−8.80, 5.19]	−2.86 [−9.77, 4.06]	2.07 [−5.37, 9.52]	1.48 [−5.83, 8.80]	−1.81 [−9.15, 5.53]	−2.47 [−9.55, 4.61]
Track 3 (mid initial Hb-decline)	−2.06 [−3.74, −0.37]	−1.09 [−2.79, 0.61]	−0.89 [−2.83, 1.04]	0.42 [−1.51, 2.35]	−0.42 [−2.01, 1.16]	−0.06 [−1.67, 1.55]	−1.33 [−3.02, 0.35]	−0.58 [−2.28, 1.12]	−1.57 [−3.23, 0.09]	−0.41 [−2.06, 1.23]
N	969	947	969	947	967	945	969	947	967	945

¹Track 4 (high initial Hb-decline) is the reference category; Values are (β [95% CI]).
Models adjusted for maternal ethnicity age, education, SES, infant age and sex, intervention group, home environment, and mother depression. VCI, verbal comprehension index; PRI, perceptual reasoning index; WMI, working memory index; PSI, processing speed index; FSIQ, the full-scale intelligence quotient.

greater iron deficiency burden. Further research is needed to identify and examine the impact of maternal Hb trajectories in other contexts.

Our study provides novel insight on the importance of maternal Hb during pregnancy for CHD outcomes. While maternal Hb trajectories were associated child Hb concentrations across the first 2 years of life, we did not find associations with birth outcomes or long-term child development. We also found that maternal Hb trajectories across pregnancy were largely set by preconception Hb concentrations, and the continued monitoring of Hb across pregnancy added limited further insight compared to the effects of preconception Hb alone. These findings indicate the need for early targeting of women before pregnancy in this context. Our findings also indicate the need to examine the role of the etiology of anemia to better understand the underlying mechanisms and context specific findings. Future research may be merited to examine interventions above and beyond IFA supplementation during pregnancy to optimize maternal Hb and child health and development outcomes across different contexts.

Data availability statement

The data analyzed in this study is subject to the following licenses/restrictions: Data available upon request and approval of study team. Requests to access these datasets should be directed to UR, uramakr@emory.edu and PN, p.h.nguyen@cgiar.org.

Ethics statement

The studies involving human participants were reviewed and approved by the Ethical Committee of the Institute of Social and Medicine Studies in Vietnam and Emory University’s Institutional Review Board, Atlanta, Georgia, USA. Written informed consent to participate in this study was provided by the participants’ legal guardian/next of kin.

Author contributions

MY, PN, RM, and UR designed the research. PN, LT, and LK conducted the field research. MY, LT, LK, ST, and PN analyzed the data. MY, PN, and UR wrote the manuscript. MY had primary responsibility for the final content of the manuscript. All authors reviewed and provided critical feedback.

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Conflict of interest

The authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

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Supplementary material

The Supplementary Material for this article can be found online at: <https://www.frontiersin.org/articles/10.3389/fnut.2023.1114101/full#supplementary-material>

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EDITED BY

Bireshwar Sinha,
Centre for Health Research and Development
Society for Applied Studies,
India

REVIEWED BY

Yuemei Fan,
Tampere University,
Finland
Catherine Schwinger,
Norwegian Institute of Public Health (NIPH),
Norway

*CORRESPONDENCE

Zulfiqar Ahmed Bhutta
✉ zulfiqar.bhutta@aku.edu

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Infections and nutrient deficiencies during infancy predict impaired growth at 5years: Findings from the MAL-ED study in Pakistan

Doris González-Fernández¹, Simon Cousens², Arjumand Rizvi³,
Imran Chauhadry³, Sajid Bashir Soofi³ and Zulfiqar Ahmed Bhutta^{1,3,4*}

¹SickKids Centre for Global Child Health, Toronto, ON, Canada, ²Department of Infectious Disease Epidemiology, Faculty of Epidemiology and Population Health, London School of Hygiene and Tropical Medicine, London, United Kingdom, ³Center of Excellence in Women and Child Health, The Aga Khan University, Karachi, Pakistan, ⁴Institute for Global Health and Development, The Aga Khan University, London, United Kingdom

Background: Socio-economic, nutritional, and infectious factors have been associated with impaired infant growth, but how the presence of these factors during infancy affects growth around 5years is not well understood.

Methods: This secondary analysis of the MAL-ED cohort included 277 children from Pakistan for whom socio-demographic, breastfeeding, complementary foods, illness, nutritional biomarkers, stool pathogens and environmental enteropathy indicators between 0 and 11 months were recorded. We used linear regression models to analyze associations of these indicators with height-for-age (HAZ), weight-for-age (WAZ) and weight-for-height (WLZ) at 54–66months (~5years), and Poisson regression with robust standard errors to estimate risk ratios for stunting and underweight ~5years, controlling for gender, first available weight, and income.

Results: Among the 237 infants followed longitudinally and evaluated at about 5years of age, exclusive breastfeeding was short (median=14days). Complementary feeding started before 6months with rice, bread, noodles, or sugary foods. Roots, dairy products, fruits/vegetables, and animal-source foods were provided later than recommended (9–12months). Anemia (70.9%), deficiencies in iron (22.0%), zinc (80.0%), vitamin A (53.4%) and iodine (13.3%) were common. Most infants (>90%) presented with diarrhea and respiratory infections in their first year. At ~5years, low WAZ (mean-1.91±0.06) and LAZ (-2.11±0.06) resulted in high prevalence of stunting (55.5%) and underweight (44.4%) but a relatively low rate of wasting (5.5%). While 3.4% had concurrent stunting and wasting ~5years, 37.8% of children had coexisting stunting and underweight. A higher income and receiving formula or dairy products during infancy were associated with a higher LAZ ~5years, but infant's history of hospitalizations and more respiratory infections were associated with lower LAZ and higher risk of stunting ~5years. Infants' intake of commercial baby foods and higher serum-transferrin receptors were associated with higher WAZ and lower risk of underweight ~5years. Presence of *Campylobacter* and fecal neopterin >6.8nmol/L in the first year were associated with increased risk of underweight ~5years.

Conclusion: Growth indicators ~5years were associated with poverty, inappropriate complementary feeding, and infections during the first year of life, which supports the early start of public health interventions for preventing growth delay ~5years.

KEYWORDS

child growth, breastfeeding, complementary feeding, illness, environmental enteropathy, socio-demographic characteristics, intestinal infections, respiratory infection

1. Introduction

Despite some reduction, undernutrition continues to affect millions of children. According to the 2021 Global Nutrition Report, 149.2 million children under 5 suffer from stunting, 45.4 million are wasted (1). Also, and 1 in 2 children suffer from hidden hunger due to deficiencies in essential vitamins and nutrients (2). Undernutrition in the first 2 years of life has been linked with shorter adult height, lower educational achievement, reduced economic productivity and with smaller infants in the next generation (3). Linear growth is considered the best indicator of child well-being with stunting, defined as length/height < -2 SDs below the WHO child growth standard (4) indicative of past deprivation and predictive of future poverty (2). On the other hand, underweight (low weight-for-age), is known to increase the risk of viral, helminth and malaria infections in children (5). Wasting refers to children < 2 SDs below the WHO standards weight-for-length/height median (6), reflecting a recent loss of weight from severe poor nutrient intake, illness or both (2). Children presenting both stunting and wasting have the highest risk of mortality, even higher than those with WLZ < -3 SD (7). Although recent reports show a decline in the global prevalence of stunting (from 32.5 to 21.9%) and wasting (from 10 to 7.3%) between 2000 and 2017, important disparities continue to be observed, south Asia presenting higher wasting at birth (19%) compared with African (8%) and Latin-American infants (2%) (7).

The origin of undernutrition is complex and multifactorial. The Etiology, Risk Factors and Interactions of Enteric Infections and Malnutrition and the Consequences for Child Health and Development (MAL-ED) study, followed children from eight LMIC (Bangladesh, India, Nepal, Pakistan, Brazil, Peru, South Africa and Tanzania), and showed, for example, that low energy and protein density of complementary foods and a high prevalence of enteropathogens in non-diarrheal stools were associated with reduced weight and length by age 24 months (8). MAL-ED studies have contributed to our understanding of the impact of environmental enteropathy (EE) on child growth. EE has been described as phenotypic intestinal alterations that affect the health status of the host, following repeated enteric infections even in the absence of diarrhea or acute gastrointestinal illnesses (9). The MAL-ED study used three fecal biomarkers of gut inflammation and immunity. Myeloperoxidase (ng/mL) is a marker of neutrophil activity in the intestinal mucosa, neopterin indicates T-helper cell 1 activity and alpha-1 antitrypsin is an indicator of protein loss and intestinal permeability (9). Indicators of EE were associated with reduced stature, weight, weight-for-height, and BMI at 5 years, but no associations were found between illness symptoms and size at 5 years (10).

Among countries in the MAL-ED study, Pakistan had a high prevalence of wasting (15%) and stunting (44%) according to the 2011 National Nutrition Survey (11). Pakistan also had the lowest mean WAZ (-1.4) and the highest prevalence of anemia in infants (88%) (12) compared with other cohorts in the study. Comparisons of home environment among MAL-ED sites found that children from Pakistan had the highest food insecurity scores (13), the shortest duration of exclusive breastfeeding (14) and the highest frequency of reported coughing (27%) (15). The prevalence of acute lower respiratory infections (ALRI) and ear pain were 6 and 7 times higher, respectively, compared with the next highest site (India) (15). In the MAL-ED cohort of Pakistan, persistent infection with *Giardia* was found to be associated with lower weight-for-age and length-for-age Z scores at 2 years (16). Although associations of other nutritional and infectious indicators, have been reported for other MAL-ED sites (8–10, 17, 18) similar analysis

had not previously been performed for Pakistan after having detected field bias in length/height data collection.

Undernutrition is a major driver of health and economic consequences in Pakistan, and given stunting rates of 40%, wasting stagnating at around 15–17%, this is estimated to result in an approximate 3% loss of annual gross domestic product (19). Given that the highest incidence of stunting and wasting occurs in infancy (7), our objectives were to explore socio-demographic, nutrition, and infection factors in the first year of life and their association with anthropometry at 5 years in children from Pakistan.

2. Methods

This is a secondary analysis of data from the MAL-ED cohort of children from Pakistan, which recruited 277 healthy singleton newborns (≤ 17 days) from the Naushahro Feroze district in the Sindh province between January 2010 and February 2012 (11). Children were followed up to 66 months of age as shown in Figure 1, with a final available sample of 237 children at 54–66 months (86% of the original cohort). Length and weight were measured by trained personnel following standard procedures as previously described (8). A rigorous revisiting of length/height individual trajectories was performed, eliminating observations with possible bias during field data collection.

Our conceptual framework (Figure 2) identified possible early factors at 0–11 months of age that have known associations with child growth in Pakistan (20) or the MAL-ED cohort in other countries (8–10): (a) biological drivers (low birth weight), (b) adverse socio-demographic factors (c) inappropriate breastfeeding and weaning practices, (d) biomarkers of micronutrient deficiencies (iron indicators, vitamin A, zinc and iodine concentrations), (e) history of illness, and (f) biomarkers of infection and environmental enteropathy. These factors were grouped in clusters for further analyses.

2.1. Possible early determinants of impaired growth

- (a) Biological drivers: Birth weight data was not available, but we controlled analyses for the first available weight, measured between 0 and 17 days of age. Early length data was missing for more than half of the sample ($n = 111$ infants) and was not used for analyses.
- (b) Socio-demographic factors: number of assets (1–8 score including the sum of: bank account, chair, refrigerator, table, separate kitchen, TV, mattress, < 2 people per room); food insecurity (mild, moderate, severe), material/kind of floor, roof walls and toilet (categorical variables); having sanitation at home (yes/no), household income (rupees/month) and number of people per room (continuous variables). Information on income, assets, maternal education, house characteristics (floor, roof and toilet material, having water/sanitation) has been previously reported (13). A nine-question survey adapted by the Food and Nutrition Technical Assistance (FANTA) project for use in low resource settings was used to assess food insecurity. The scale uses a four-week recall period and captures three dimensions of the access component of household food insecurity: anxiety and uncertainty about household food access, insufficient quality, and insufficient food intake and its physical consequences, that were used to categorize households as food access secure, and mildly, moderately

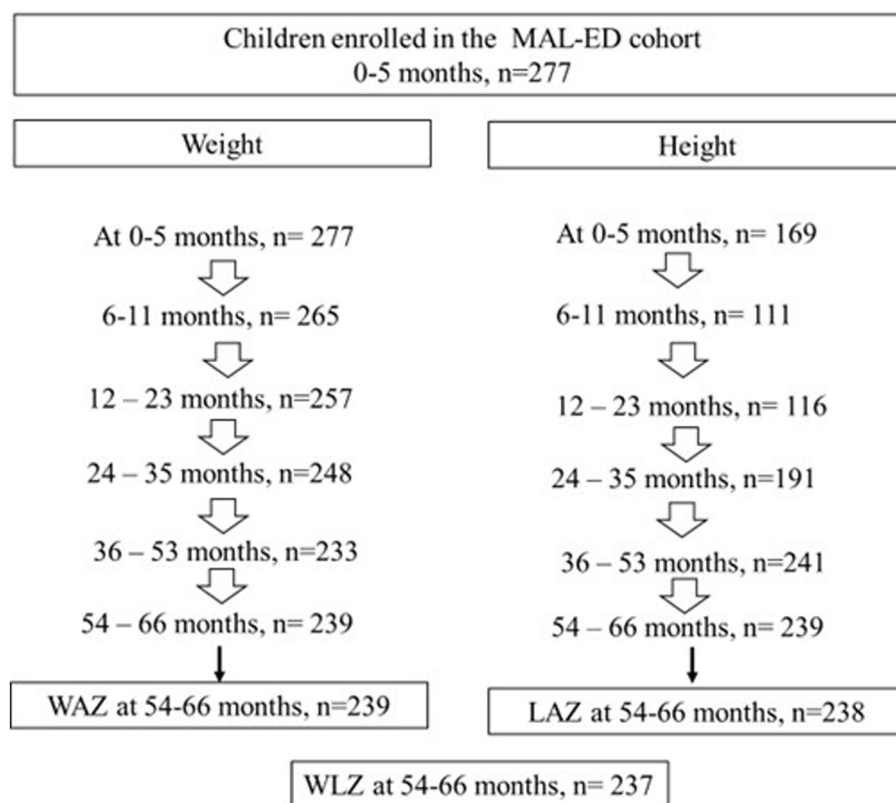


FIGURE 1

Sample size flow chart of children enrolled and followed between 0 and 5 years of age in the MAL-ED cohort in Pakistan.

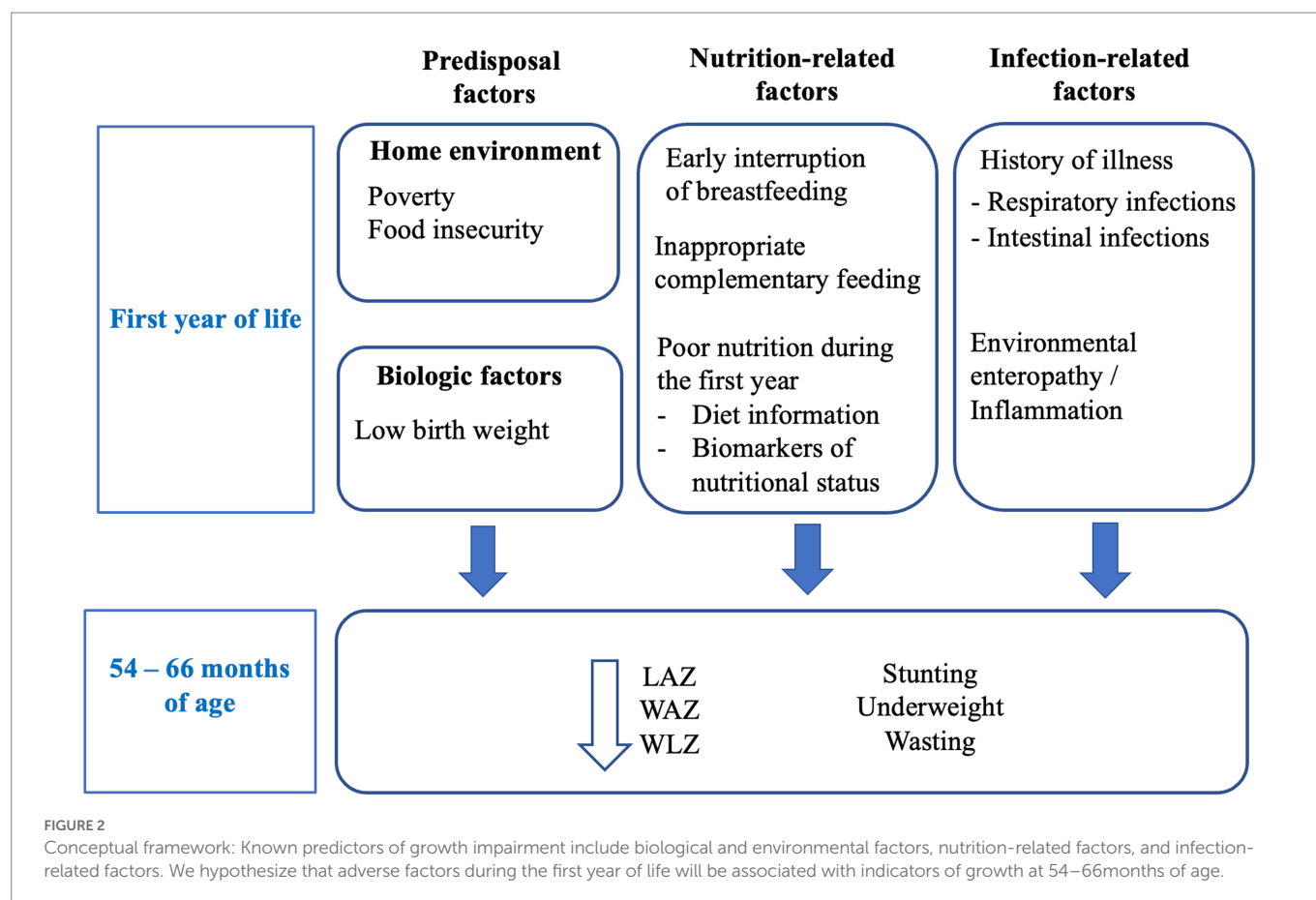
and severely food access insecure (13). Socio-demographic variables did not differ between children with and without anthropometry information.

(c) Breastfeeding and weaning practices: Number of days receiving exclusive, predominant, partial or no breastfeeding (continuous variables), age of weaning, age at which non-milk fluids, milk and solid/semisolid foods were started (continuous variables), frequency (times/d) of breastfeeding, formula, milk, and meals between 0 and 5 months and between 6 and 8 months. Intake (yes/no) and age of starting different food groups: non-milk fluids, tea/coffee, formula, milk, grains, roots, legumes, fruits/vegetables, sweets, baby commercial foods, dairy products, animal-source foods. Groups of foods combinations (staples alone or in combination with legumes, food from animals, dairy products, fruits/vegetables) received between 6 and 11 months and the age of starting different foods were also explored. The age at which food groups (non-milk fluids, tea/coffee, milk, grains, legumes, dairy products, and animal-source foods) were introduced into child's diet were previously described (21). More children with anthropometry data were fed with animal milk (74.5%) than children without anthropometry data (57.1%, $p=0.032$). Children included in analyses had an earlier introduction of sweets in their diet [median: 5.9 months, range: (0.9–22.0) vs. 6.9 months (2.1–10.2), $p=0.009$]. Other variables did not differ by having or not anthropometry data.

(d) Blood-urine biomarkers (in a subset of the population): alpha-1 glycoprotein (AGP, mg/dL), hemoglobin (g/dL), ferritin ($\mu\text{g/L}$), serum transferrin receptor (sTfR, mg/L), vitamin A ($\mu\text{g/dL}$), zinc ($\mu\text{mol/L}$), and urinary iodine ($\mu\text{mol/L}$) were assessed (21). Biomarkers did not differ in children who had and had not anthropometry data.

(e) Presence and severity of illness: mean days/month presenting fever (as reported by mothers, and temperature $>38^{\circ}\text{C}$ as taken by interviewer), somnolence, low appetite, ALRI, diarrhea, ear pain/pulling, taking antibiotics; number of ALRI and diarrheal episodes, mean severity score of diarrheal episodes, mean proportion of days with diarrhea taking oral rehydration therapy (ORT). They were reported by mothers and by trained interviewers, together with the intake of oral rehydration solutions and antibiotics, and the need of hospitalization (22). Of note, diarrhea was defined as ≥ 3 loose stools in 24-h, or at least 1 loose stool with blood present, with episodes of diarrhea were separated by at least 3 diarrhea-free days (22). The severity of the episode was scored adding symptoms' scales, taking in account duration (1: 2–4 days, 2: 5–7 days, 3: 8+ days), number of loose stools (1: <5 , 2: 5–7, 3: 8+), days with vomit (1: 1 day, 2: 2 days, 3: 3+ days), dehydration (2: some dehydration, 3: severe dehydration), and presence of fever (0: no, 1: reported fever, 3: temperature $>37.5^{\circ}\text{C}$ (23). Acute low respiratory infection (ALRI) was defined as the presence of cough and/or shortness of breath plus high respiratory rate (22). A higher proportion of children with data on anthropometry presented with diarrhea (99.2% vs. 84.2%, $p<0.0001$), vomiting (96.2% vs. 81.6%, $p<0.0001$), ALRI (95.8% vs. 81.6%, $p=0.001$) and ear pain/pulling (82.8% vs. 60.5%, $p=0.001$) than those without anthropometry data. Days per month presenting any illness did not differ between children with and without anthropometry information.

(f) Stool samples for microbiological analyses (24) and for fecal biomarkers of environmental enteropathy (25) were also collected:



Pathogens: detection in stools at least once between 0 and 11 months of: Human astroviruses, human adenoviruses, *Norovirus*, *Aeromonas*, *Escherichia coli* (and pathotypes: enteroaggregative, enteroinvasive, enterotoxigenic, enteropathogenic, enterohemorrhagic and shiga-toxin producing *E. coli*), *Salmonella*, *Shigella*, *Vibrio*, *Campylobacter*, *Cryptosporidium*, *Entamoeba histolytica*, and *Giardia lamblia*. Other pathogens studied had too low positive observations to be included in analyses: *Endolimax nana* ($n=2$), *Iodamoeba buetschlii* ($n=3$), *Yersinia enterocolitica* ($n=1$), *Balantidium coli* ($n=0$). A higher proportion of children with anthropometry data were found positive for *Campylobacter* (98.3%) compared with those without anthropometry data (85.7%, $p=0.002$).

Indicators of environmental enteropathy: myeloperoxidase (ng/mL), neopterin (nmol/L) and alpha-1 antitrypsin (mg/g). Given the lack of cut-offs indicating abnormal concentrations of fecal biomarkers in early infancy, if fecal biomarkers entered ≥ 500 repetitions, the Youden cut-point, which maximizes the sum of sensitivity and specificity (26) was calculated for the detection of the specific outcome of interest. Myeloperoxidase concentration was higher in children not included in analyses [median: 11.5 ng/mL, range (0.2–84.4 ng/mL)] compared with children with anthropometry information [2.2 (0.2–85.8) ng/mL]. Neither neopterin nor alpha-1 antitrypsin differed.

2.2. Statistical analyses

Outcome variables: Z-scores for weight-for-age (WAZ), height for age (HAZ), and weight for height (WHZ) at 5 years were calculated

applying WHO reference data using STATA 16 (27) and analyzed as continuous variables, as well as their derivative binary variables underweight, stunting and coexistent underweight + stunting. The small number of wasted children at 5 years (5.5%) did not allow us to run models for this variable.

Spearman correlations among independent variables were explored for descriptive and modeling purposes. Descriptive statistics of variables for children having information on weight or height at 54–66 months were run ($n=239$). Fisher's exact, χ^2 or Kruskal-Wallis's test were performed according to variable's nature to identify if they differed between children with ($n=239$) and without anthropometry data ($n=38$).

2.2.1. Variable pre-selection

Based on our conceptual framework, variables were aligned in groups of possible predictors. In order to select covariates that would best fit future modeling and discard noise variables (28), we used a bootstrapping procedure based on a backward stepwise algorithm with 1,000 repetitions (29), where groups of variables were tested avoiding the simultaneous inclusion of highly correlated variables, which were run separately.

2.2.2. Univariate models

Only variables entering ≥ 500 repetitions were further analyzed in: (a) univariate models for binary (stunting, underweight, stunting + underweight) and (b) continuous (LAZ, WAZ, and WLZ) outcomes. We used generalized linear models (GLM) Poisson and linear regression models, respectively. Dichotomous covariates with <10 events per

variable were excluded (30). The univariate modeling process is shown in detail as [Supplementary Material](#).

2.2.3. Multivariable models

Variables with value of p is less than 0.05 in univariate models were further analyzed in multivariable regression models. We controlled all models for gender, first available weight and income (only socio-demographic variable entering ≥ 500 repetitions). GLM Poisson regression with robust standard errors were used to estimate risk ratios for binary outcomes, and multiple linear regression was used for continuous outcome variables. Backwards stepwise elimination (initially specifying value of $p < 0.10$, and decreasing value of p to < 0.05 depending on the number of variables entering) were used to obtain final models including no more than 10 variables to avoid overfitting, using variables that are likely to be amenable to and influenced by interventions. Only final models are shown. Final models were tested for collinearity using a variance inflation factor < 10 and a condition number < 30 (31). Tests for covariate-dependent missingness (CDM) were conducted, allowing unequal variances between missing-value patterns (32).

3. Results

Characteristics of the population are described in [Tables 1, 2](#); [Figures 3, 4](#).

3.1. Socio-demographic characteristics and food security

Characteristics of children's families recruited in the study are shown in [Table 1](#). Children came from families with low incomes, where 23.4% of them earned $< 8,000$ rupees/month (equivalent to 100 USD), the minimal wage at the time of the study. Also, 81.5% lived with some degree of food insecurity. Overcrowding was common, with > 3 people per room observed in 75% of homes. Although all households had water from tube well or borehole, 15% did not have sanitation. Among mothers, 50% had not received any education. Gender distribution of our sample showed similar proportions of boys and girls (50.4% girls).

3.2. Prevalence of stunting, underweight and wasting

First available weights (mean $\pm$ SD: 2.8 ± 0.5 kg between 0 and 17 days) found that 20.9% of children were below 2.5 kg. Among children with length available during the first month of age ($n = 111$), 39 (29.5%) were already stunted. Of note, most of these children continued to be stunted at 54–66 months ($n = 25$, 64.1%).

[Figure 3](#) shows trajectories of WAZ, LAZ and WLZ of children from 0–5 years. Mean yearly lengths-for-age indicate that prevalence of stunting increased with age from 39.6% in the first year to 55.5% at 54–66 months. Similarly, underweight increased from 30% in the first year to 44.4% at 54–66 months. The presence of wasting (5.5% at 54–66 months) did not reflect the high proportions of underweight and stunting, as parallel and symmetric low weights and heights were

TABLE 1 Population characteristics.

Gender, girls	$n=120$ (50.4%)
¹ Socio-demographic characteristics ($n = 239$)	Median (min-max) or prevalence, %
² Sum of assets	2 (0–8)
Maternal education, years	1 (0–16)
Non-educated mothers	49.8%
No. people living in the house	10 (3–29)
Floor material	
Earth, sand, clay, mud, dung	69.5%
Wood, ceramic, cement	30.5%
Roof material	
Thatch	17.2%
Metal, wood	12.1%
Brick, tiles	70.7%
Having sanitation at home	84.9%
Type of toilet	
No facility	19.6%
Pit latrine	8.4%
Flush to septic/sewer system	72.0%
³ Monthly income (rupees $\times 10^3$), quantiles	12.5 (2.0–70.0)
$< 8 \times 10^3$ rupees	23.4%
8–12.5	28.4%
> 12.5 –20	26.4%
> 20 –70	21.8%
⁴ Food insecurity category	
No food insecurity	18.4%
Mild	9.2%
Moderate	64.0%
Severe	8.4%

¹Socio-demographic information was collected at recruitment. ²Items included in the count of assets were mattress, chair, table, TV, refrigerator, bank account, having a separate kitchen and < 2 people per room. ³One minimal wage at the time of the study was 8,000 rupees. ⁴Food insecurity questionnaires were administered at 0 and 6 months of age. Mean scores were used for analyses.

observed in this population, but 37.8% had coexisting stunting and underweight. Overlapping proportions of stunting, underweight and wasting at 54–66 months are shown in [Figure 4](#).

3.3. Breastfeeding and complementary feeding practices

Feeding practices are summarized in [Table 2](#). Although all children received breastfeeding for some time between 0 and 5 months with a median frequency of 16 times/d, the median duration of exclusive breastfeeding was only 14 days. During their first month of age, most children (80.8%) received non-milk fluids (sugar water, thin soup or broth, fruit juice, tea, other fluids), animal milk/formula (29.2%) or both (25.5%). Between 0 and 5 months, most children received animal milk (74.5%, median frequency 2

TABLE 2 Feeding practices and infections of Pakistani children during the first year of life.

¹ A. Breastfeeding practices (<i>n</i> =239)	Children receiving specific feeding (any duration) between 0 and 5 months		# Days between 0 and 5 months receiving specific feeding	
			Median (range)	IQR
Exclusive breastfeeding			14 (0–154)	8, 20
Predominantly breastfeeding			41 (0–164)	8, 89
Partial breastfeeding			99 (0–168)	41, 140
Frequency of feeding per day 0–5 months	<i>n</i>	%	Times/day between 0 and 5 months receiving specific feeding	
Breastmilk	239	100.0	16 (4–25)	14, 17
Formula	31	13.0	3 (1–16)	2, 4
Animal milk	178	74.5	2 (1–14)	1, 4
² B. Complementary feeding (<i>n</i> = 239)	Children receiving specific foods between 6 and 11 months (<i>n</i> = 258–277)		Age in months of complementary foods introduction	
	<i>n</i>	%	Median (range)	IQR
Non-milk fluids (e.g., water, tea/coffee, fruit juice, broth)	239	100.0	0.7 (0–10.1)	0.4, 2.0
Milk	153	64.3	1.0 (0–15.9)	0.5, 2.5
Formula	13	5.5	1.9 (0.9–7.0)	0.9, 3.0
Solid/semisolid foods	232	97.5	3.5 (0.03–10.0)	1.8, 4.8
Grains (e.g., rice, porridge, bread, noodles) (<i>n</i> = 232)	225	97.0	5.0 (0.8–10.9)	4.0, 6.0
Sugary foods (e.g., pastries, cakes, biscuits) (<i>n</i> = 232)	219	94.4	5.9 (0.9–22.0)	3.9, 6.9
Commercial baby foods (<i>n</i> = 232)	23	9.9	7.0 (4.0–8.1)	6.0, 7.9
Dairy products (e.g., cheese, yogurt) (<i>n</i> = 232)	10	4.3	9.0 (0.9–17.1)	8.9, 9.1
Roots (e.g., potatoes, yams, manioc) (<i>n</i> = 232)	80	34.5	9.1 (4.9–22.1)	7.9, 11.9
Fruits/vegetables (<i>n</i> = 232)	20	8.6	13.0 (4.0–59.5)	9.9, 17.0
Legumes (<i>n</i> = 232)	13	5.6	20.9 (3.8–60.1)	15.9, 27.9
Animal-source foods (<i>n</i> = 232)	14	6.0	22.0 (6.0–59.8)	13.2, 28.1
Age (months) stopping breastfeeding (<i>n</i> = 232)	230		19 (2–35)	14, 24
³ C. Biomarkers (evaluated between 6 and 8 months)	# Samples	Deficiency, cut-off	Concentrations of blood/urine biomarkers	
		%	Median (range)	IQR
Hemoglobin (g/dL)	220	70.9% <11.0 g/dL	10.3 (7.0–14.5)	9.3, 11.1
Ferritin (μg/L)	185	22.0% <12 μg/L	22.5 (2.0–293.0)	14.0, 40.0
sTfR (mg/L)	216	1.4% >8.3 mg/L	2.9 (0.2–10.0)	1.7, 4.5
Vitamin A (μg/dL)	206	53.4% <20 μg/dL	19.3 (4.6–66.9)	14.4, 28.5
Zinc (μmol/L)	215	80.0% <10.7 μmol/L	8.9 (4.7–22.8)	7.8, 10.4
Urine iodine (μmol/L)	233	13.3% <100 μmol/L	240.4 (29.9–863.1)	143.2, 374.4
AGP (mg/dL)	215	36.7% >100 mg/dL	89 (1–223)	65.0, 115.0
⁴ D. Reported illness information (<i>n</i> = 239)	Children presenting illness at least once between 0 and 11 months		Days per month having illness or number of hospitalizations between 0–11 months	
	<i>n</i>	%	Median (range)	IQR
Any illness	239	100	23 (5–30)	17, 26
Diarrhea	237	99.2	3 (0–25)	1.5, 5.6
Vomiting	230	96.2	1 (0–30)	0.4, 5.9
Acute low respiratory infection	229	95.8	1 (0–4)	0.2, 1.1
Ear pain/pulling	198	82.8	1 (0–26)	0.2, 3.9
Receiving antibiotics	238	99.6	5 (0–18)	3.2, 8.0
Hospitalized in the first year	13	5.4	In <i>n</i> = 13: 2 (1–8)	2, 4

(Continued)

TABLE 2 (Continued)

E. Fecal biomarkers, 0–11 months (<i>n</i> = 239)			Fecal concentration	
	<i>n</i>		Median (range)	IQR
Myeloperoxidase (ng/mL)	239		2.2 (0.2–85.8)	1.1, 7.4
Neopterin (nmol/L)	239		2.2 (0.02–56.9)	1.2, 4.9
Alpha-1-antitrypsin (μg/g)	239		4.7 (0.1–84.5)	1.8, 9.3
F. Pathogens in stools during diarrheal episodes (0–11 months) (<i>n</i> = 239)		Children (+) for pathogens at least once between 0 and 5 months	Children (+) for pathogens at least once between 6 and 11 months	
	<i>n</i>	%	<i>n</i>	%
<i>Escherichia coli</i>	239	100	239	100
Enterococci	214	89.5	216	90.4
Enteropathogenic	97	40.6	124	51.9
Enterotoxigenic	56	23.4	94	39.3
Shiga-toxin producing	10	4.2	8	3.3
Enterohemorrhagic	10	4.2	8	3.3
Enteroinvasive	1	0.4	5	2.1
<i>Campylobacter</i>	192	80.3	231	96.6
<i>Norovirus</i>	122	51.0	127	53.1
<i>Giardia</i>	104	43.5	176	73.6
<i>Aeromonas</i>	84	35.1	106	44.3
<i>Cryptosporidium</i>	71	29.7	78	32.6
Astroviruses	58	24.3	48	20.1
Adenoviruses	29	12.1	53	22.2
<i>Rotavirus</i>	32	13.4	33	13.8
<i>Vibrio</i>	18	7.5	20	8.4
<i>Shigella</i>	3	1.3	15	6.3
<i>Salmonella</i>	5	2.1	18	7.5
<i>Entamoeba histolytica</i>	4	1.7	8	3.3

¹Daily breastfeeding information was available. Mean days per month children were fed exclusive, predominantly, partial or no breastfeeding were calculated for the first 6 months of life. ²Dietary information was recorded monthly during the first 8 months of life and food frequency questionnaires took place quarterly between 8 and 12 months of age. Compiled information was used to assess complementary feeding practices. ³An average of 3 blood/urine samples for nutritional biomarkers were taken between 6 and 8 months of age. Means of these three samples were used for calculating statistics. ⁴Daily illness information was recorded. Mean days per month presenting illness were calculated. ⁵Fecal biomarkers were available biweekly from 0 to 12 months of age. Mean concentrations during this period were calculated. ⁶Detection of pathogens in stools was performed monthly from 0 to 12 months of age.

times/d) or formula (13.0%, median frequency 3 times/d) starting at a median age of 1 month (Table 2A).

Complementary feeding with solid/semisolid foods started at a median age of 3.5 months, and was composed mainly of grains (rice, porridge, bread, noodles) and sugary foods (pastries, cakes, biscuits). After 6 months, children started receiving other dairy products (e.g., cheese, yogurt) and roots, whereas other nutritious foods such as legumes, fruits, and animal-source foods (animal flesh, eggs) were mostly introduced after 1 year of age (Table 2B).

3.4. Nutritional biomarkers

In the subsample of children (*n* = 186–220) with blood samples taken between 6 and 8 months of age, 89.0% had zinc deficiency, 71.3% had anemia, 53.7% had vitamin A deficiency, 22.1% had low ferritin but only 1.2% had elevated sTfR. Moreover, urine iodine was low in 13.2% of children. Finally, inflammation indicated by AGP >100 mg/dl was found in 38.7% (Table 2C). Of note, among children with anemia,

88.4% had also zinc deficiency, 57.4% had low vitamin A, 43.1% had elevated AGP, and 25.8% were iron deficient.

3.5. Illness information

On average, children spend 3 weeks/month presenting some type of illness, notably diarrhea, vomiting, respiratory infection, or ear pain/pulling, and nearly all of them received at least one cycle of antibiotics in the first month of life (Table 2D).

Microbiological stool sample analyses showed that the predominant pathogens present during diarrheal episodes were Enterococci and Enteropathogenic *E. coli*, *Campylobacter* and *Norovirus*, which were isolated in more than half of children with diarrhea between 0 and 11 months (Table 2F).

3.5.1. Fecal biomarkers

Concentrations of fecal biomarkers myeloperoxidase, neopterin and alpha-1-antitrypsin are shown in Table 2E. When assessing

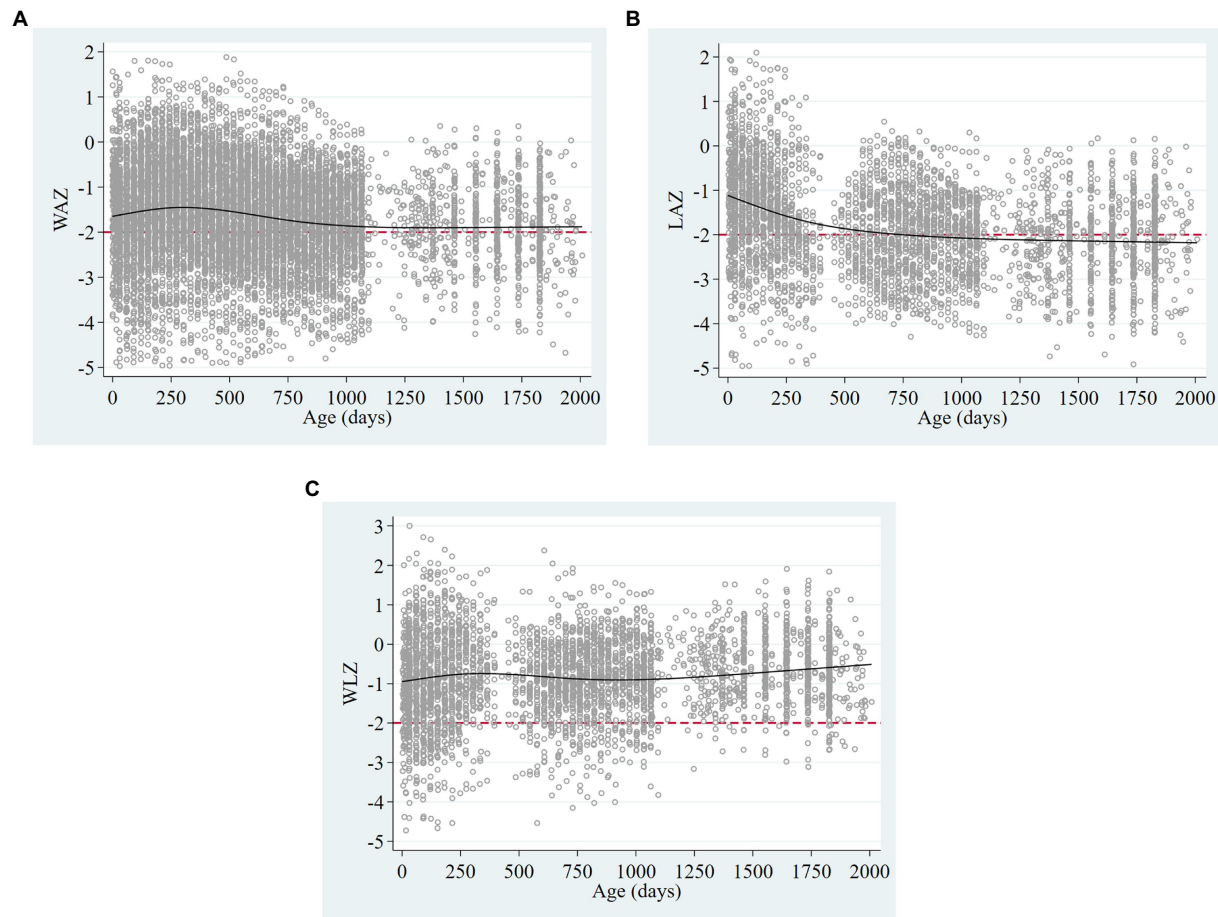


FIGURE 3 Scatter plots of (A) weight for age, (B) length/height, and (C) weight for length/height Z-scores, showing restricted cubic splines (solid black lines) and the cut-off of -2 standard deviations (dashed red lines) in children 0–5years in the MAL-ED cohort of Pakistan.

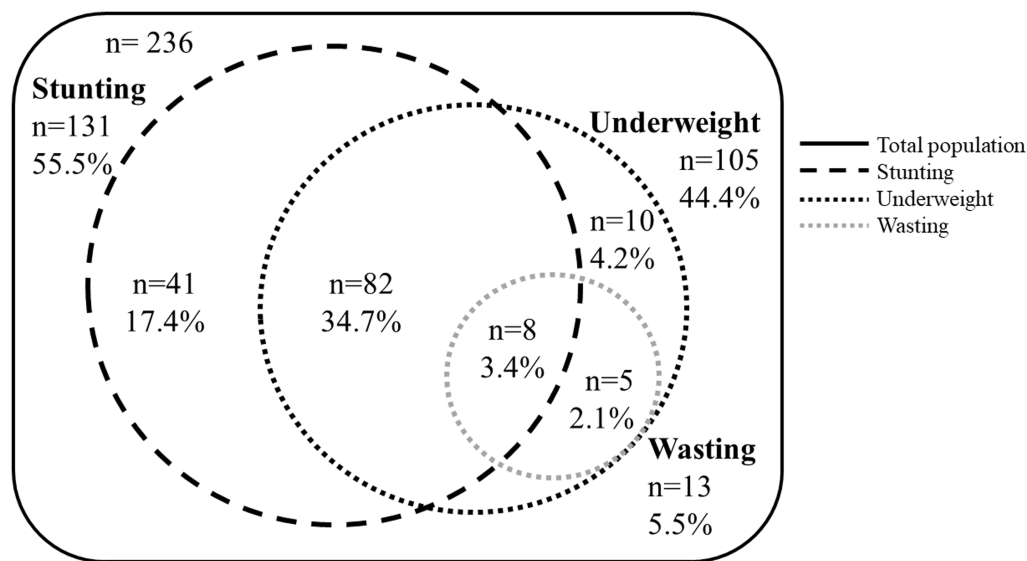


FIGURE 4 Venn diagram showing overlapping proportions of stunting, underweight, and wasting in children 54–66months from Pakistan.

correlations between mean fecal biomarkers during the first year with indicators of infection/inflammation, neither mean myeloperoxidase nor neopterin concentrations correlated with serum AGP concentrations, but mean alpha-1-antitrypsin had a weak negative correlation with AGP ($r_s = -0.16$, $p = 0.015$). Fecal biomarkers did not correlate with the number of diarrheal episodes and did not differ by the presence/absence of intestinal pathogens in the first year. Higher mean concentrations of myeloperoxidase ($r_s = -0.13$, $p = -0.029$), neopterin ($r_s = 0.17$, $p = 0.004$) and alpha-1-antitrypsin ($r_s = 0.32$, $p < 0.0001$) were correlated with days/month presenting vomiting, and higher neopterin ($r_s = 0.12$, $p = 0.04$) and alpha-1 antitrypsin ($r_s = 0.19$, $p = 0.001$) were correlated with more days/month presenting any illness during the first year of life. The cut-point of elevated neopterin for the detection of underweight using the Youden index was calculated at >6.8 nmol/L, and for the detection of underweight + stunting was >2.4 nmol/L.

3.6. Early predictors of impaired growth at 54–66 months of age

Univariate models for stunting, underweight and stunting + underweight are presented in [Supplementary Tables S1–S3](#), respectively. Results of multivariate GLM-Poisson regression models are as follows:

3.6.1. Stunting

Among variables selected using univariate models, only the average of ≥ 2 days per month presenting ALRI during the first year of life was associated with increased risk of stunting at 54–66 months ([Table 3A](#)). Variables with weak evidence of an association with increased risk of stunting at 54–66 months (entered the model with value of $p > 0.05$) were being a girl, lower weight during the first years of life, lower income, and history of hospitalization in the first year.

3.6.2. Underweight

The multivariable regression model for underweight at 54–66 months indicated that a higher weight in the first days of life, receiving formula in the first 6 months and receiving commercial baby foods between 6 and 11 months were associated with decreased risk of underweight at 54–66 months. Higher concentrations of sTfR (but below pathological concentrations, between 4.6 and 10 mg/L) were also associated with decreased risk of underweight at 54–66 months. Having *Campylobacter* infection in the first 6 months and having mean concentrations of neopterin >6.8 nmol/L in the first year of life were associated with increased risk of underweight at 54–66 months ([Table 3B](#)). Neither gender nor income appeared to be associated with underweight at 54–6 months.

3.6.3. Underweight + stunting

When looking at early factors that might drive the presence of both stunting and underweight at 54–66 months compared with non-stunted/non-underweight children, having lower weight the first days of life, family income in the lower quantiles, more days/month presenting ALRI and neopterin >6.8 nmol/L in the first year (Youden's cut-point for underweight) were associated with higher risk of underweight + stunting at 54–66 months ([Table 3C](#)). The Youden's cut-point of neopterin >2.4 nmol/L for the detection of underweight + stunting at 54–66 months was not associated with this outcome when running the univariate or multivariate model. Gender was not

associated with the presence of underweight + stunting at 54–66 months, and “hospitalized between 0 and 11 months” showed weak evidence of an association to increased risk of underweight + stunting at 54–66 months with a value of $p = 0.105$.

3.7. Early predictors of LAZ, WAZ, and WLZ at 54–66 months

Univariate models for LAZ, WAZ and WLZ are presented in [Supplementary Tables S4–S6](#), respectively. Results of multivariate linear regression models are as follows ([Table 4](#)):

3.7.1. LAZ

Increases in child length at 54–66 months were associated with a greater weight in the first days of life, higher family income, receiving formula and dairy products in the first 6 months of life, while lower child length was associated with having been hospitalized and the number of ALRI episodes during the first year of life. There was only weak evidence of an association between gender and LAZ ($p = 0.076$) ([Table 4A](#)).

3.7.2. WAZ

Higher weight at 54–66 months was associated with greater weight during the first days of life, having received baby commercial foods after 6 months and a higher sTfR (but below abnormal values, between 4.6 and 10 mg/L) ([Table 4B](#)). Other variables that entered ≥ 500 repetitions but only showed weak evidence of an association with WAZ were “gender,” “income,” and “mean days/month having low appetite in the first 5 months.”

3.7.3. WLZ

A higher weight-for-length was associated with greater weight during the first days of life, and with indicators of food availability during the complementary-food period. A too-early start of non-breast milk (1–2 months of age) was associated with lower WLZ at 54–66 months, but those children receiving baby commercial foods between 6 and 11 months and fluids such as sugar water, thin soup or broth or carbonated drinks between 0 and 11 months had higher WLZ at 54–66 months. sTfR in its highest quartile (4.6–10 mg/L) at 6–8 months was also associated with higher WLZ at 54–66 months. Neither gender nor income nor infection-related variables were associated with WLZ at 54–66 months ([Table 4C](#)).

4. Discussion

This study explored early predictors of undernutrition at 5 years among socio-demographic, breastfeeding and complementary feeding practices, illness, intestinal pathogens and indicators of environmental enteropathy during the first year of age in children from Pakistan. Chronic undernutrition was highly prevalent, evidenced by high rates of stunting and underweight (but not wasting) at 5 years. The low adherence to exclusive breastfeeding, combined with an early start of weaning consisting of non-milk fluids (sugar water, thin soup or broth, fruit juice, tea), and “empty-caloric” foods added to frequent and persisting infections, characterized the infancy of this cohort. Main findings that distinguished this cohort from other MAL-ED studied countries (10) included that infection during infancy, mainly lower

TABLE 3 Multivariate logistic regression models for (A) stunting, (B) underweight, and (C) combined stunting + underweight compared with non-stunted/ non-underweight children at 54–66 months.

(A) Model for stunting at 54–66 months	RR	95% CI	Value of <i>p</i>
Girls (<i>n</i> = 120)	1.26	0.99, 1.60	0.054
First available weight, kg	0.82	0.64, 1.05	0.118
Income (rupees × 10 ³ , quantiles) base: 20.1–70 (<i>n</i> = 52)			
<8 (<i>n</i> = 56)	1.38	0.97, 1.96	0.074
8–12.5 (<i>n</i> = 67)	1.31	0.92, 1.85	0.130
12.6–20 (<i>n</i> = 63)	1.09	0.75, 1.58	0.645
Hospitalized at least once between 0 and 11 months (<i>n</i> = 13)	1.32	0.98, 1.78	0.070
Mean days/month presenting ALRI between 6 and 11 months base: 0 (<i>n</i> = 119)			
1 (<i>n</i> = 94)	1.05	0.82, 1.36	0.679
2 (<i>n</i> = 16)	1.55	1.09, 2.20	0.015
3–4 (<i>n</i> = 9)	1.71	1.22, 2.41	0.002
Constant	0.50	0.20, 1.24	0.137
(B) Model for underweight at 54–66 months	RR	95% CI	value of <i>p</i>
Girls (<i>n</i> = 111)	1.05	0.81, 1.37	0.685
First available weight, kg	0.33	0.23, 0.46	<0.0001
Income (rupees × 10 ³ , quantiles) base: 20.1–70 (<i>n</i> = 44)			
<8 (<i>n</i> = 51)	1.20	0.82, 1.77	0.347
8–12.5 (<i>n</i> = 62)	1.22	0.83, 1.80	0.314
12.6–20 (<i>n</i> = 59)	0.97	0.64, 1.47	0.897
<i>Campylobacter</i> (+) at least once between 0 and 5 months (<i>n</i> = 174)	1.78	1.17, 2.70	0.007
Received formula between 0 and 5 months (<i>n</i> = 25)	0.53	0.30, 0.96	0.036
Received commercial foods between 6 and 11 months (<i>n</i> = 23)	0.31	0.15, 0.62	0.001
sTfR (mg/L), quantiles base: 0.2–1.8 mg/L (<i>n</i> = 58)			
1.81–3.0 (<i>n</i> = 54)	0.96	0.67, 1.37	0.811
3.1–4.5 (<i>n</i> = 52)	1.01	0.73, 1.38	0.965
4.6–10.0 (<i>n</i> = 52)	0.55	0.35, 0.85	0.008
Neopterin 0–11 months >6.8 nmol/L (<i>n</i> = 21)	1.76	1.32, 2.35	<0.0001
Constant	5.99	1.98, 18.18	0.002
(C) Model for underweight + stunting at 54–66 months	RR	95% CI	value of <i>p</i>
Girls (<i>n</i> = 97)	1.24	0.92, 1.67	0.151
First available weight, kg	0.53	0.38, 0.73	<0.0001
Income (rupees × 10 ³ , quantiles) base: 20.1–70 (<i>n</i> = 49)			
<8 (<i>n</i> = 55)	2.08	1.25, 3.47	0.005
8–12.5 (<i>n</i> = 53)	1.77	1.05, 2.98	0.032
12.6–20 (<i>n</i> = 40)	1.34	0.77, 2.37	0.299
Hospitalized between 0 and 11 months (<i>n</i> = 11)	1.40	0.94, 2.10	0.101
Mean days/month presenting ALRI between 6 and 11 months base: 0 (<i>n</i> = 98)			
1 (<i>n</i> = 80)	1.07	0.77, 1.47	0.695
2 (<i>n</i> = 13)	1.41	0.85, 2.32	0.179
3–4 (<i>n</i> = 6)	1.63	1.08, 2.44	0.019
Neopterin 0–11 months >6.8 nmol/L (<i>n</i> = 23)	1.56	1.13, 2.26	0.009
Constant	0.99	0.32, 3.09	0.986

(A) Model *n* = 238, VIF = 1.02, condition number = 18.79. (B) Model *n* = 210, VIF = 1.07, condition number = 20.55. (C) Model *n* = 197, VIF = 1.02, condition number = 19.08. Little's CDM test: *p* = 0.99.

TABLE 4 Multivariate linear regression models for (A) LAZ, (B) WAZ, and (C) WLZ.

(A) Model for LAZ at 54–66months	Coeff±SE	95% CI	Value of p
Girls	−0.22 ± 0.12	−0.46, 0.02	0.076
First available weight, kg	0.53 ± 0.12	0.29, 0.78	<0.0001
Income (rupees × 10 ³ , quantiles) Base: 20.1–70 (<i>n</i> = 49)			
<8 (<i>n</i> = 55)	−0.43 ± 0.18	−0.79, −0.08	0.016
8–12.5 (<i>n</i> = 53)	−0.37 ± 0.17	−0.71, −0.03	0.031
12.6–20 (<i>n</i> = 40)	−0.16 ± 0.17	−0.50, 0.18	0.361
Received formula between 0 and 5 months (<i>n</i> = 31)	0.63 ± 0.18	0.27, 0.99	0.001
Received dairy products between 0 and 5 months (<i>n</i> = 19)	0.49 ± 0.21	0.08, 0.91	0.020
Hospitalized at least once between 0 and 11 months (<i>n</i> = 13)	−0.83 ± 0.28	−1.38, −0.28	0.003
Number of ALRI episodes between 0 and 11 months base: 0–1 (<i>n</i> = 47)			
2–4 (<i>n</i> = 124)	−0.37 ± 0.15	−0.67, −0.07	0.017
5–10 (<i>n</i> = 67)	−0.50 ± 0.18	−0.85, −0.15	0.005
Constant	−2.80 ± 0.47	−3.72, −1.88	<0.0001
(B) Model for WAZ at 54–66 months	Coeff. ± SE	95% CI	Value of <i>p</i>
Girls (<i>n</i> = 111)	−0.05 ± 0.11	−0.28, 0.16	0.610
First available weight, kg	0.69 ± 0.11	0.47, 0.92	<0.0001
Income (rupees × 10 ³ , quantiles) base: 20.1–70 (<i>n</i> = 44)			
<8 (<i>n</i> = 51)	−0.12 ± 0.17	−0.45, 0.21	0.487
8–12.5 (<i>n</i> = 62)	−0.29 ± 0.16	−0.61, 0.03	0.078
12.6–20 (<i>n</i> = 59)	−0.05 ± 0.16	−0.37, 0.27	0.749
Receiving baby commercial foods between 6 and 11 months (<i>n</i> = 23)	0.69 ± 0.11	0.41, 1.12	<0.0001
Mean days/month presenting low appetite between 0 and 5 months base: 0 (<i>n</i> = 157)			
1 (<i>n</i> = 45)	−0.12 ± 0.15	−0.42, 0.17	0.408
2–8 (<i>n</i> = 14)	−0.40 ± 0.25	−0.88, 0.09	0.107
sTfR (mg/L), quantiles base: 0.2–1.8 mg/L (<i>n</i> = 58)			
1.81–3.0 (<i>n</i> = 54)	0.22 ± 0.16	−0.10, 0.55	0.171
3.1–4.5 (<i>n</i> = 52)	0.10 ± 0.17	−0.24, 0.45	0.545
4.6–10.0 (<i>n</i> = 52)	0.59 ± 0.18	0.24, 0.94	0.001
Constant	−3.97 ± 0.43	−4.81, −3.13	<0.0001
(C) Model for WLZ at 54–66 months	Coeff. ± SE	95% CI	Value of <i>p</i>
Girls (<i>n</i> = 111)	0.12 ± 0.11	−0.09, 0.33	0.272
First available weight, kg	0.46 ± 0.11	0.23, 0.68	<0.0001
Income (rupees × 10 ³ , quantiles) base: 20.1–70 (<i>n</i> = 44)			
<8 (<i>n</i> = 50)	0.20 ± 0.17	−0.13, 0.53	0.235
8–12.5 (<i>n</i> = 61)	0.07 ± 0.16	−0.25, 0.38	0.669
12.6–20 (<i>n</i> = 59)	0.12 ± 0.16	−0.20, 0.44	0.460
Age starting milk base: 6–20 months (<i>n</i> = 24)			
<1 month (<i>n</i> = 105)	−0.28 ± 0.18	−0.64, 0.07	0.116
1–2 months (<i>n</i> = 53)	−0.44 ± 0.19	−0.83, −0.06	0.024
3–5 months (<i>n</i> = 28)	−0.01 ± 0.22	−0.42, 0.44	0.950
Received other fluids between 6 and 11 months (<i>n</i> = 153)	0.25 ± 0.12	0.004, 0.49	0.046
Received baby commercial foods between 6 and 11 months (<i>n</i> = 22)	0.67 ± 0.18	0.32, 1.03	<0.0001
Norovirus (+) at least once between 0 and 11 months (<i>n</i> = 153)	−0.19 ± 0.13	−0.44, −0.05	0.127

(Continued)

TABLE 4 (Continued)

(C) Model for WLZ at 54–66 months	Coeff. $\pm$ SE	95% CI	Value of p
sTfR (mg/L), quantiles base: 0.2–1.8 mg/L ($n = 57$)			
1.81–3.0 ($n = 54$)	0.31 $\pm$ 0.15	0.01, 0.61	0.043
3.1–4.5 ($n = 51$)	0.04 $\pm$ 0.15	–0.26, 0.34	0.786
4.6–10.0 ($n = 52$)	0.58 $\pm$ 0.15	0.27, 0.88	<0.0001
Constant	–2.39 $\pm$ 0.46	–3.390–1.47	<0.0001

(A) Model $n = 207$, $p < 0.0001$, adj. $R^2 = 0.24$, VIF = 1.07, condition number = 20.85. A preliminary backwards stepwise regression models specifying a $p < 0.10$, took out “receiving commercial products between 0 and 5 months” ($p = 0.243$) and “Mean days/month presenting vomit between 0 and 5 months.” The variable “Received ≥ 1 portion/d of protein between 8 and 11 months ($n = 12$)” added heteroscedasticity to the model and was taken out. (B) Model $n = 210$, $p < 0.0001$, adj. $R^2 = 0.266$, VIF = 1.15, condition number = 21.40. A preliminary backwards stepwise regression model specifying a $p < 0.10$, took out the variables “Taking ≥ 1 portion/d of animal-source foods between 8 and 11 months” and “Received ≥ 1 portion/d of fruit between 8 and 11 months.” (C) Model $n = 194$, $p < 0.0001$, adj. $R^2 = 0.22$, VIF = 1.04, condition number = 24.11. A preliminary backwards stepwise regression models specifying a $p < 0.05$, adjusting for gender, income, first weight and hospitalizations in the first 5 months, took out the variables “Received any quantity of animal-source foods/d between 8 and 11 months,” “Days presenting low appetite between 0 and 5 months,” “Mean days/month presenting ALRI between 0 and 5 months.” Little’s CDM test: $p = 0.99$.

respiratory infections, emerged as a strong predictor of LAZ at 5 years, whereas early infant intestinal colonization by *Campylobacter*, and one indicator of environmental enteropathy (neopterin >6.8 nmol/L) were associated with underweight at 5 years. Among nutritional indicators, initiation of complementary feeding with nutrient-dense foods was associated with higher WAZ and WLZ. Surprisingly, lower sTfR in the presence of anemia and iron deficiency during infancy was a predictor for impaired weight at 5 years, probably indicating a blunted erythropoietic response and early protein-calorie malnutrition, which may help to explain this unexpected association.

We acknowledge our limitation of a reduced sample size for children with accurate data on length/height between 0 and 35 months, but the rigorous data cleaning makes us confident of the accuracy of reported results. We lacked information on size at birth for many children, a possible parameter of importance for determining size at 5 years, and the lower sample size of children with blood biomarkers during the first year might have limited the power to find possible associations of specific nutrient deficiencies or systemic inflammation with growth at 5 years. Although the number of wasted children at 5 years did not allow to run analyses for this binary variable, the continuous WLZ was explored as continuous variable. Moreover, the richness of information gathered by the MAL-ED investigators allowed to elucidate important targets for future interventions to reduce child impairment in this population.

The prevalence of stunting (55.5%), underweight (44.4%) and wasting (5.5%) found in the MAL-ED cohort of children at 54–66 months from the Sindh province in 2015 was consistent with the prevalence reported by the Pakistan Demographic and Health Survey 2012–2013, where 45.6% stunting, 30.0% underweight and 4.8% wasting in children 48–59 months were reported (33). Although the use of stunting as an indicator of undernutrition has been debated (34), in particular the cut-off of -2 LAZ as definition of “chronic malnutrition” (35), it is clear that stunting reflects adverse growth conditions starting *in utero* and continuing during infancy, involving not only nutritional factors (36), but also the lack of appropriateness of children’s environment (37). Our results in this population with mean LAZ and WAZ <0 , indicate that children are not achieving their growth potential (35), where 37.8% had coexistent underweight and stunting. Moreover, deficiencies in micronutrients that are essential for growth and development were extremely high in this population, in particular anemia (71.3%) and zinc (89.0%) deficiencies.

The importance of coexisting wasting and stunting has been emphasized as an indicator of children with higher risk of mortality

(38, 39). Despite the low prevalence of wasting in our study, our results showed that predictors of WLZ were similar to those of WAZ. We also showed a high prevalence of concurrent low WAZ and LAZ. Our results add to the literature information on predictors of concurrent underweight and stunting, where most predictors of the coexistent condition overlap with those of stunting, suggesting a major contribution of illnesses (history of hospitalization and ALRI) and inflammation (elevated neopterin) over nutritional indicators as possible drivers of a more worrisome condition. These findings support the need of addressing infections together with nutritional interventions in the presence of coexisting underweight and stunting.

Among the multiple factors studied during the first year of life, only few remained as predictors of undernutrition at 5 years after a strict bootstrapping-selecting procedure. Other studies have shown lower income as a main determinant of undernutrition (19), but in our study lower LAZ was the only indicator associated with lower income. In contrast with other MAL-ED sites that did not find an association between illness and growth at 5 years (10), we found that history of hospitalization and more days/month presenting ALRI were associated with lower LAZ, and ALRI infections increased the risk of stunting at 5 years, in agreement with current knowledge of undernutrition and inflammation as common pathways for reduced linear growth in children (36).

The WHO recommends that infants initiate breastfeeding within the first hour of birth, and continue exclusively breastfeeding for the first 6 months of life (40). This is far from the case of the Pakistan MAL-ED cohort, where exclusive breastfeeding was provided with a median duration of only 2 weeks. Analyses showed that providing formula between 0 and 5 months was associated with reduced risk of underweight, and increased WAZ and LAZ. Of note, early start of complementary feeding was a common practice, where mothers provided mainly clear fluids or animal milk, but only 6% of children received formula, and those children came from families with higher incomes. Our findings highlight the importance of reinforcing the message of exclusive breastfeeding during the first 6 months in these communities, which would overcome the lack of resources to afford appropriate complementary foods at that early age. Providing formula has been suggested as a therapeutic approach to correct weight deficits in developing settings (41), but for populations like the MAL-ED cohort, such approach would not be neither financially nor context appropriate. On the other hand, a recent systematic review found that bovine/cow milk supplementation had unfavorable effects on infant morbidity and mortality (42), which aligns with our finding of earlier start of milk compared with starting milk after 6 months of age associated with lower WLZ. Also subject of controversy, commercial infant foods have

shown a contribution of 70% of recommended nutrient intakes in children 13–23 months in Ghana (43), which suggest that our finding of better WAZ and WLZ in children who had consumed commercially available infant foods may be related to an improvement in their micronutrient status, but this would require further study.

It was intriguing to find that higher sTfR in the first year, at concentrations below the cut-off for iron deficiency, was associated with higher WAZ and decreased risk of underweight at 5 years. Of note, no other iron status indicators were associated with child growth indicators at 5 years. It is known that transferrin, the acute-phase reactant protein that transports iron, has been used as well as a marker of nutritional status, given that it parallels prealbumin concentrations during nutritional interventions and is decreased in severe malnutrition (44). Moreover, the total mass of sTfR depends on the number of erythroid precursors in the bone marrow (45), and that those are in turn decreased in protein-energy malnutrition (44). Our findings suggest that a deprived erythropoiesis during infancy expressed as low concentrations of sTfR despite iron deficiency and anemia are reflecting protein-energy malnutrition. Our findings mimic those of other MAL-ED sites, where higher sTfR were associated with higher WAZ (10).

The association between ALRI and impaired growth has been previously documented. Stunting increased the risk of ALRI in infants from Turkey (46) and in children under 5 in Sri Lanka (47), and acute respiratory infection was the major predictor of underweight in children under 5 from India (48). To our knowledge, ours is the first study reporting the association of ALRI in the first year of life with impaired growth at 5 years. Whereas much attention has been paid to diarrheal disease as a major cause of mortality in developing countries, ALRI is also an important cause of morbidity and mortality, which are proportional to socio-demographic conditions (49). Both viruses and bacteria share the etiology of ALRI in children, but the severity of bacterial ALRI largely exceeds that of viral ALRI. However, by the time of the study, Pakistan National data shows that 46.2% of children were not fully immunized (33). Vaccines against bacteria and viruses implicated in morbidity and mortality due to ALRI such as measles, diphtheria, pertussis, *Haemophilus influenzae* b, pneumococcus and influenza have the potential to reduce the burden of the disease (50), and therefore, could help in reducing growth failure in this particular setting.

A consistent association between intestinal *Campylobacter* infection and lower LAZ together with increased intestinal and systemic inflammation was found across other MAL-ED sites (51). Our findings extend this association from the earliest age of infection at 0–5 months to low WAZ at 5 years. The association of *Campylobacter* with malnutrition indicated by WAZ has been previously reported in children 6–23 months from Bangladesh (52). Given that host factors such as shifts in diet and microbiota can modify colonization resistance to the infection, *Campylobacter* has been proposed as a biomarker of enteropathy and is a potential target for interventions intending to improve child growth in developing countries (53).

The MAL-ED cohorts from Nepal and Bangladesh found an association of myeloperoxidase between 3 and 6 months with growth velocity from 9 to 24 months (54) and between myeloperoxidase between 3 and 21 months and successive 3-month change in LAZ (55) respectively, but did not find an association of neopterin or alpha-1 antitrypsin with linear growth. In the present study, we only found an association between higher neopterin at concentrations ≥ 6.8 nmol/L and increased risk of underweight at 5 years, but no association was found between any of the three EE indicators with LAZ or stunting. A higher fecal neopterin in children hospitalized with severe acute malnutrition compared with

controls was found in a study from Uganda (56), and given that neopterin in our study was positively correlated with the number of days presenting all-cause illness in the first year, it is possible that a high fecal neopterin might be reflecting systemic inflammation to some extent. At this regard, there is strong evidence that the association between fecal biomarkers and impaired child growth is mediated through systemic inflammation (9). Therefore, neopterin appeared in our study as the earliest fecal biomarker that predicted undernutrition at 5 years.

5. Conclusion

Chronic malnutrition was highly prevalent in children from Pakistan, and our study evidenced associations with early inappropriate complementary feeding practices and illnesses, particularly respiratory infections, with lower growth indicators. Analyses suggested that the pathway for these associations could be early malnutrition indicated by low sTfR in the presence of iron deficiency and anemia, and inflammation indicated by higher fecal neopterin, which was in turn correlated with overall illness. Taken together, our findings suggest that reinforcing exclusive breastfeeding, facilitating the intake of nutritious foods after 6 months of age and preventing respiratory infections might help reducing the prevalence of child growth impairment in the Pakistani population.

Data availability statement

The Mal-ED data sets are centrally available upon request from the MAL-ED data repository at the University of Pennsylvania. The analytical codes used for this analysis can be requested from the study authors.

Ethics statement

The studies involving human participants were reviewed and approved by Ethics Review Committee Aga Khan University and the Foundation for the National Institutes of Health. Written informed consent to participate in this study was provided by the participants' legal guardian/next of kin.

Author contributions

ZB is the principal investigator for the Pakistan MalED cohort. For this analysis DG-F, SC and ZB jointly developed the analytical design, the conceptual framework and wrote the manuscript. DG-F and SC performed statistical analysis. AR, IC, SS, and the MAL-ED Pakistan investigators coordinated field and laboratory analyses, read, and approved the final manuscript. All authors contributed to the article and approved the submitted version.

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Conflict of interest

The authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

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Supplementary material

The Supplementary material for this article can be found online at: <https://www.frontiersin.org/articles/10.3389/fnut.2023.1104654/full#supplementary-material>

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Jai Das,
Aga Khan University, Pakistan

REVIEWED BY

Dongning Yao,
Nanjing Medical University, China
Ravi Prakash Upadhyay,
Society for Applied Studies, India

*CORRESPONDENCE

Qian Zhao
✉ zhaoqian6628@163.com

[†]These authors have contributed equally to this work

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The efficacy and safety of complementary and alternative medicine in the treatment of nausea and vomiting during pregnancy: A systematic review and meta-analysis

Mo-Yao Tan^{1†}, Shi-Hong Shu^{2†}, Run-Lei Liu^{3,4} and Qian Zhao^{1*}

¹Chengdu Integrated TCM and Western Medicine Hospital, Chengdu, China, ²Clinical Medical School, Chengdu University of Traditional Chinese Medicine, Chengdu, Sichuan, China, ³School of Pharmacy, Chengdu University of Traditional Chinese Medicine, Chengdu, Sichuan, China, ⁴School of Modern Chinese Medicine Industry, Chengdu University of Traditional Chinese Medicine, Chengdu, Sichuan, China

Background: Complementary and alternative medicine (CAM) therapies are widely used for nausea and vomiting during pregnancy (NVP) due to the limitations of conventional medicine. However, their efficacy and safety remain controversial. Therefore, this meta-analysis was performed to assess the improvement of CAM therapy on NVP.

Methods: Randomized controlled trials (RCTs) were searched for where the trial group was CAM and the control group was a conventional medicine or a placebo for NVP. This was done via 8 databases, including PubMed, EMBASE, the Cochrane Library, Web of Science, China National Knowledge Infrastructure, Wanfang, SinoMed, and VIP, from inception to October 25, 2022. The Grades of Recommendation, Assessment, Development and Evaluation (GRADE) was used to assess the quality of evidence. The Stata 15.0 software was used to perform the meta-analysis.

Results: Thirty-three RCTs were included in this study. The acupuncture treatment was superior to conventional medicine at the effective rate [RR = 1.71, 95% CI (1.02, 2.86), $P = 0.042$; Low-quality evidence]. Ginger had more significant effects than conventional medicine at the Rhodes index [WMD = -0.52 , 95% CI (-0.79 , -0.24), $P \leq 0.001$; Moderate-quality evidence] and it had the same effect as drugs to relieve vomiting [SMD = 0.30, 95% CI (-0.12 , 0.73), $P = 0.160$; Low-quality evidence]. Compared with placebo, ginger had a higher effective rate [RR = 1.68, 95% CI (1.09, 2.57), $P = 0.018$; Low-quality evidence], and lower Visual analog scale (VAS) of Nausea [WMD = -1.21 , 95% CI (-2.34 , -0.08), $P = 0.036$; Low-quality evidence]. Ginger had the same antiemetic effect as placebo [WMD = 0.05, 95% CI (-0.23 , 0.32), $P = 0.743$; Low-quality evidence]. Acupressure was superior to conventional medicine at the reduction of antiemetic drugs [SMD = -0.44 , 95% CI (-0.77 , -0.11), $P = 0.008$; Low-quality evidence], and at the effective rate [RR = 1.55, 95% CI (1.30, 1.86), $P \leq 0.001$; Low-quality evidence]. Acupressure had the same effect as placebo at the effective rate [RR = 1.25, 95% CI (0.94, 1.65), $P = 0.124$; Low-quality evidence]. Overall, CAM therapy was safer than conventional medicine or a placebo.

Conclusion: The results showed that CAM therapies were able to alleviate NVP. However, due to the low quality of existing RCTs, more RCTs with large sample sizes are needed to validate this conclusion in the future.

KEYWORDS

complementary and alternative medicine, nausea and vomiting, meta-analysis, pregnancy, GRADE

Introduction

Nausea and vomiting are common symptoms of pregnancy, also known as nausea and vomiting during pregnancy (NVP) or morning sickness, as it often occurs in the morning (1). The mechanism is unclear but it may be related to hormonal, immunological, or anatomical changes during pregnancy (2). About 50–80% of pregnant women experience NVP, primarily between weeks 6 and 12 of pregnancy, and subsides by week 20. For 9–20% of women, however, NVP may last longer (2, 3). The symptoms are severe enough to cause fluid and electrolyte imbalance and nutritional deficiencies and require hospitalization (4–6). Thus, NVP significantly impacts the quality of life of pregnant women in terms of social, emotional, and psychological health, as well as increasing the economic burden (7). Although there is medication available to treat NVP, some physicians and patients are reluctant to use these drugs due to reports of fetal malformations associated with antiemetic medications (8). One study showed that many NVP patients did not use drugs, or at least used lower than the prescribed doses, due to a lack of trust in the safety of chemical medications, such as vitamin B6, antihistamines, or H1 receptor antagonists (9).

In recent years, CAM therapy has become common in many western countries, with nearly half of all women of childbearing age using this method (9). Considering that CAM is safe, inexpensive, and convenient, patients and clinicians need to understand and promote CAM for those who do not want to be treated with traditional medications or are dissatisfied with them. CAMs such as ginger, acupuncture, and acupressure, are already widely used in clinical practice. The US Food and Drug Administration (FDA) considers ginger to be a safe herbal preparation (10, 11), containing essential oils that block the vomiting reflex, as well as curcumin and sugorol, which both have anti-nausea, anti-vomiting, sedative, and analgesic effects that may be the key to their action (12). Acupressure and acupuncture have similar mechanisms, by applying pressure and activating mast cells at acupuncture points and specific components such as nerve fibers to release endorphins, thus increasing endogenous antiemetic tension (13, 14).

In the past, there have been some meta-analyses on related aspects, such as that by Kannan Sridharan et al., who conducted a net meta-analysis on interventions for NVP (15). However, they did not compare treatment modalities with first-line drugs, which may be out of clinical reality. Estelle Viljoen and Rebecca conducted meta-analyses of ginger and acupressure for NVP, respectively (16, 17). However, more RCTs have been published to date and

a pooled update is urgently needed to ensure the integrity and reliability of the findings.

Due to the controversy surrounding the treatment of NVP with CAM therapy and to update the existing evidence, as well as address the limitations of past meta-analyses, this meta-analysis comprehensively includes updated RCTs of clinically used CAM therapies, including acupuncture, ginger, and acupressure, to explore their differences in efficacy with first-line medications and placebo therapy. This aims to offer clinicians and pregnant women who experience NVP the possibility of an alternative treatment option that is effective, safe, and affordable.

Methods

This study was registered on PROSPERO (CRD42022375440). It was conducted following the Preferred Reporting Items for Systematic Evaluations and Meta-Analysis (PRISMA) guidelines and the recommendations of the Cochrane Collaboration (18, 19).

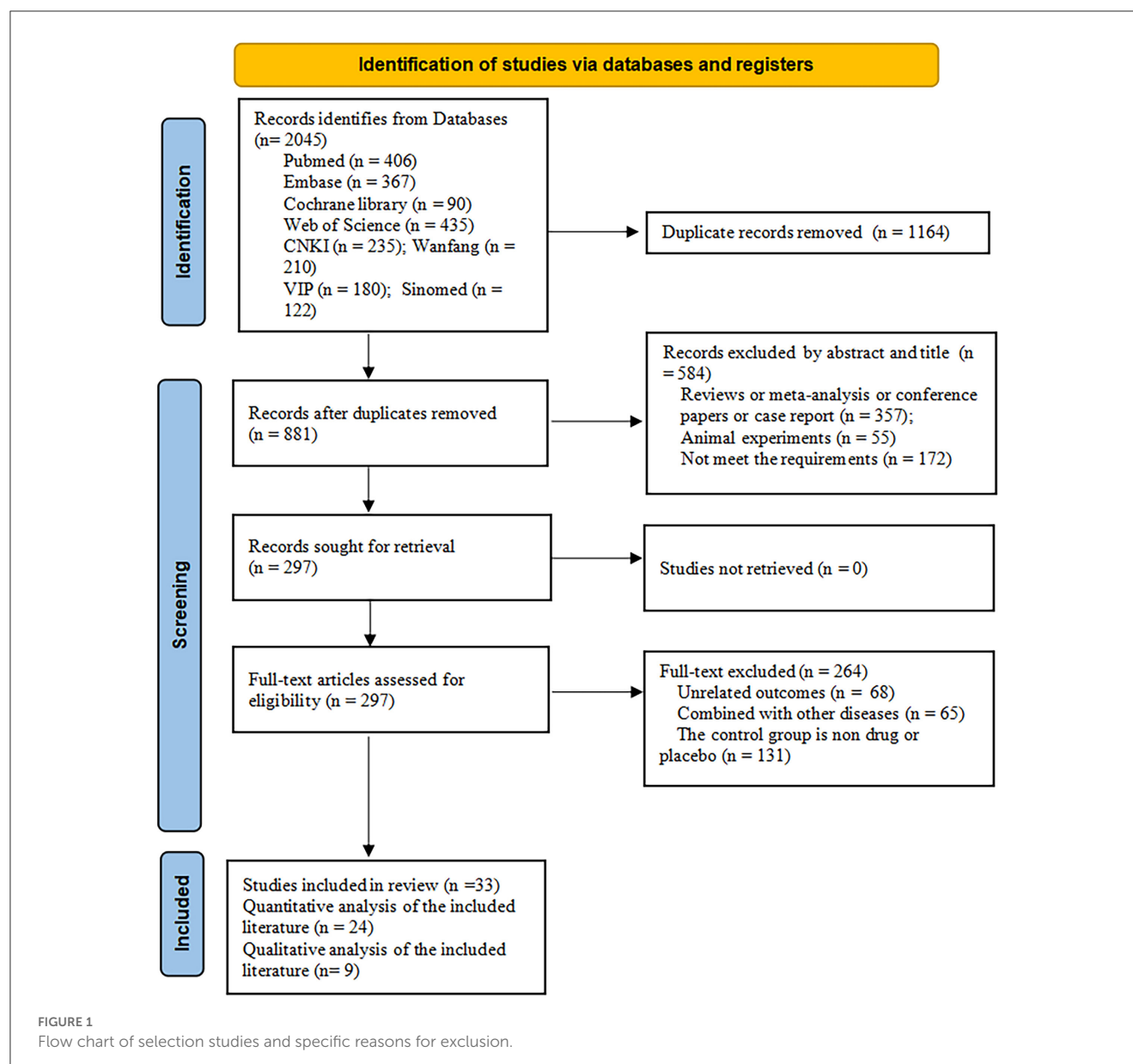
Search strategy

To ensure the completeness and readiness of the literature search, the two authors (MYT and SHS) independently searched eight electronic databases, including PubMed, EMBASE, the Cochrane Library, Web of Science, China National Knowledge Infrastructure, Wanfang Database, SinoMed, and VIP Database, from their inception to October 25, 2022, without age, race, or language restrictions.

The reference lists from published reviews of related directions and the critical articles retrieved were used for further research, as well as the links in the gray literature.

For English databases, a combination of subject terms and free words were used for searching. The English database search included four core components, which used AND operator for logical connections: (1) complementary and alternative medicine (e.g., herb, acupuncture, acupressure, ginger, Shiatsu, Zhi Y, Chih Ya, and Zingiber officinal); (2) pregnancy (e.g., Pregnancies, gestation, and pregnant woman); (3) vomiting (e.g., emese, emesia, and vomitus); (4) nausea.

For the Chinese database, we searched using keywords such as '孕妇', '妊娠期', '恶心呕吐', '补充替代疗法', '针灸', '生姜', '指压'. The detailed retrieval process is shown in [Supplementary material 1](#).



Inclusion and exclusion criteria

- (1) *Type of study*: This meta-analysis only included RCTs on CAM therapy for NVP; case reports, conference papers, and RCTs without relevant outcomes were excluded.
- (2) *Type of participants*: As symptoms are judged in NVP, no diagnostic criteria are used. Patients who experienced NVP were included and those who presented with nausea and vomiting in the postpartum period were excluded.
- (3) *Type of interventions and controls*: RCTs, where patients in the trial group were treated with CAM therapy, were included, including acupuncture, acupressure, and ginger, while the control group was treated with conventional western medicine or a placebo treatment. If the trial group was treated with a combination of multiple CAM therapies and a control group that was not a conventional medicine or placebo-treated RCT, the literature was excluded.
- (4) *Type of outcomes*: Outcome indicators for RCTs included at least one of the following. The primary outcomes were the effective rate, the Rhodes scale, and the number of vomiting. The secondary outcomes were measured using the VAS, dose of antiemetic drugs, and adverse events. VAS allowed participants to score their symptoms using a 10 cm line from 0 (no nausea or vomiting) to 10 (severe nausea or vomiting). The Rhodes index included three nausea items (duration, frequency, pain) and two vomiting items (quantity and frequency), with the five items being scored by the Likert scale. The effective rate was the proportion of the number of people who have significantly improved and recovered symptoms in the number of people in the test or the control group. The effect of CAM was evaluated laterally by reducing the number of vomiting and the reduction of vomiting drugs for patients after using CAM. The adverse events of CAM mentioned in each

article were counted and included to evaluate the safety of this measure.

Screening and data extraction

Two researchers (MYT and RLL) independently read the titles and abstracts for screening based on inclusion and exclusion criteria, and then the selected articles were read in full for final selection. If there was any dispute, it would be resolved by the corresponding author (QZ).

Two researchers (MYT and SHS) independently screened the literature and extracted author, year, region, age, sample, interventions, gestation, acupoint, dose or frequency, duration, and outcome from each RCT. If there was any dispute, it would be resolved by the team discussion. When the data included in RCTs were defective or missing, the first author or corresponding author was contacted to seek data information.

Assessment of risk of bias

Two authors (MYT and RLL) independently assessed the risk of bias of the included RCTs using the Cochrane Risk of Bias Version 2 (RoB 2) assessment tool (20). RoB 2 has six evaluation items: (1) the random sequence generation, (2) deviations from the intended interventions, (3) missing outcome data, (4) measurement of the outcome, (5) selection of the reported result, (6) and overall bias. Each section is graded “low risk,” “some concern,” and “high risk” according to the actual situation of the article. If there were disagreements, a third author (Qian Zhao) would evaluate until a consensus was reached.

Grade evaluation

The GRADE approach was used to evaluate the quality of evidence and strength of recommendations (21). GRADE considers the following five elements: the risk of bias, inconsistency, indirectness, inaccuracy, and publication bias. The outcomes of the included literature were classified as very low, low, moderate, and high quality according to the content of the assessment.

Data analysis

The Stata 15.0 software was used to perform the meta-analysis. The standard mean difference (SMD) or weighted mean difference (WMD) was used for data analysis for continuous variables. The dichotomous variables were analyzed by the risk ratio (RR), with a 95% confidence interval (CI). Due to differences in the study methods, basic characteristics of the participants, and the doses and frequency of the interventions, there was significant clinical heterogeneity in the included studies. So, regardless of statistical heterogeneity, we would use a random effects model to analyze the data. To further analyze and identify sources of heterogeneity,

subgroup analyses of sample sizes, types of medications, and year of publication were performed.

To test the robustness of the outcome, a sensitivity analysis was performed by removing included studies one by one or by performing only descriptive analysis. If an article was excluded and the result was reversed, the article would be shown to be a source of heterogeneity and the article was analyzed in depth regarding its sample size and year of publication. Otherwise, the results were robust.

When the number of included articles was more than 10, the underlying publication bias was identified *via* an informal visual examination of a funnel plot. Publication bias was evaluated with Begg's tests (22). When the study provided only the median, the mean, standard deviation, and range were calculated based on the methods described by Hozo et al. (23). $P < 0.05$ was used to indicate statistical significance.

Results

Study selection

A total of 2,045 articles were identified from the eight databases. One thousand one hundred and sixty-four articles were excluded due to duplication. After reading the titles and abstracts, 297 articles remained for full-text review. After scanning the full texts, 33 articles were included. The specific literature screening process is shown in Figure 1.

Study characteristics

A total of 33 articles (24–56) were included in this paper, of which 24 RCTs (24, 26–30, 33, 35, 37–44, 46, 49–53, 55, 56) were analyzed for quantitative analysis due to sufficient sample size data. The remaining 9 articles (25, 31, 32, 34, 36, 45, 47, 48, 54) were about side effects, for which there were only descriptive discussions provided due to the small sample size data. Three articles (24, 35, 37) only offered the median and interquartile range, which we algorithmically converted to the mean and standard deviation (23).

The included RCTs were published from 2002 to 2022. Eleven (24, 27–29, 31, 33, 35, 36, 38, 39, 45) were conducted in Iran, five (25, 30, 37, 40, 41) in Thailand, five (26, 32, 47, 49, 55) in Australia, four (43, 51–53) in China, two (42, 44) in Malaysia, two (46, 54) in the UK, one (50) in Sweden, one (34) in Indonesia, one (48) in the USA, and one (56) in Croatia. The sample sizes of the included RCTs ranged from 18 to 340. The mean age of pregnant women was between 19 and 35 years old and the gestation period was between 1 and 17 weeks at baseline.

The CAM interventions were classified into acupuncture, acupressure, and ginger. Six articles (49–54) reported on the efficacy of acupuncture with a treatment period of 5 days to 4 weeks. Twelve articles (38–48, 55) reported about acupressure and the treatment period was 1 day to 4 weeks. There were 14 articles (24–37) studying ginger with a dosage of between 500 and 2,500 mg. Also, 1 article (56) had two experimental groups: acupuncture and acupressure, lasting for 1 week.

TABLE 1 Basic characteristics of the included studies.

References	Region	Sample (T/C)	Age		Gestation		Interventions		Dose or frequency		Duration	Acupoint	Outcome
			T	C	T	C	T	C	T	C			
Ensiyeh and Sakineh (24)	Iran	35/34	25.0 ± 4.2	24.2 ± 3.9	<17 (w)	<17 (w)	Ginger	Vitamin B6	1 g/d	40 mg/d	4 d	NR	Number of vomiting, total efficiency, adverse events
Pongrojpraw et al. (25)	Thailand	85/85	27.85 ± 5.3	26.38 ± 5.8	10.25 ± 2.8 (w)	9.3 ± 3.1 (w)	Ginger	Dimenhydrinate	1 g/d	100 mg/d	7 d	NR	Adverse events
Smith et al. (26)	Australia	145/146	29.6 ± 5.2	28.41 ± 5.4	8.5 ± 1.75 (w)	8.6 ± 1.75 (w)	Ginger	Vitamin B6	1,050 mg/d	75 mg/d	3 w	NR	Total efficiency
Firouzbakht et al. (27) ^a	Iran	24/35	24.9 ± 5.5	24.03 ± 3.7	9.1 ± 4.6 (w)	8.9 ± 2.9 (w)	Ginger	Vitamin B6	1,000 mg/d	160 mg/g	4 d	NR	Number of vomiting, adverse events
Firouzbakht et al. (27) ^b	Iran	24/28	24.9 ± 5.5	25.39 ± 5.24	9.1 ± 4.6 (w)	9.1 ± 3.6 (w)	Ginger	Placebo	1,000 mg/d	160 mg/g	4 d	NR	Adverse events, VAS
Mohammadbeigi et al. (28)	Iran	34/34	26.94 ± 3.94	27.88 ± 3.21	9.5 ± 2.02 (w)	10.03 ± 1.99 (w)	Ginger	Metoclopramide	600 mg/d	30 mg/d	5 d	NR	Adverse events, Rhodes
Sharifzadeh et al. (29)	Iran	28/26	28.95 ± 0.5	28.03 ± 3.7	10.9 ± 4.6 (w)	10.8 ± 4.8 (w)	Ginger	Vitamin B6	1,000 mg/d	80 mg/d	4 d	NR	Number of vomiting, Rhodes, adverse events
Chittumma et al. (30)	Thailand	61/62	23.8 ± 5.1	24.4 ± 5.3	12 ± 2 (w)	11 ± 2 (w)	Ginger	Vitamin B6	650 mg/d	15 g/d	4 d	NR	Adverse events, Rhodes
Haji Seid Javadi et al. (31)	Iran	47/48	26 ± 4	27 ± 4.2	62.9 ± 8.1 (d)	62.9 ± 8.6 (d)	Ginger	Vitamin B6	1,000 mg/d	80 mg/d	4 d	NR	Adverse events
Willetts et al. (32)	Australia	48/51	33 ± 5.25	31 ± 6.25	9 ± 3.125 (w)	9 ± 3.125 (w)	Ginger	Placebo	500 mg ginger extract /d	NR	4 d	NR	Adverse events
Ozgoli et al. (33)	Iran	32/35	24.1 ± 4.8	23.3 ± 5	13 ± 3 (w)	13 ± 3 (w)	Ginger	Placebo	1,000 mg/d	1,000 mg/d	4 d	NR	Total efficiency, adverse events
Abidah et al. (34)	Indonesia	48/48	20–35	20–35	1–12 (w)	1–12 (w)	Ginger	Placebo	2.5 g/d	10 g/d	7 d	NR	Adverse events
Zahra et al. (35)	Iran	32/30	19–35 (y)	19–35 (y)	7–17 (w)	7–17 (w)	Ginger	Placebo	2.5 g/d	2.5 g/d	4 d	NR	VAS, adverse events
Saberi et al. (36)	Iran	37/36	27.35 ± 5.93	26.85 ± 4.90	8.97 ± 0.05 (w)	9.85 ± 2.27 (w)	Ginger	Placebo	NR	NR	3 w	NR	Adverse events

(Continued)

TABLE 1 (Continued)

References	Region	Sample (T/C)	Age		Gestation		Interventions		Dose or frequency		Duration	Acupoint	Outcome
			T	C	T	C	T	C	T	C			
Vutyavanich et al. (37)	Thailand	32/35	28.3 ± 5.8	28.6 ± 5.5	10.4 ± 2.3 (w)	10.3 ± 2.6 (w)	Ginger	Placebo	1 g/d	1 g/d	4 d	NR	VAS, adverse events
Tara et al. (38) ^a	Iran	30/30	26.0 ± 4.7	26.6 ± 5.2	9.6 ± 1.7 (w)	8.7 ± 2.2 (w)	Acupressure	Placebo	4 times/d	4 times/d	4 d	PC6, TE5	Rhodes, adverse events, total efficiency, number of vomiting
Tara et al. (38) ^b	Iran	30/30	26.0 ± 4.7	26.5 ± 4.3	9.6 ± 1.7 (w)	9.3 ± 1.3(w)	Acupressure	Vitamin B6 plus metoclopramide	4 times/d	4 times/d	4 d	PC6, TE5	Total efficiency, adverse events
Negarandeh et al. (39)	Iran	64/64	30.46 ± 5.07	29.95 ± 5.23	77.95 ± 15.61 (d)	77.34 ± 16.97 (d)	Ear acupressure	Placebo	3 times/d	3 times/d	4 d	Point zero, Sympathetic Autonomic, Shen Men, cardia	Rhodes, adverse events
Jamigorn and Phupong (40)	Thailand	33/33	28.2 ± 5.1	28.1 ± 5.6	8.1 ± 1.7 (w)	8.9 ± 3.5 (w)	Acupressure	Vitamin B6	NR	100 mg/d	7 d	PC6	Rhodes, reduction of antiemetics
Puangsrirachern et al. (41)	Thailand	45/46	26.4 ± 5.6	27.0 ± 5.74	11.1 ± 2.1 (w)	11.2 ± 2.3 (w)	Ear acupressure	Oral anti-emetic drug	4 times/d	NR	4 d	On the inner surface of the auricle at the concha ridge zone	Rhodes, reduction of antiemetics
Adlan et al. (42)	Malaysia	60/60	29.0 ± 4.92	28.4 ± 4.34	9.7 ± 2.09 (w)	9.2 ± 2.03 (w)	Acupressure	Placebo	12 h/d	12 h/d	3 d	PC6	Total efficiency
Zhu et al. (43)	China	30/30	29.97 ± 2.61	30.25 ± 2.53	<12 (w)	<12 (w)	Electro acupressure	Sodium Lactate Ringer's Injection	24 h	1 time/d	4 w	PC6	Total efficiency, adverse events
Mohd Nafiah et al. (44)	Malaysia	45/45	29.3 ± 4.5	30.8 ± 4.1	10 ± 2.8 (w)	10.16 ± 2.2 (w)	Acupressure	Venous metoclopramide	3 times/d	3 times/d	1 d	NR	Total efficiency
Naeimi Rad et al. (45)	Iran	40/40	26.03 ± 4.18	25.88 ± 5.58	9.55 ± 1.81 (w)	9.45 ± 2.02 (w)	Acupressure	Placebo	2 times/d	2 times/d	4 d	NR	Adverse events

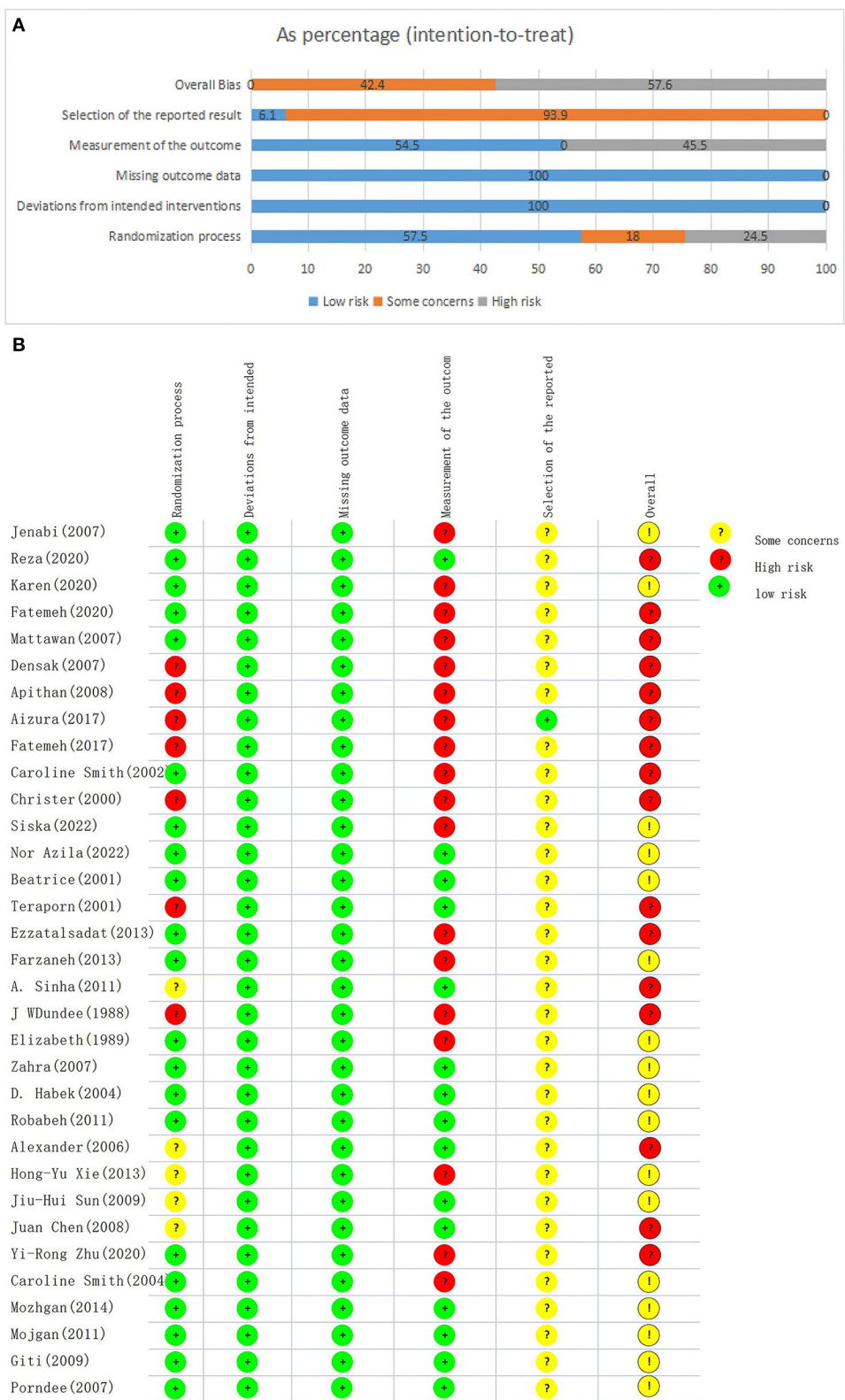
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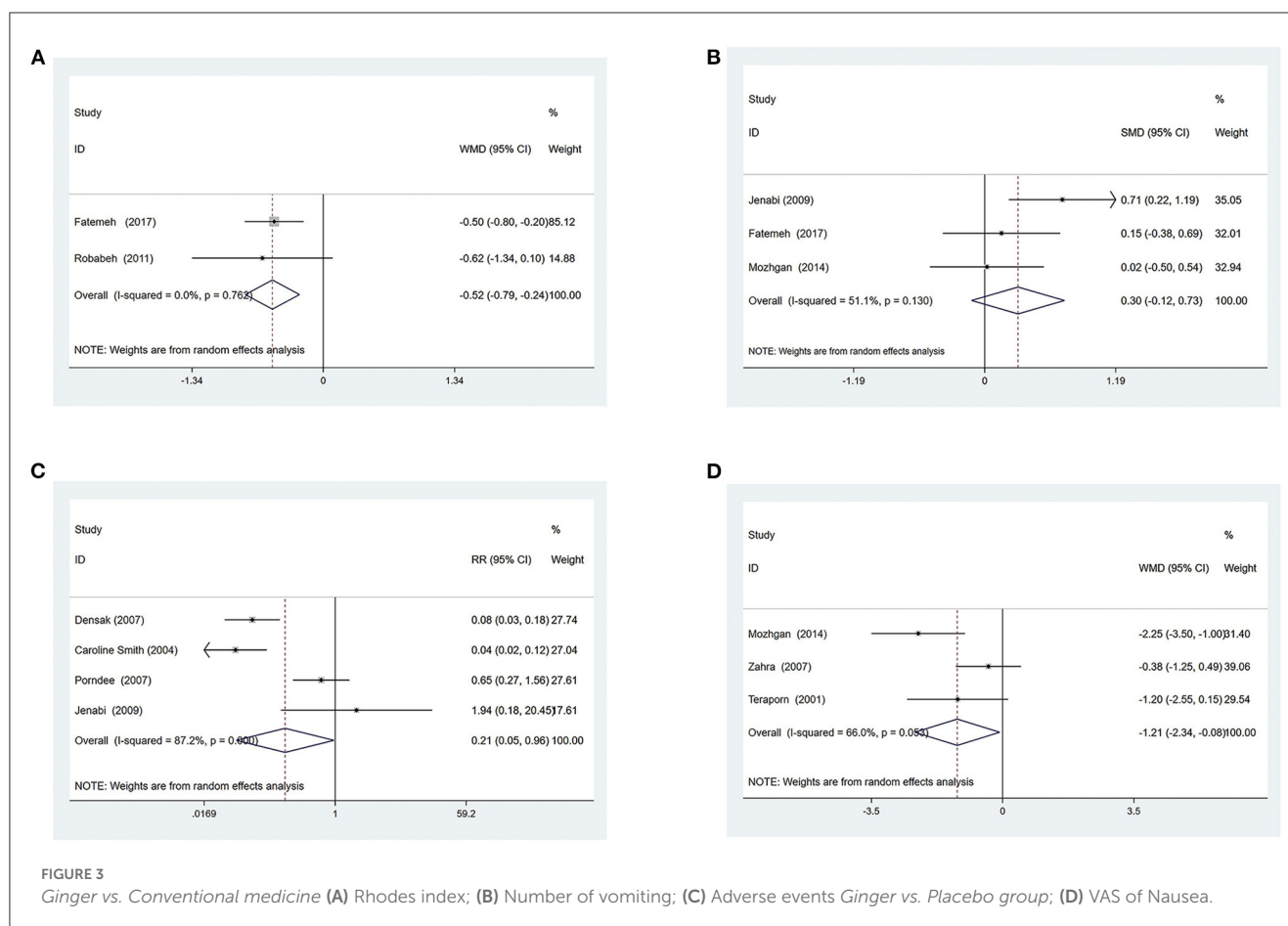
TABLE 1 (Continued)

References	Region	Sample (T/C)	Age		Gestation		Interventions		Dose or frequency		Duration	Acupoint	Outcome
			T	C	T	C	T	C	T	C			
Root (46)	UK	119/112	NR	NR	11.4 ± 3.0 (w)	10.6 ± 2.3 (w)	Acupressure	Placebo	2 times/d	2 times/d	4 d	NR	Total efficiency
Heazell et al. (47)	Australia	40/40	25.4 ± 0.95	27.7 ± 0.89	8.5 ± 0.32 (w)	9.0 ± 0.36 (w)	Acupressure	Placebo	8 h/d	8 h/d	NR	NR	Adverse events
Hyde (48)	USA	8/8	NR	NR	NR	NR	Acupressure	Placebo	NR	NR	5 d	NR	Adverse events
Smith et al. (49)	Australia	148/148	30.1 ± 4.8	29.6 ± 4.6	8.3 ± 2.5 (w)	8 ± 2.25 (w)	Acupuncture	Placebo	2 times/w	2 times/w	4 w	PC6	Rhodes, total efficiency, adverse events
Carlsson et al. (50)	Sweden	17/16	28.4 ± 3.5	28.4 ± 3.5	9.9 ± 2.5 (w)	9.9 ± 2.5 (w)	Acupuncture	Placebo	3 times/d	3 times/d	8 d	PC6	Total efficiency, adverse events
Xie (51)	China	47/47	26 ± 4	27 ± 4	NR	NR	Manual acupuncture	Vitamin B	1 time/d	1 time/d	10 d	Scalp Acupuncture Stomach Area: RN12, PC6, ST36	Total efficiency
Sun (52)	China	50/50	NR	NR	NR	NR	Manual acupuncture	10% glucose+5% glucose saline+Vitamin B6+5% sodium bicarbonate+Phenobarbital	1 time/d	3 times/day	2 w	RN12, PC6, ST36	Total efficiency
Chen and Ning (53)	China	18/18	22–34	22–34	NR	NR	Electroacupuncture	Ringer's Solution+Vitamin B+Vitamin C	1 time/d	1 time/d	5 d	PC6, CV17, CV12	Total efficiency
Knight et al. (54)	UK	28/27	30.7 ± 4.5	30.3 ± 4.5	7.8 ± 1.0 (w)	8.0 ± 1.0 (w)	Acupuncture	Placebo	2 times/w	2 times/w	2 w	ST36, SP4, CV12, PC6	Adverse events
Sinha et al. (55)	Australia	170/170	29 ± 6.67	31 ± 5.93	NR	NR	Acupressure	Placebo	24 h/d	24 h/d	NR	NR	Total efficiency
Habek et al. (56) ^a	Croatia	10/8	20.4 ± 4.7	20.8 ± 4.1	7 ± 0.75 (w)	8 ± 1.25 (w)	Manual acupuncture	Placebo	1 time/d	1 time/d	1 w	PC6	Adverse events
Habek et al. (56) ^b	Croatia	11/7	21.3 ± 3.1	22.1 ± 3.9	8 ± 1 (w)	8 ± 1.25 (w)	Acupressure	Placebo	1 time/d	1 time/d	1 w	PC6	Total efficiency, adverse events

^{a,b}It represents different test and control groups for the same article.

w, week; d, day; NR, not report; T, test group; C, control group; VAS, visual analog scale.





In the control group, interventions included sodium lactate ringer's injection, dimenhydrinate, vitamin B6, metoclopramide, antiemetics, sodium bicarbonate + phenobarbital, ringer's solution+vitamin B+vitamin C, or placebo. We referred to these medications as conventional medicine. Because, based on our clinical experience and the collection of numerous documents, they are currently the most widely used and extensively researched medications in the clinical treatment of NVP. The specific characteristics are detailed in Table 1.

Risk of bias of included studies

The risk of bias in the included RCTs is listed in Figure 2. Eight articles (24, 29, 31, 34, 41, 42, 48, 49) did not use allocation concealment, so they were judged as "N", and the other five articles (43, 46, 51–53) did not mention allocation concealment, so were judged as "NI". In terms of random sequence, the results showed that 57.5% of the articles (25–28, 30, 32, 33, 35–39, 44, 45, 47, 50, 54–56) were judged as "low risk", 18.0% as "some concern" (40, 43, 46, 51–53) and 24.5% as "high risk" (24, 29, 31, 34, 41, 42, 48, 49). All articles did not deviate from the intended interventions and were therefore judged to be "low risk". All articles had no data loss or data loss within acceptable limits, so they were judged to be "low risk". For the measurement of results, the results showed that 45.5% of the articles (24–26, 29, 31, 32, 34, 36, 38, 40–43, 46, 48–51) were judged as "high risk" and 54.5% (27, 28, 30, 33, 35, 37, 39, 44,

45, 47, 52–56) as "low risk". Thirty articles (25–28, 30–55) did not elaborate on the pre-planned or detailed full protocol, so were judged to be "NI". For the selection of the reported result, our results showed that 93.9% of the articles (25–28, 30–56) were judged as "some concern" and 6.1% as "low risk" (24, 29). To summarize the risk assessment results of all sections, we could see that 42.4% (28, 30, 33, 35, 37, 39, 44, 45, 47, 52–56) of the articles were "some concern" and 57.6% (24–27, 29, 31, 32, 34, 36, 38, 40–43, 46, 48–51) were "high risk".

Effects of interventions

Ginger

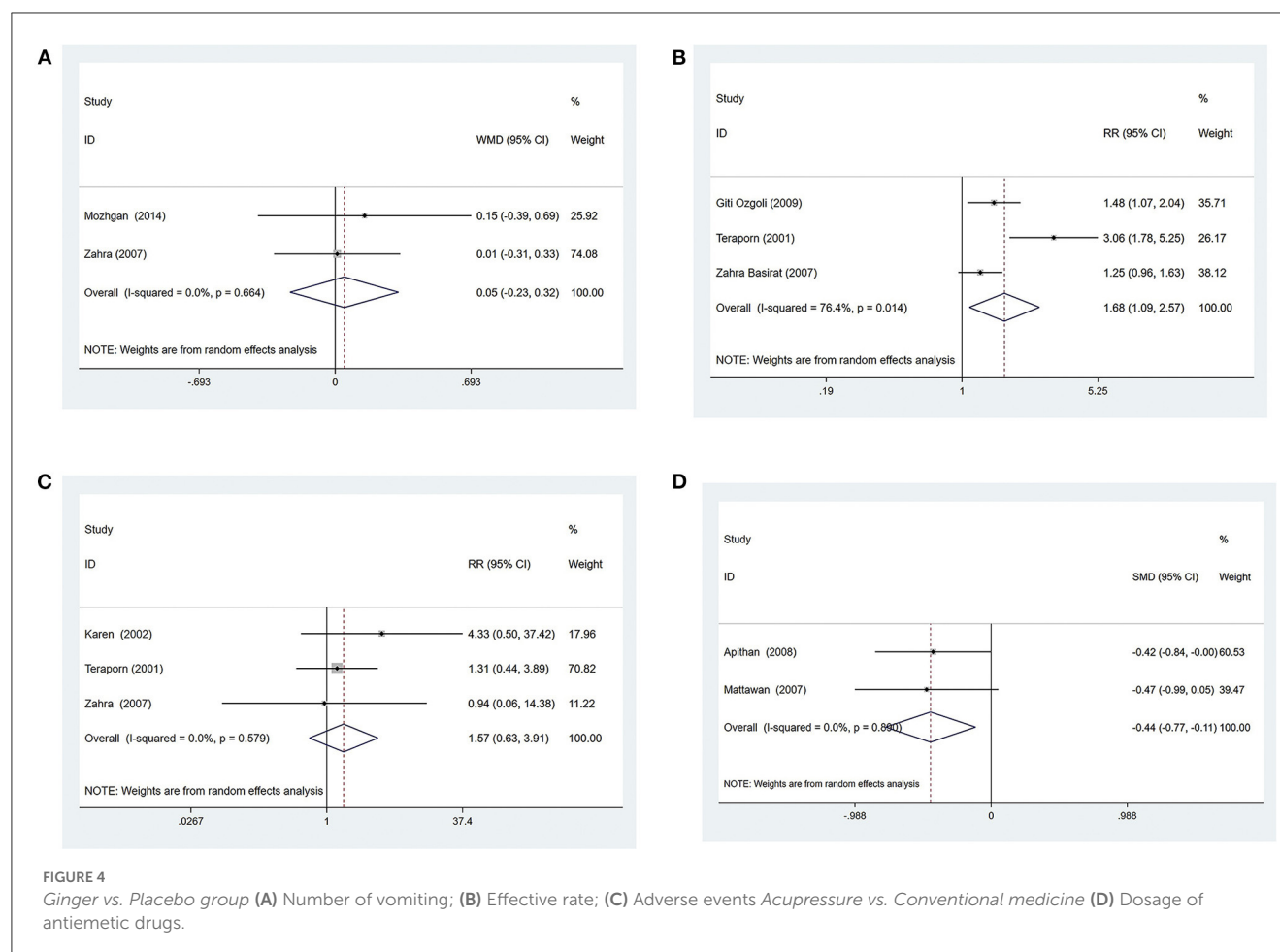
Ginger vs. conventional medicine

Rhodes index

Two trials (28, 29) compared ginger with conventional medicine, evaluating 122 patients with NVP. The pooled results showed that ginger could better relieve NVP symptoms compared to conventional medicine [WMD = -0.52 , 95% CI (-0.79 , -0.24), $P \leq 0.001$] (Figure 3A), and the quality of evidence was moderate based on GRADE analysis (Supplementary material 2).

Number of vomiting

Three trials (24, 27, 29) compared ginger with conventional medicine, evaluating 182 patients with NVP. The pooled results showed that ginger had no obvious effect on reducing the number



of vomiting for patients compared to conventional medicine [SMD = 0.30, 95% CI (−0.12, 0.73), $P = 0.160$] (Figure 3B). The GRADE analysis revealed that the overall level of quality of the evidence to support this conclusion was low (Supplementary material 2).

Adverse events

A total of five articles (24–27, 30) mentioned adverse events, one of which (27) reported severe NVP, stomachache, and heartburn during the treatment, but did not specify the number of people. In the remaining four studies (24–26, 30), 137 of 326 patients (42%) allocated to the ginger group experienced adverse events compared with 278 of 327 patients (85%) assigned to the control group. Side effects described in these articles included heartburn, drowsiness, belching, congenital abnormality, sedation, arrhythmia, headache, dry retching, and spontaneous abortions. By summarizing and analyzing the available data, the results showed that ginger had fewer side effects when treating NVP than conventional medicine [RR = 0.21, 95% CI (0.05, 0.96), $P = 0.045$] (Figure 3C). The quality of evidence was low based on GRADE analysis (Supplementary material 2).

Ginger vs. the placebo group

VAS of nausea

Three trials (27, 35, 37) compared ginger with a placebo, evaluating 181 patients with NVP. The pooled results showed that

ginger had more significant effects on patients' nausea symptoms compared to the placebo group [WMD = −1.21, 95% CI (−2.34, −0.08), $P = 0.036$] (Figure 3D). The GRADE analysis revealed that the overall level of quality of the evidence to support this conclusion was low (Supplementary material 2).

Number of vomiting

Two trials (27, 35) compared ginger with a placebo, evaluating 114 patients with NVP. The pooled results showed that ginger had no obvious effect on reducing the number of vomiting of patients compared to the placebo [WMD = 0.05, 95% CI (−0.23, 0.32), $P = 0.743$] (Figure 4A). The quality of evidence was low based on GRADE analysis (Supplementary material 2).

Effective rate

Three trials (33, 35, 37) compared ginger with a placebo, evaluating 196 patients with NVP. The pooled results showed that the effective rate was higher compared with the placebo when patients received ginger [RR = 1.68, 95% CI (1.09, 2.57), $P = 0.018$] (Figure 4B), and the quality of evidence was low based on GRADE analysis (Supplementary material 2).

Adverse events

A total of 6 articles (27, 32, 33, 35–37) mentioned adverse events, evaluating 420 patients with NVP, one of which (27)

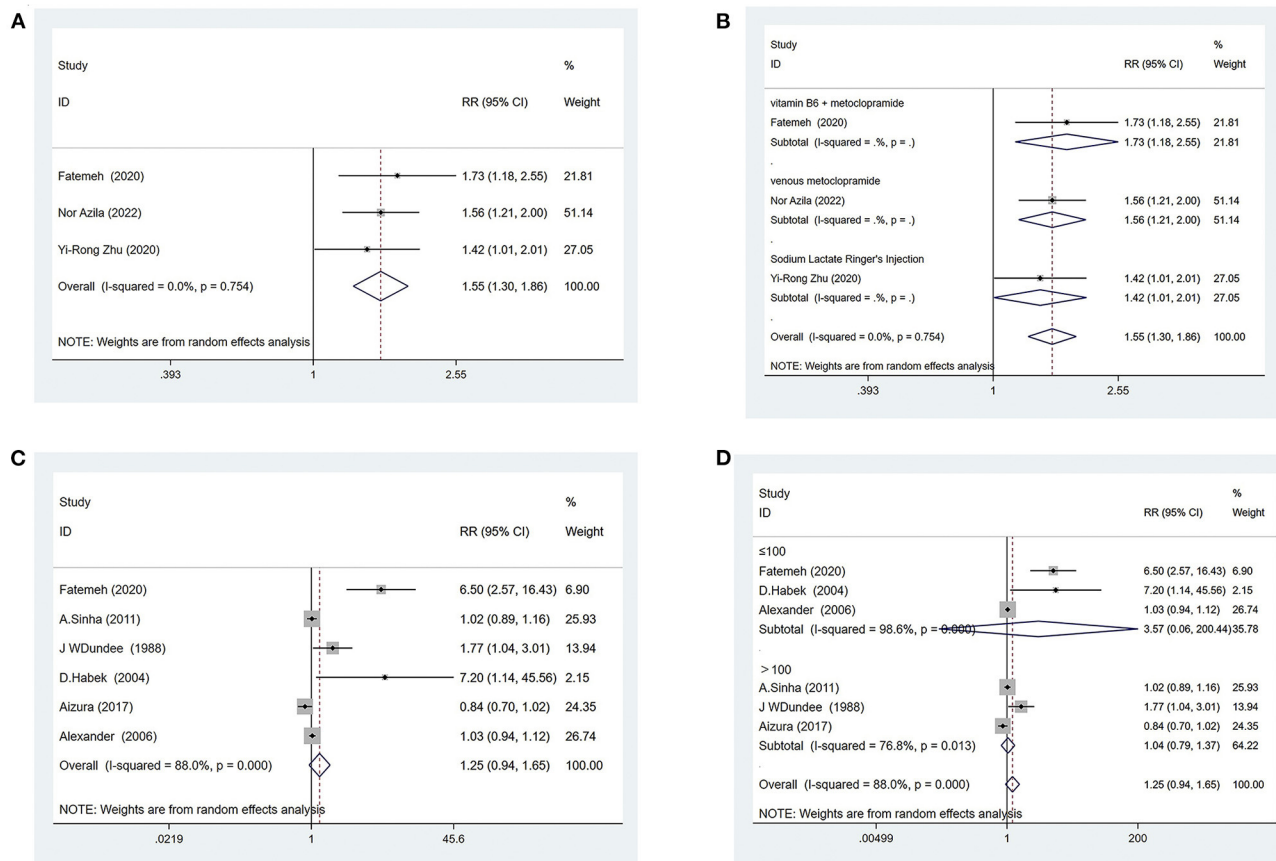


FIGURE 5

Acupressure vs. Conventional medicine (A) Effective rate; (B) Subgroup analysis based on different medications; Acupressure vs. Placebo group; (C) Effective rate; (D) subgroup analysis based on sample size.

reported stomachache and heartburn during the treatment, but did not specify the number of affected individuals. Another article (36) mentioned heartburn, but there was also no specific number of cases. One article (33) clearly stated that participants had no adverse effects. In the remaining three studies (32, 35, 37), 18 of 112 patients (16%) allocated to the ginger group experienced adverse events compared with 10 of 116 patients (9%) assigned to the control group. The available data were summarized and analyzed and the results showed that side effects of ginger were equivalent to those of placebo when treating NVP [RR = 1.57, 95% CI (0.63, 3.91), $P = 0.336$] (Figure 4C). The GRADE analysis revealed that the overall level of quality of the evidence to support this conclusion was very low (Supplementary material 2).

Acupressure

Acupressure vs. conventional medicine

Dosage of antiemetic drugs

Two trials (40, 41) compared acupressure with conventional medicine, evaluating 151 patients with NVP. The pooled results showed that acupressure could further reduce the number of antiemetic drugs used by patients compared with conventional medicine [SMD = -0.44, 95% CI (-0.77, -0.11), $P = 0.008$] (Figure 4D). The GRADE analysis revealed that the overall level

of quality of the evidence to support this conclusion was low (Supplementary material 2).

Effective rate

Three trials (38, 43, 44) compared acupressure with conventional medicine, evaluating 210 patients with NVP. The pooled results showed that the effective rate was higher when patients received acupressure compared with conventional medicine [RR = 1.55, 95% CI (1.30, 1.86), $P \leq 0.001$] (Figure 5A). The GRADE analysis revealed that the overall level of quality of the evidence to support this conclusion was low (Supplementary material 2).

For further analysis, we grouped the different types of medications for subgroup analysis. The results showed that acupressure was superior to vitamin B6 + metoclopramide [RR = 1.73, 95% CI (1.18, 2.55), $P = 0.005$] (Figure 5B), venous metoclopramide [RR = 1.56, 95% CI (1.21, 2.00), $P = 0.001$] (Figure 5B) and sodium lactate ringer's injection [RR = 1.42, 95% CI (1.01, 2.01), $P = 0.046$] (Figure 5B).

Adverse events

A total of five articles (38, 40, 41, 43, 44) evaluating 367 patients with NVP mentioned no adverse events.

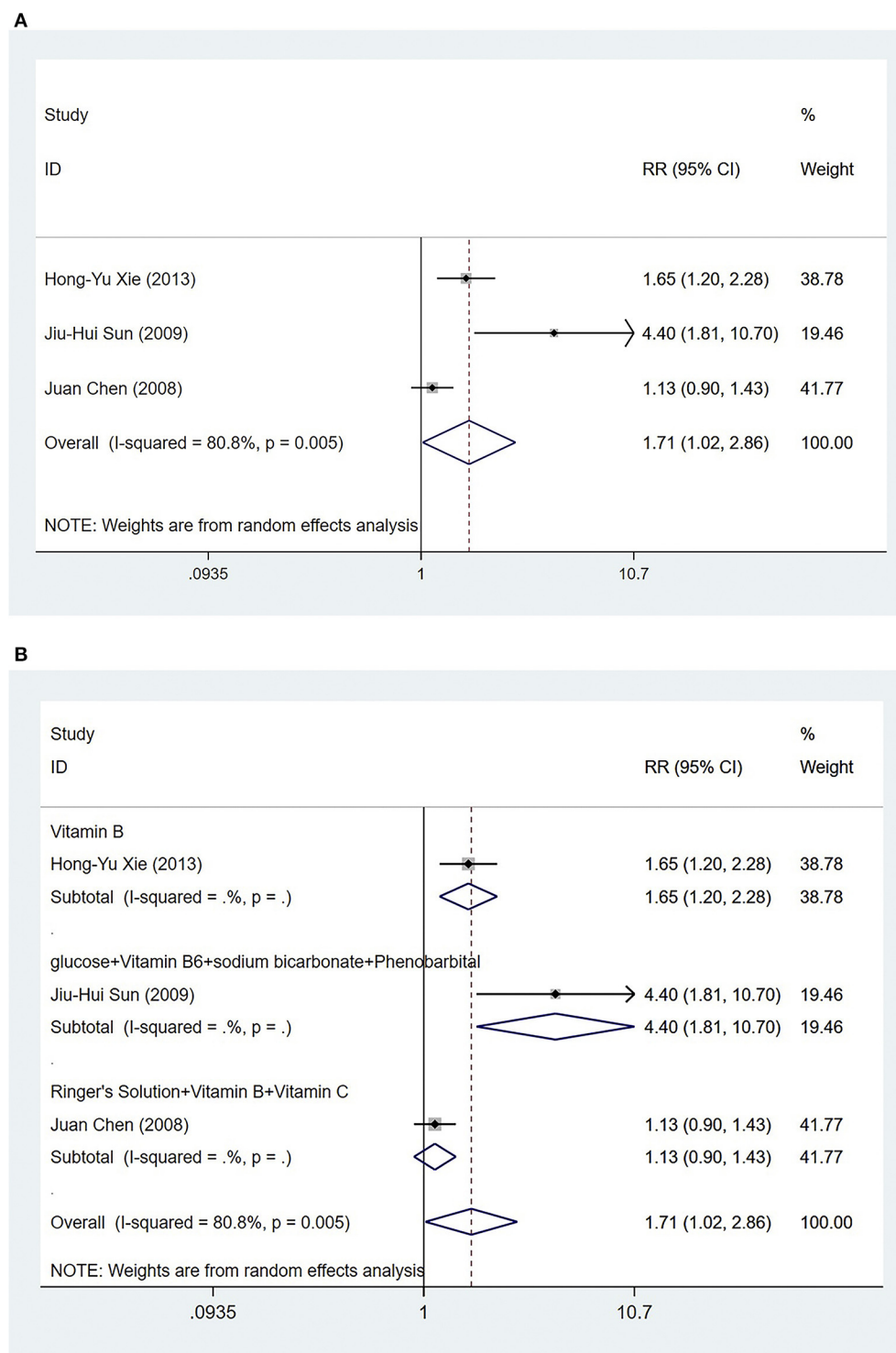


FIGURE 6

Acupuncture vs. Conventional medicine: (A) Effective rate; (B) Subgroup analysis based on different medications.

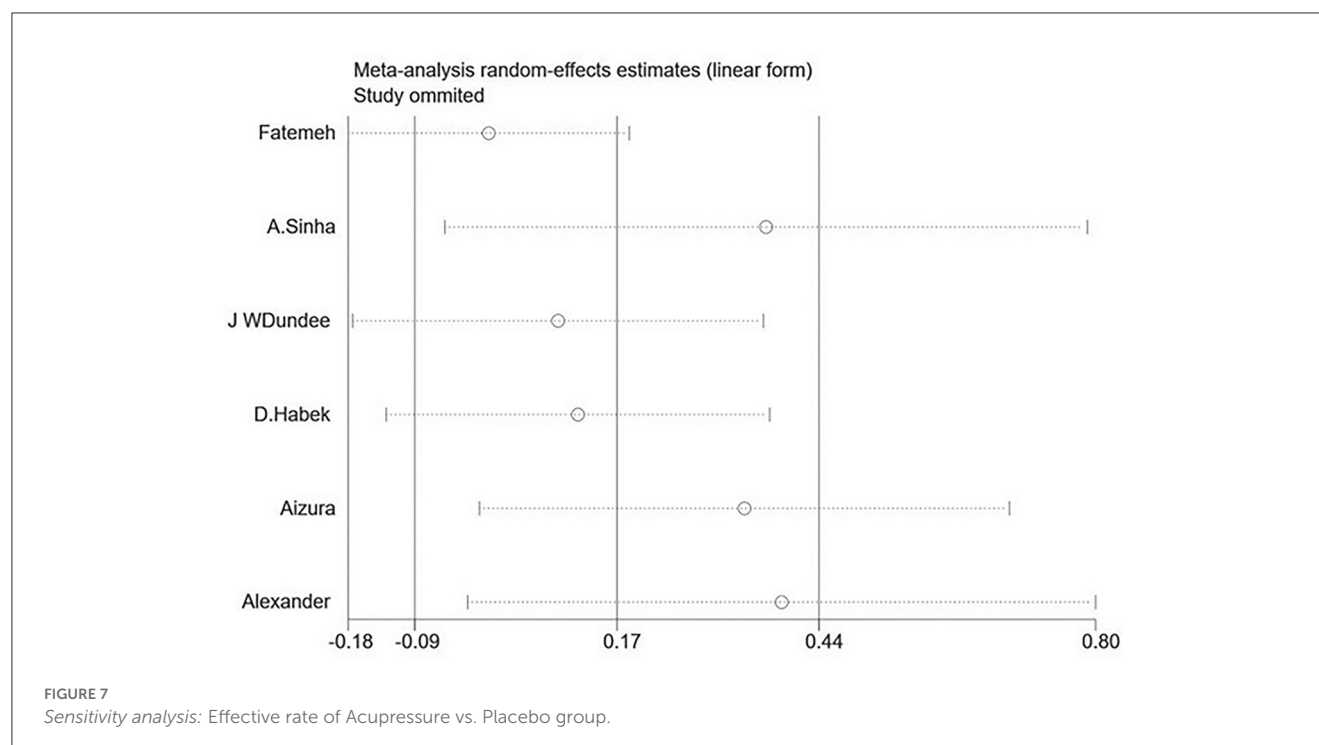
Acupressure vs. the placebo group

Effective rate

Six trials (38, 42, 46, 47, 55, 56) compared acupressure with placebo, evaluating 849 patients with NVP. The pooled results showed that acupressure had the same effect as placebo at the

effective rate [RR = 1.25, 95% CI (0.94, 1.65), $P = 0.124$] (Figure 5C), and the quality of evidence was low based on GRADE analysis (Supplementary material 2).

To find sources of heterogeneity, subgroup analyses were conducted for sample size, as well as year separately, and it was



found that the results did not change whether the sample size was >100 or <100 (Figure 5D). The results also did not change depending on whether the year of publication was before or after 2010 (Supplementary material 3).

Adverse events

A total of 9 articles (38, 39, 42, 45–48, 55, 56) mentioned adverse events, evaluating 1,073 patients with NVP, eight of which (38, 39, 42, 45, 46, 48, 55, 56) did not mention adverse effects. One paper (47) reported side effects in which one miscarriage occurred in a trial group of 40 patients, yet two cases occurred in a control group with the same number of patients. These could not be combined for analysis because too little data were available. However, this article showed that the safety of acupressure was better than traditional medicine.

Acupuncture

Acupuncture vs. conventional medicine

Effective rate

Three trials (51–53) compared acupuncture with conventional medicine, evaluating 230 patients with NVP. The pooled results showed that the effective rate was higher compared with conventional medicine when patients received acupuncture [RR = 1.71, 95% CI (1.02, 2.86), $P = 0.042$] (Figure 6A). The GRADE analysis revealed that the overall level of quality of the evidence to support this conclusion was low (Supplementary material 2).

For further analysis, we grouped the different types of medications for subgroup analysis. The results showed that acupuncture treatment was more effective than vitamin B [RR = 1.65, 95% CI (1.20, 2.28), $P = 0.002$] (Figure 6B). Compared

with glucose+vitamin B6+sodium bicarbonate+phenobarbital, acupuncture treatment had a higher effective rate [RR = 4.40, 95% CI (1.81, 10.70), $P = 0.001$] (Figure 6B). Acupuncture treatment was as effective as ringer's solution+vitamin B+vitamin C [RR = 1.13, 95% CI (0.90, 1.43), $P = 0.297$] (Figure 6B).

Adverse events

A total of three articles (51–53) evaluating 230 patients with NVP mentioned no adverse events.

Acupuncture vs. placebo group

Adverse events

A total of four articles (49, 50, 54, 56) mentioned adverse events, evaluating 402 patients with NVP, two of which (49, 56) did not mention adverse effects. One article (50) clearly stated that participants had no adverse effects. One paper (54) reported 11 adverse events in the trial group, including fatigue, sleep disturbance, and arm heaviness, and 8 adverse events in the same number of controls, including vomiting, flatulence, dreaming, and a feeling of coldness, which seemed to indicate that acupuncture had similar safety profile to placebo.

Sensitivity analysis and publication bias

Sensitivity analysis (Figure 7) showed that no single study significantly affected the results, reflecting that the results were statistically robust.

A funnel analysis and Begg's test were not performed due to limitations of the number of articles in the *per* outcome.

TABLE 2 The outcome of the meta-analysis.

Outcomes	Number	T/C	End of treatment					
			WMD/RR/SMD	95%CI	Heterogeneity	P-value	F/R	GRADE
Ginger vs. placebo								
VAS	3	88/100	WMD = −1.21	(−2.34)−(−0.08)	66.0%	P = 0.036	R	Low
Adverse events	3	112/116	RR = 1.57	(0.63)−(3.91)	0.0%	P = 0.336	R	Very low
Number of vomiting	2	56/65	WMD = 0.05	(−0.23)−(0.32)	0.0%	P = 0.743	R	Low
Effective rate	3	96/100	RR = 1.68	(1.09)−(2.57)	76.4%	P = 0.018	R	Low
Ginger vs. CM								
Number of vomiting	3	87/95	SMD = 0.30	(−0.12)−(0.73)	51.1%	P = 0.160	R	Low
Rhodes index	2	62/60	WMD = −0.52	(−0.79)−(−0.24)	0.0%	P ≤ 0.001	R	Moderate
Adverse events	4	76/77	RR = 0.21	(0.05)−(0.96)	87.2%	P = 0.045	R	Low
AP vs. placebo								
Effective rate	6	429/420	RR = 1.25	(0.94)−(1.65)	88.0%	P = 0.124	R	Low
AP vs. CM								
Effective rate	3	105/105	RR = 1.55	(1.30)−(1.86)	0.0%	P ≤ 0.001	R	Low
Number of anti-emetic drug	2	75/76	SMD = −0.44	(−0.77)−(−0.11)	0.0%	P = 0.008	R	Low
AT vs. CM								
Effective rate	3	115/115	RR = 1.71	(1.02)−(2.86)	80.8%	P = 0.042	R	Low

WMD, weighted mean difference; SMD, standard mean difference; RR, risk ratio; CI, confidence interval; VAS, visual analog scale; P, P-value represents clinical significance; CM, conventional medicine; AP, acupressure treatment; AT, acupuncture treatment; T, test group; C, control group; F, Fixed effects model; R, Random effects model; GRADE, Grades of Recommendation, Assessment, Development, and Evaluation; Very low, very low quality; Low, low quality; Moderate, Moderate quality.

High quality: Further research is very unlikely to change our confidence in the estimate of effect. Moderate quality: Further research is likely to have an important impact on our confidence in the estimate of effect and may change the estimate. Low quality: Further research is very likely to have an important impact on our confidence in the estimate of effect and is likely to change the estimate. Very low quality: We are very uncertain about the estimate.

Level of overall evidence

Table 2 presents the quality evaluation of each outcome of CAM on NVP.

In the comparison of ginger with conventional medicine, the quality of evidence suggested that the Rhodes in the outcome indicators was of moderate quality, while the number of vomiting and adverse events was of low quality. The evidence for the comparison of ginger with placebo was variable in VAS (low), number of vomiting (low), effective rate (low), and adverse events (very low).

In the comparison of acupuncture with conventional medicine, the quality of evidence suggested that the effective rate in the outcome indicators was of low quality. Evidence for the comparison of acupressure with conventional medicine was variable in the dosage of antiemetic drugs (low) and effective rate (low).

In the comparison of acupressure with placebo, the quality of evidence suggested that the effective rate in the outcome indicators was of low quality.

Discussion

Summary of results

The results showed that ginger could improve patients' Rhodes index compared with conventional medicine, with fewer side effects but no significant improvement in the number of vomiting.

Ginger improved nausea symptoms more than placebo and was more effective, but the improvement in vomiting was not obvious. Compared with conventional medicine, acupressure could reduce the amount of vomiting medication a person takes and be more effective. Compared with a placebo, acupressure was more effective and had the same side effects. Acupuncture was more effective in treating NVP than conventional medication and placebo. Acupuncture had a similar safety profile to a placebo. The specific results of the meta-analysis are shown in Tables 2, 3.

Discussion of CAM vs. conventional medicine

The results showed that ginger is as effective as conventional medicine in treating NVP, which remains consistent with the meta-results of Estelle et al. (16). Ginger can protect the gastric mucosa, promote gastrointestinal motility and block gastrointestinal adverse reactions, which has a good effect on nausea and vomiting (57). Fatemeh et al. studied pregnant women in the 6–16 weeks' gestation period and found that ginger and vitamin B6 were equivalent in improving NVP (29). Mattawan randomly divided pregnant women into a test and a control group with 85 people each (40). It was concluded that ginger was as effective as diphenhydramine in treating nausea and vomiting during pregnancy (40). The above studies were consistent with the results of this meta-analysis.

TABLE 3 Subgroup analysis results.

Outcome	Subgroup	Studies	Patients	RR	95% CI	Heterogeneity	P-value	F/R
Effective rate	Types of medications (AP vs.CM)							
	Vitamin B6 + metoclopramide	1	60	RR = 1.73	(1.18–2.55)	NR	P = 0.005	R
	Venous metoclopramide	1	90	RR = 1.56	(1.21–2.00)	NR	P = 0.001	R
	Sodium lactate ringer's injection	1	60	RR = 1.42	(1.01–2.01)	NR	P = 0.046	R
Effective rate	Sample size (AP vs. placebo)							
	≤100	3	158	RR = 3.57	(0.06–200.44)	98.60%	P = 0.536	R
	>100	3	691	RR = 1.04	(0.79–1.37)	76.80%	P = 0.781	R
Effective rate	Publication year (AP vs. placebo)							
	>2010	3	520	RR = 1.28	(0.79–2.06)	91.00%	P = 0.313	R
	<2010	3	329	RR = 1.93	(0.50–7.40)	94.40%	P = 0.340	R
Effective rate	Types of medications (AT vs.CM)							
	Vitamin B	1	94	RR = 1.65	(1.20–2.28)	NR	P = 0.002	R
	Glucose+Vitamin B6+sodium bicarbonate+Phenobarbital	1	100	RR = 4.40	(1.81–10.70)	NR	P = 0.001	R
	Ringer's solution+vitamin B+vitamin C	1	36	RR = 1.13	(0.90–1.43)	NR	P = 0.297	R

RR, risk ratio; F, Fixed effects model; R, Random effects model; CI, confidence interval; NR, not report; AP, acupressure; AT, acupuncture treatment; CM, conventional medicine.

The conventional medicines mainly included in this article included diphenhydramine, vitamin B6, metoclopramide, and so on. Among them, diphenhydramine has the effect of antihistamine H1 receptor and has a strong inhibitory effect on the central nervous system (58). Metoclopramide has a solid central antiemetic and gastrointestinal excitatory effect (59). Combined with the above results, ginger positively impacts NVP compared with conventional medicine. Considering that ginger has fewer side effects, it is an excellent complementary replacement therapy when patients are not well treated with traditional drugs or are unwilling to take it because of concerns about side effects.

Combined with the full-text results, acupuncture, and acupressure were more effective in treating NVP than conventional medicine and there was a high level of safety. Acupuncture and pressure points are similar, mostly PC6, TE5, N12, ST36, CV17, CV12, and SP4. Among them, PC6 was the most commonly used infusion point and Chinese medicine believes that stimulating and pressing this point has a good effect on relieving NVP. Vickers reviewed 16 RCTs and found that the stimulation of PC6 was an effective antiemetic based on consistent results found by researchers using various acupuncture techniques in different patient populations (60). O'Brien et al. subjected 161 symptomatic volunteers to bilateral PC6 acupoint stimulation, bilateral sham acupoint stimulation, or a no-banding control condition. Nausea and vomiting were assessed by self-report every 12 h. Of the 161 women, 149 (92.5%) completed the protocol and reported a significant decrease in NVP (61), which was consistent with the results of this meta-analysis. This may be related to the fact that PC6 concentrates its action on the AP *via* the vagal pathway to potentially affect the areal postrema by reducing hormone release (62). One study found that electroacupuncture of PC6 by the intravenous drip of pressing significantly reduced the number of NVPs and inhibited retrograde peristaltic contractions (63). From the above results, it can be seen that acupuncture or acupressure

is a good choice when the patient does not want to take any medication, even ginger.

To further study specific drugs, we performed subgroup analyses of the medications. The results showed that acupressure was superior to vitamin B6 + metoclopramide, venous metoclopramide, and sodium lactate ringer's injection. Acupuncture treatment was more effective than vitamin B and glucose+vitamin B6+sodium bicarbonate+Phenobarbital. Acupuncture treatment was as effective as ringer's solution+vitamin B+vitamin C. It is worth noting that due to the limitation of the number of relevant literature, the results need to be treated with caution. More clinical trials will be needed in the future to verify this result.

Discussion of CAM vs. placebo

Placebo measures included stimulating non-acupuncture points, taking nitroglycerin, or using flour. In general, CAM was superior to placebo for NVP. Combined with the comparison of CAM and conventional medicine, it can be concluded that the effect of CAM on NVP is definite. As for the security of CAM, the results showed that it was close to a placebo, which also proves the high level of security of CAM.

For the high heterogeneity of acupressure vs. placebo for NVP, a subgroup analysis of sample size and year of publication was performed, which showed the same result regardless of whether the year of publication was before or after 2010 and whether the sample size was greater or <100. By reading these articles, it was discovered that some articles stimulated only the PC6. In contrast, some stimulated other points in addition to the PC6, and not all with the same frequency and treatment periods, which may also contribute to the heterogeneity. Due to the limitation

of the number of articles, the frequency, acupuncture points, and treatment duration in further subgroups were not analyzed. Further large-sample RCTs are needed to verify this in the future.

Strength and limitation

Firstly, this is the first meta-analysis to examine CAM for NVP, ensuring accuracy while comprehensively including all RCTs. Secondly, a comprehensive set of outcome indicators to evaluate the efficacy of CAM for NVP in comprehensive aspects were included. Finally, a placebo control was included, and more accurately and objectively analyzed the therapeutic effects of CAM. However, this study has the following limitations: (1) the RCT included in this paper may be sources of heterogeneity due to the different frequency and types of acupuncture, the different experiences of acupuncturists, the different amounts of acupoints and ginger pressed; (2) it must be considered that the degree of vomiting varies by trimester. However, further exploration of the efficacy of CAM for treating different degrees of vomiting in different trimesters was not conducted due to the limitation of the number of included articles; (3) through a comprehensive search, it was found that the number of articles reporting CAM for NVP is still low, the sample size is small and since there were some results with a relatively large confidence interval, false positive results may occur; and (4) although we searched eight databases comprehensively, the languages were limited to Chinese and English and the studies included were mostly conducted in Asia, which may have led to some limitations regarding population outreach.

Conclusion

The current evidence showed that CAM was superior to placebo or conventional medicine with fewer side effects.

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Therefore, it is recommended that clinicians use CAM for NVP. However, due to the small number of RCTs and the small sample size, more rigorously designed, large-sample multicenter RCTs will be needed to prove these results in the future.

Author contributions

Conception and design of the study: M-YT, S-HS, and QZ. Data collection and analysis: M-YT, R-LL, and QZ. Draft paper: M-YT, S-HS, R-LL, and QZ. Approve the final paper to be published: All authors.

Conflict of interest

The authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

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Supplementary material

The Supplementary Material for this article can be found online at: <https://www.frontiersin.org/articles/10.3389/fpubh.2023.1108756/full#supplementary-material>

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EDITED BY

Nita Bhandari,
Society for Applied Studies,
India

REVIEWED BY

Harish Chellani,
All India Institute of Medical Sciences,
India
Ramachandran Thiruvengadam,
Pondicherry Institute of Medical Sciences,
India
Uttara Partap,
Harvard University,
United States

*CORRESPONDENCE

Rinawati Rohsiswatmo
✉ rinarohsis@gmail.com

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Defining postnatal growth failure among preterm infants in Indonesia

Rinawati Rohsiswatmo*, Risma Kerina Kaban,
Muhamad Azhar Rully Sjahrulla,
Hardya Gustada Hikmahrachim,
Putri Maharani Tristanita Marsubrin, Rosalina Dewi Roeslani,
Adhi Teguh Perma Iskandar, Distyayu Sukarja, Ahmad Kautsar
and Ivo Urwah

Division of Perinatology, Department of Child Health, Faculty of Medicine Universitas Indonesia, Cipto Mangunkusumo General Hospital, Jakarta, Indonesia

Background: Postnatal growth failure (PGF) frequently occurred among preterm infants with malnutrition. The decline in a weight-for-age z-score of ≥ 1.2 has been proposed to define PGF. It was unknown whether this indicator would be useful among Indonesian preterm infants.

Methods: Infants of <37 weeks of gestational age born between 2020 and 2021, both stable and unstable, were recruited for a prospective cohort study during hospitalization in the level III neonatal intensive care unit at the Cipto Mangunkusumo General Hospital, Jakarta, Indonesia. The prevalence of PGF as defined by a weight-for-age z-score of <-1.28 (<10 th percentile) at discharge, a weight-for-age z-score of <-1.5 (<7 th percentile) at discharge, or a decline in a weight-for-age z-score of ≥ 1.2 from birth till discharge was compared. The association between those PGF indicators with the preterm subcategory and weight gain was assessed. The association between the decline in a weight-for-age z-score of ≥ 1.2 with the duration to achieve full oral feeding and the time spent for total parenteral nutrition was analyzed.

Results: Data were collected from 650 preterm infants who survived and were discharged from the hospital. The weight-for-age z-score of <-1.28 or <-1.5 was found in 307 (47.2%) and 270 (41.5%) subjects with PGF, respectively. However, both indicators did not identify any issue of weight gain among subjects with PGF, questioning their reliability in identifying malnourished preterm infants. By contrast, the decline in a weight-for-age z-score of ≥ 1.2 was found in 51 (7.8%) subjects with PGF, in which this indicator revealed that subjects with PGF had an issue of weight gain. Next, a history of invasive ventilation was identified as a risk factor for preterm infants to contract PGF. Finally, the decline in a weight-for-age z-score of ≥ 1.2 confirmed that preterm infants with PGF took a longer time to be fully orally fed and a longer duration for total parenteral nutrition than the ones without PGF.

Conclusion: The decline in a weight-for-age z-score of ≥ 1.2 was useful to identify preterm infants with PGF within our cohort. This could reassure pediatricians in Indonesia to use this new indicator.

KEYWORDS

preterm infant, malnutrition, postnatal growth failure, Indonesia, indicator

Introduction

Neonatal nutritional care is aimed to maintain postnatal growth linear to normal intrauterine growth (1). Preterm infants with various morbidities are prone to malnutrition, which results in poor growth or even postnatal growth failure (PGF) (2). The risk of postnatal malnutrition is related to decreased nutrient stores at birth, organ immaturity and reduced nutrient absorption, existing comorbidities, dependence on correct identification of malnutrition among infants, and timing of adequate nutrient provision (2). It is, therefore, prudent to correctly identify preterm infants who are malnourished to mitigate or even prevent the potential long-term sequelae of PGF, such as poor neurodevelopment (3).

Various growth parameters have been used to identify infants with PGF, including a weight-for-age *z*-score of <-2.0 at term and 8-month corrected age (4), a weight-for-age *z*-score of <-1.28 (<10 th percentile) (5), and a weight-for-age *z*-score of <-1.5 (<7 th percentile) at discharge or at approximately 36–40 weeks of postmenstrual age (6). However, those parameters are problematic in accurately identifying preterm infants with growth problems and in predicting their negative adverse outcome (3). Those one-time weight-based indicators have several limitations, including (i) not being predictive of adverse neurodevelopment and (ii) not considering normal postnatal weight loss (3). Other indicators of malnutrition for preterm infants and neonates that focus on a growth pattern (instead of one-time data) had recently been proposed, such as a decline in weight-for-age *z*-score. This indicator is based on an observation that infants with uncomplicated postnatal adaptation or no malnutrition should have a decline in a weight-for-age *z*-score of <0.8 from birth till discharge (2). In addition, this indicator with relatively small cutoffs for mild, moderate, and severe malnutrition suggests that uncomplicated preterm infants are expected to gain weight very rapidly (2). As this indicator is based on differences between the *z*-score at birth and *z*-score at discharge (as opposed to one-time indicators), it has the potential to be more useful in defining PGF among preterm infants. However, as the characteristics of preterm populations might differ between countries, due to genetic variation, social behavior, and existing medical facilities, it is important to assess this new indicator in various preterm populations.

We recently initiated a prospective cohort study in Jakarta, Indonesia [the Cohort of Indonesian PreTerm infants for long-term Outcomes (CIPTO) study] to study preterm infants born at the Cipto Mangunkusumo General Hospital. The CIPTO study is the first and expected to be the largest prospective pediatric cohort in Indonesia. The aims of the CIPTO study were determining the outcomes of those ex-preterm infants and generating an evidence-based reference of preterm care to achieve optimum outcomes. The CIPTO study will be a long-term study as it follows the ex-preterm infants until 8 years old (i.e., school-age children). Hereby, the first part of the CIPTO study was reported, investigating the usefulness of the new indicator of malnutrition (i.e., decline in weight-for-age *z*-score), as compared with common one-time weight-for-age indicators, to identify PGF among Indonesian preterm infants. We observed that this new indicator was useful to define PGF among Indonesians as well.

Methods

Study design

The Cohort of Indonesian PreTerm infants for long-term Outcomes (CIPTO) study was a prospective cohort study conducted to observe preterm infants born between 2020 and 2030 at the Cipto Mangunkusumo General Hospital, Jakarta, Indonesia (article of its study protocol is in submission). This report was a part of the CIPTO study, presenting the observational results on preterm infants born between 2020 and 2021 during their perinatal care in the hospital. The Cipto Mangunkusumo General Hospital is a teaching hospital that serves as the national reference hospital and has a level III neonatal intensive care unit (NICU) and greater coverage of diagnosis-related group reimbursement from the National Health Insurance. In addition, this hospital is in Jakarta, the capital city of Indonesia, in which its population comprises various ethnic groups living in the Indonesian archipelago. We recruited preterm infants (<37 weeks of gestational age) who were born during the period of 2020–2021, both stable and unstable, and who survived the neonatal care period and are living in Jakarta and its greater area. The exclusion criteria were parents unwilling to participate, self-discharged before receiving a recommendation from pediatricians, or parents planning to relocate from Jakarta in the subsequent 2 years. The dropout criterion was subjects deceased during the neonatal period. Anthropometric measurement was performed by a trained nurse, nutritionist, or physician. Calibrated tools were used to measure weight. Ethical approval was granted by the Ethical Committee of Faculty of Medicine Universitas Indonesia and Cipto Mangunkusumo General Hospital.

Exposures and outcomes

The main outcome of this analysis was the incidence of PGF at discharge. We compared the currently used indicators of PGF (i.e., weight-for-age *z*-score below either -1.28 [<10 th percentile] or -1.5 [<7 th percentile] at discharge without considering the birth weight value) with the new indicator (i.e., a decline in weight-for-age *z*-score ≥ 1.2 from birth to discharge). All indicators are based on the Fenton preterm growth charts. Subgroups of no malnutrition, mild malnutrition, moderate malnutrition, and severe malnutrition were classified based on the decline in weight-for-age *z*-score of <0.8 , $0.8-1.2$, $1.2-2.0$, and >2.0 standard deviation (SD), respectively (2). For this analysis, we used the decline in a weight-for-age *z*-score of ≥ 1.2 to define PGF. Potential predictors in our analysis were gestational age, birth weight, type of enteral feeding, and comorbidities related to prematurity. Diagnosis of comorbidities was based on current literature and was decided by the attending neonatologists. We measured the association between several growth parameters preceding PGF (weight gain, time to full enteral feeding, and duration of parenteral nutrition) and those weight-based indicators of PGF. Measurement of average weight gain was assessed with methods of early 1-point, average 2-point average, and exponential 2-point (7). The formula to calculate early 1-point was $(W_2 - W_1) / (W_1 / 1000) / \text{number of days}$. The formula to calculate the average 2-point average was $(W_2 - W_1) / [(W_2 + W_1) / 2] / 1,000 / \text{number of days}$. The formula to calculate exponential 2-point was $1,000 \times \ln(W_2 / W_1) / \text{number of days}$.

days, where W_1 indicates weight at the earliest time point and W_2 indicates weight at the latest time point. The unit was gram per kilogram per day. Full-enteral feeding was defined as enteral feeding above 120 kcal/kg/day. For infants born <32 weeks, aggressive parenteral nutrition was initiated from birth, but it was not mandatory for infants born >32 weeks.

Statistical analyses

Data analyses were performed using the STATA software version 15 for Windows. Descriptive statistics was presented according to the type of data. For continuous data, the difference between the two groups was calculated using the Mann–Whitney U-test, while those with more than two groups were calculated using the Kruskal–Wallis test, which was further confirmed by *post hoc* Dunn's test. Categorical data were analyzed using the chi-square test and Cohen's kappa test as well as Cox regression for a multivariate analysis. A statistical significance is considered with a p -value of <0.05.

Results

A total of 650 preterm infants were recruited during the study period (Table 1). There were 367 (56.5%) male and 283 (43.5%) female infants who participated in this study. The average gestational age of the subjects at the beginning of the study was 33.1 weeks, while the average gestational age at discharge was 36 weeks. The average birth weight, birth length, and birth head circumference of the subjects were 1,898 g, 41.2 cm, and 29.8 cm, respectively. The majority of subjects received either a mixture of breast milk and formula milk (48.6%) or exclusively breast milk (40.3%). The most and least frequent comorbidities were early-onset sepsis (22.3%) and bronchopulmonary dysplasia (3.7%).

The decline in a weight-for-age z -score of ≥ 1.2 SD was chosen with the premise that preterm infants with moderate and severe malnutrition were the ones who were likely to suffer from PGF (2). This indicator was compared with two common weight-for-age indicators of PGF, i.e., a weight-for-age z -score of < -1.28 (<10th percentile) and a weight-for-age z -score of < -1.5 (<7th percentile), to assess the frequency of PGF within three subcategories of preterm (Table 2). The number of preterm infants with PGF as defined by common weight-based indicators was arguably high ($n = 307$ [47.2%] and $n = 270$ [41.5%] based on a weight-for-age z -score of < -1.28 and < -1.5 , respectively). This contrasted with the numbers indicated by the decline in a weight-for-age z -score of ≥ 1.2 ($n = 51$ [7.8%]). This difference was presumably contributed by a strong tendency of those common weight-based indicators to define PGF among moderate-to-late preterm infants (81.4 and 80.4%) but a not too strong tendency based on the decline in a weight-for-age z -score of ≥ 1.2 (52.9%).

Preterm infants with PGF by definition should accumulate less weight (2). In contrast to a weight-for-age z -score of < -1.28 and < -1.5 , the decline in a weight-for-age z -score of ≥ 1.2 could better distinguish preterm infants with PGF from the ones with no PGF in terms of weight gain (Table 3). Irrespective of the calculation methods, preterm infants with PGF identified by a decline in a weight-for-age z -score of ≥ 1.2 accumulated less weight as compared with the ones without PGF ($p < 0.05$). Intriguingly, a paradoxical association was observed between

TABLE 1 Demographic data of the study participants.

Characteristics	<i>n</i>	%
Sex		
Boy	367	56.5
Girl	283	43.5
Gestational age (week)		
Mean (SD)	33.1 (2.3)	-
Median (min-max)	33 (26–36)	-
Birth weight (gram)		
Mean (SD)	1,898 (497)	-
Median (min-max)	1,855 (720–4,680)	-
Birth length (centimeter)		
Mean (SD)	41.2 (3.8)	-
Median (min-max)	41 (39–54)	-
Birth head circumference (centimeter)		
Mean (SD)	29.8 (2.6)	-
Median (min-max)	30 (28–31)	-
Type of enteral feeding		
Breast milk only	262	40.3
Breast milk and formula	316	48.6
Formula only	72	11.1
Gestational age at discharge (week)		
Mean (SD)	36 (1.8)	-
Median (min-max)	36 (35–43)	-
Length of hospitalization (day)		
Mean (SD)	27 (16)	-
Median (min-max)	22 (9–79)	-
Comorbidities		
Early-onset sepsis	145	22.3
Late-onset sepsis	62	9.5
Necrotizing enterocolitis	38	5.9
History of invasive ventilation	58	8.9
Bronchopulmonary dysplasia	24	3.7
Intraventricular hemorrhage	27	4.2

SD, standard deviation.

a weight-for-age z -score of < -1.28 and < -1.5 with weight gain, in which PGF preterm infants identified by these indicators gained more weight than the non-PGF ones ($p < 0.001$). These findings, indeed, question the reliability of those current one-time weight-based indicators to define preterm infants with PGF (2).

Next, analyses of several potential risk factors to develop PGF, as defined by those weight-based indicators, were conducted (Table 4). First, as compared with preterm infants who exclusively received breast milk, no statistical difference in terms of risk to develop PGF was observed among preterm infants who were fed with formula milk only. Intriguingly, the decline in a weight-for-age z -score of ≥ 1.2 (RR = 0.28; 95% CI: 0.12–0.65; $p = 0.003$), but not other indicators, suggested that the preterm infants who received a combination of

breast milk and formula milk had a lower risk than the ones who exclusively received breast milk to develop PGF. Second, several comorbidities (i.e., early-onset neonatal sepsis; late-onset neonatal sepsis; necrotizing enterocolitis; bronchopulmonary dysplasia; and intraventricular hemorrhage) were prominent in not increasing the risk of PGF, irrespective of the definitions. However, while a weight-for-age z -score of <-1.28 and <-1.5 did not identify any statistical difference in the history of invasive ventilation, the decline in a weight-for-age z -score of ≥ 1.2 suggested that preterm infants with a history of invasive ventilation had a higher risk to develop PGF (RR = 3.04; 95% CI: 1.41–6.53; $p = 0.004$). Collectively, the decline in a weight-for-age z -score of ≥ 1.2 was able to define the population with PGF as well as its associated risk factor.

The association between the decline in weight-for-age z -score and duration of total parenteral nutrition or time to achieve full oral feeding was finally analyzed. Preterm infants identified by the decline in a weight-for-age z -score of ≥ 1.2 had a longer duration of total parenteral nutrition and the time to achieve full oral feeding, as compared with the ones identified by the decline in z -scores of <1.2 (Figure 1; median of total parenteral nutrition = 2 vs. 0.5 days; median of achieving full oral feeding = 10 vs. 5 days). Taken together, this finding supports the usefulness of the decline in a weight-for-age z -score of ≥ 1.2 to identify preterm infants with PGF.

Discussion

We hereby report the first part of the CIPTO study, focusing on 650 infants of <37 weeks of gestational age at birth between 2020 and 2021 at the perinatal unit of Cipto Mangunkusumo General Hospital, Jakarta, Indonesia. Our results could be summarized into three points. First, the decline in a weight-for-age z -score of ≥ 1.2 (indicating moderate and severe malnutrition) was useful to identify preterm infants with PGF in this cohort. While the decline in a weight-for-age z -score of ≥ 1.2 identified only 51 subjects with PGF, a weight-for-age z -score of <-1.28 and <-1.5 somehow identified 250 and 217 subjects with PGF,

TABLE 2 Incidence of postnatal growth failure across subcategories of preterm.

Subcategory of Preterm	Indicator of Postnatal Growth Failure					
	Weight z -score <-1.28		Weight z -score <-1.5		Decline in weight-for-age z -score ≥ 1.2	
	<i>n</i>	%	<i>n</i>	%	<i>n</i>	%
Moderate-late preterm (<i>n</i> = 518)	250	48.3	217	41.9	27	5.2
Very preterm (<i>n</i> = 113)	49	43.4	45	39.8	18	15.9
Extreme preterm (<i>n</i> = 19)	8	42.1	8	42.1	6	31.6

Chi-square result for the column of weight z -score <-1.28 was $p = 0.577$. Chi-square result for the column of weight z -score <-1.5 was $p = 0.920$. Chi-square result for the column of decline in a weight-for-age z -score of ≥ 1.2 was $p = 0.000$. Cohen's kappa statistic: Weight z -score <-1.28 versus decline in a weight-for-age z -score of ≥ 1.2 : kappa 0.071; agreement 61.09%. Weight z -score <-1.5 versus decline in a weight-for-age z -score of ≥ 1.2 : kappa 0.085; agreement 65.95%. Percentages were calculated per subcategory of preterm. Weight z -score <-1.28 is weight <10 th percentile. Weight z -score <-1.5 is weight <7 th percentile.

TABLE 3 Association between various weight-based indicators of postnatal growth failure and weight gain during admission in neonatal care.

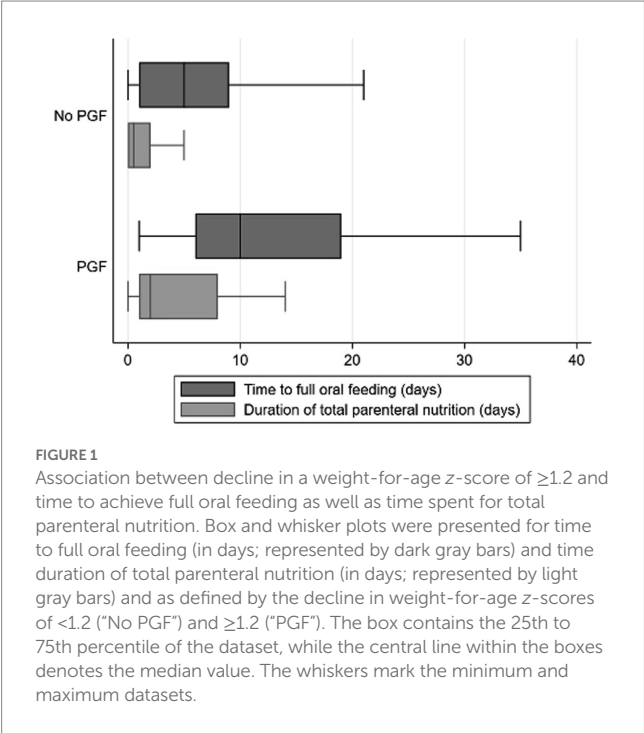
Indicator	Early 1-point (g/kg/day)			Average 2-point average (g/kg/day)			Exponential 2-point (g/kg/day)		
	PGF		<i>p</i> value	PGF		<i>p</i> value	PGF		<i>p</i> value
	No PGF	No PGF		No PGF	No PGF		No PGF	No PGF	
Weight z -score <-1.28	8.79 (4.14–14.38)	5.72 (0.00–13.61)	<0.001	8.04 (4.03–11.35)	5.43 (0.00–11.06)	<0.001	8.07 (4.03–11.46)	5.14 (0.00–11.12)	<0.001
Weight z -score <-1.5	8.89 (4.55–14.77)	5.74 (0.00–13.60)	<0.001	8.05 (4.37–11.53)	5.48 (0.00–11.05)	<0.001	8.08 (4.37–11.84)	5.20 (0.00–11.11)	<0.001
Decline in weight-for-age z -score ≥ 1.2	4.44 (–1.04–9.40)	8.04 (0.00–14.11)	<0.001	4.22 (–1.05–8.04)	7.43 (0.00–11.39)	<0.001	4.44 (–1.04–9.40)	8.04 (0.00–14.11)	<0.001

Data were presented as median (25th–75th percentile). Measurement of average weight gain was assessed by using three formulas. Formula to calculate early 1-point = $(W2 - W1) / (W1 / 1000) / \text{number of days}$. Formula to calculate average 2-point average = $(W2 - W1) / [(W2 + W1) / 2] / 1000 / \text{number of days}$. Formula to calculate exponential 2-point = $1,000 \times \ln(W2 / W1) / \text{number of days}$. W1 indicates weight at the earliest time point. W2 indicates weight at the latest time point. The Mann–Whitney U-test was used to compare the medians from PGF and no PGF in the same row. Weight z -score <-1.28 is weight <10 th percentile. Weight z -score <-1.5 is weight <7 th percentile. PGF, postnatal growth failure.

TABLE 4 Multivariate analysis on risk factors associated with postnatal growth failure.

Risk factor	Weight z-score<−1.28		Weight z-score<−1.5		Decline in weight-for-age z-score≥1.2	
	RR	95% CI	RR	95% CI	RR	95% CI
Enteral feeding (versus breast milk)						
Breast milk and formula	0.84	0.64–1.09	0.79	0.60–1.05	0.28	0.12–0.65
Formula only	0.86	0.58–1.27	0.80	0.52–1.22	0.90	0.37–2.19
Early-onset neonatal sepsis	0.93	0.66–1.32	0.91	0.63–1.33	2.11	0.93–4.79
Late-onset neonatal sepsis	1.01	0.63–1.63	0.89	0.52–1.50	1.97	0.76–5.13
Necrotizing enterocolitis	1.49	0.94–2.38	1.55	0.95–2.53	0.54	0.19–1.54
Bronchopulmonary dysplasia	0.97	0.52–1.79	1.05	0.57–1.96	1.98	0.83–4.73
Intraventricular hemorrhage	0.58	0.28–1.18	0.58	0.27–1.23	0.94	0.29–3.11
History of invasive ventilation	1.04	0.65–1.64	1.13	0.70–1.83	3.04	1.41–6.53

Weight z-score < −1.28 is weight of <10th percentile. Weight z-score < −1.5 is weight of <7th percentile. RR, relative risk; CI, confidence interval. Bold letters indicate a value of *p*-value of <0.05.



respectively. We argue that this was an issue of overestimation, as a weight-for-age z-score of <−1.28 and <−1.5 reported that subjects with PGF in our cohort did not have any issue with weight accumulation, as compared with the subjects without PGF. This interpretation was in line with a recent challenge to the usefulness of a weight-for-age z-score of <−1.28 as an indicator of PGF (3) due to its inability to predict any adverse outcome and its inability to adequately identify malnourished preterm infants. The latter notion could result in nutrition intake above infants’ actual requirement, predisposing those infants to later develop metabolic diseases (8). Another supporting finding of the usefulness of the decline in a weight-for-age z-score of ≥1.2 to identify preterm infants with PGF was that the identified subjects had a protracted time receiving parenteral nutrition or a delayed time in receiving full enteral nutrition.

Second, we observed that formula feeding or breast milk plus formula feeding did not increase the risk of PGF as compared with exclusive breast milk feeding. This finding suggests that, irrespective of the mode of enteral feeding, timely initiation of enteral feeding with adequate calories was the important factor to prevent malnutrition and PGF among preterm infants (9, 10). An interesting observation from our cohort was that breast milk plus formula feeding was associated with a lower risk to develop PGF than exclusive breast milk feeding when evaluated by the decline in a weight-for-age z-score of ≥1.2. Exclusive breast milk feeding for 6 months is a well-known fact to support infants to be healthy and to grow and develop adequately. However, if exclusive breast milk feeding is not possible or is insufficient for optimal growth and development, we believe that the mode of breast milk plus formula feeding or the nutrient fortification of breast milk would allow preterm infants to enjoy the immuno-nutrient advantage of breast milk as well as the higher amounts of important nutrients of formula (11, 12). This could help to reduce the risk to develop PGF. It is important to consider, however, that this interpretation might be skewed due to the low numbers of infants receiving exclusive breast milk feeding at the NICU. It is commonly acknowledged that rates of breastfeeding initiation and duration were lower among infants treated at the NICU, particularly in developing countries, due to various reasons, including unstable infant condition in the first 24–48 h of life, maternal health issues, and anguish related to their hospitalized infants, the detachment between mothers and infants due to physical separation, lack of maternal privacy to lactate, and inadequate support for exclusive breast milk feeding (13–18).

Finally, we noted that the decline in a weight-for-age z-score of ≥1.2 identified that a history of invasive ventilation was associated with a higher risk among preterm infants to develop PGF. This is not surprising since the history of invasive ventilation, in particular, the prolonged one, increased the risk of respiratory morbidity (e.g., bronchopulmonary dysplasia) (19, 20), which could result in a higher risk of PGF (19–21).

Postnatal growth failure is commonly caused by pediatric malnutrition, in which preterm infants are prone to suffer from nutritional deficits (2). This implies the importance to have a standardized indicator to identify malnutrition among preterm infants as a surrogate indicator of PGF, which can be properly utilized by

pediatricians worldwide (3). Various data could be used to identify malnutrition among preterm infants, comprising changes in weight, length, head circumference, body composition, body mass index, mid-upper arm circumference, and nutrition-focused physical exam (2). Weight and its changes are the most common indicator to be used as preterm infants with adequate nutrition should gain weight rapidly and as these data could be accurately collected (2). It should be noted, however, that weight measurement alone might not accurately identify infants who had weight gain disproportionate to their growths in length and head circumference (16, 17). Hence, some experts recommended calculating the decline in both length-for-age and head circumference-for-age z-scores as well, to complement the indicator of decline in weight-for-age z-score (2). Nonetheless, as length and head circumference assessments are only useful if they are accurately measured, the same experts proposed that the decline in weight-for-age z-score could be used as a single primary indicator to diagnose PGF (2).

A good definition of PGF allows early detection of the true population-at-risk, which thus could minimize problems with overdiagnosis and intervention-related adverse risk, such as risks for obesity and cardiovascular disease in later life due to overfeeding (22). It was concerning, therefore, to observe a trend of PGF overdiagnosis within our cohort when the single-point definitions of a weight-for-age z-score of <-1.28 and <-1.5 at discharge had been deployed. A recent review by Fenton et al (3), indeed, challenged the usefulness of a weight-for-age z-score of <-1.28 as the obtained result was solely based on the weight, was measured without correction, and was not predictive of poor neurodevelopment. A similar argument was presented by Zozaya et al (6) when they observed that a weight-for-age z-score of <-1.5 at 36 weeks was not associated with a worse Bayley II mental development index. By contrast, the definitions of decline in a weight-for-age z-score of ≥ 1.2 (2) provided a useful estimation of PGF within our cohort, corroborated by association with issues of weight accumulation and a history of invasive ventilation. It is important to note, however, that the accuracy of the definition is influenced by the growth charts as well. The INTERGROWTH-21st Preterm Postnatal Growth Standards curves were created as a better alternative than size-at-birth charts (23, 24), in which a recent study suggested an alternative definition of PGF (i.e., a decline in a weight-for-age z-score of 1.0 or higher) based on INTERGROWTH-21st growth curves to predict the risk of cognitive delay (25). It would be of interest in future to assess PGF among preterm infants by using this alternative growth curve.

There were several limitations found in our study. One limitation is that it was a single-center study design with a small number of infants born at 26–27 weeks (i.e., extremely preterm) recruited in this report. Our cohort did not have preterm infants born below 26 weeks. Thus, the reliability of our data among extremely preterm infants might be questionable. In addition, we did not stratify our preterm cohort based on any existing comorbidity during the admission at the NICU (i.e., stable vs. unstable preterm infants). Thus, we could not compare the growth trajectory between both groups. Next, as this report described the first part of the ongoing CIPTO study, the complete data on health, growth, and development outcomes of those surviving preterm infants at 24 months and beyond are unavailable yet. This limits our ability to calculate sensitivity and specificity, as more concrete outcomes, in evaluating those weight-based indicators of PGF among preterm infants. Another limitation is that our current

cohort does not have comparable proportions of categories such as small for gestational age, appropriate for gestational age, and large for gestational age. Thus, we could not draw any conclusion regarding the impact of weight-for-gestational age at birth on the incidence and outcomes of preterm infants with PGF. We also acknowledge the possibility that different timings of discharge from the NICU might contribute to potential differences observed within our cohort since we did not stratify our cohort based on the timing of hospital discharge. Nonetheless, as the hospital discharge was primarily based on clinical judgment (i.e., age ≥ 36 weeks postmenstrual age, weight $> 2,000$ g, and no more indication for intensive monitoring), we hypothesize that the impact of timing differences in hospital discharge would be minimum. Finally, this part of the CIPTO study only assessed weight-based indicators to define PGF. It is known that chronic inadequate nutrient intake would also reduce length gain and head growth. This suggests that weight-based indicators should be accompanied by length- and head circumference-based indicators to define PGF well among preterm infants.

Further studies should be conducted based on the CIPTO cohort, such as (i) assessing the health, growth, and developmental outcomes of those surviving preterm infants, with and without PGF, at 24 months and beyond; (ii) comparing the impact of weight-for-gestational age at birth on the incidence and outcomes of preterm infants with PGF; (iii) complementing the weight-based indicator with length- and head circumference-based indicators to define PGF among preterm infants; and (iv) determining the preterm growth curve (e.g., the Fenton vs. INTERGROWTH-21st charts) that suits best in defining PGF among preterm infants.

In conclusion, the decline in a weight-for-age z-score of ≥ 1.2 was useful to define preterm infants with PGF within our cohort. This could provide reassurance to pediatricians in Indonesia for switching from the common-yet-problematic indicators, such as a weight-for-age z-score of <-1.28 or <-1.5 , to this new indicator to identify preterm infants with PGF.

Data availability statement

The original contributions presented in the study are included in the article/supplementary material, further inquiries can be directed to the corresponding author.

Ethics statement

The studies involving human participants were reviewed and approved by the ethics committee, Faculty of Medicine, Universitas Indonesia. Written informed consent to participate in this study was provided by the participants' legal guardian/next of kin.

Author contributions

The primary investigators were RR and HH. The primary data coordinator was IU. The main coordinator for data assessment and collection during the in-hospital period was MS. All other co-authors were involved in conducting this study. All authors contributed to the article and approved the submitted version.

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Conflict of interest

The authors declare that the study was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

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EDITED BY

Sunita Taneja,
Society for Applied Studies,
India

REVIEWED BY

Pratibha Dwarkanath,
St. John's Research Institute,
India

Satinder Aneja,
Sharda University,
India

*CORRESPONDENCE

Gregorio P. Milani
✉ milani.gregoriop@gmail.com

[†]These authors have contributed equally to this work

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Vitamin D in pediatric age: Current evidence, recommendations, and misunderstandings

Antonio Corsello^{1†}, Giulia C. I. Spolidoro^{1†}, Gregorio P. Milani^{1,2*†}
and Carlo Agostoni^{1,2†}

¹Department of Clinical Sciences and Community Health, University of Milan, Milan, Italy, ²Pediatric Unit, Fondazione IRCCS Ca' Granda Ospedale Maggiore Policlinico, Milan, Italy

In recent years vitamin D has been in the spotlight of many researchers for its possible role in various disorders, including autoimmune and infectious diseases. Even if vitamin D deficiency remains a major public health problem, its symptomatic manifestations are less and less common in clinical practice, and pediatric age represents a “gray area” where vitamin D supplementation is often administered in the absence of an effective evaluation of its status. Moreover, a poor knowledge about different definitions of “deficiency,” “insufficiency,” and similar terms is spread among clinicians, while guidelines are not univocal, especially after the first year of life. The aim of this brief opinion paper is to sum up recent evidence about vitamin D status and its supplementation in pediatrics, in order to better clarify a common definition of its deficiency. The aim of this opinion article is to raise awareness on this topic among clinicians and encourage a discussion on the real need for routine 25-hydroxycholecalciferol serum evaluation and its supplementation.

KEYWORDS

vitamin D, micronutrients, vitamin supplementation, pediatric screening, child public health, dietary supplements, infant nutrition, rickets

1. Introduction

The role of vitamin D for calcium metabolism and, especially, for the treatment of rickets was first identified in 1922 by the American biochemist Elmer McCollum (1879–1967) (1). After his observations, thousands of papers have shed light on its important and multifaceted function for human health, not only regarding the musculoskeletal system (2, 3). At the same time, several investigators have observed that a surprising number of patients may present deficient levels of this micronutrient, regardless of their age and origin (4–6). Vitamin D deficiency remains a major public health problem, even after a century since its discovery (7).

At least two under-rated factors might contribute to the persistence of this issue: the lack of a common definition of vitamin D deficiency and the existence of partially contrasting recommendations on vitamin D prophylaxis.

The aim of this opinion article is to highlight recent evidence about vitamin D status and its supplementation in pediatrics, to better clarify a common definition of its deficiency. Our goal is to raise awareness among clinicians of this topic and encourage a discussion on the real need for routine 25-hydroxycholecalciferol serum evaluation and supplementation.

2. The effects in pediatric age: Bone health and immune function

Vitamin D plays an important role in bone growth and remodeling by osteoblasts and osteoclasts and is essential to maintain calcium, phosphate, and magnesium body homeostasis by regulating intestinal absorption, and renal absorption/excretion, alongside the parathyroid hormone (PTH). Plasma calcium and phosphate are mainly influenced by the active form of vitamin D ($1\alpha,25$ -dihydroxyvitamin D) and PTH, while a minor role is also attained by other humoral factors (8).

Magnesium is influenced, though to a lesser degree, by the same factors that control calcium, and it indirectly influences calcium by altering PTH synthesis and secretion in response to hypocalcemia and by assisting in the activation of vitamin D (9). Indeed, magnesium functions as a cofactor in many kidneys and liver enzymatic reactions and it is required by all the enzymes that intervene in vitamin D metabolism (10). Consequently, a lack of magnesium may result in disruption to the calcium/phosphate homeostasis regulated by active vitamin D/PTH and may cause vitamin D-resistant hypocalcemia (9, 10). On the other hand, vitamin D deficiency or overload may result in hypermagnesemia (magnesium not utilized) or hypomagnesemia (excessive consumption of magnesium).

In the early stages, vitamin D deficiency results in impaired calcium intestinal absorption and consequent low serum calcium levels (hypocalcemia). In turn, hypocalcemia stimulates PTH secretion which acts to normalize serum calcium by reducing renal calcium excretion, increasing renal phosphate excretion, and stimulating renal production of active vitamin D. High levels of PTH (hyperparathyroidism) also boost osteoclast activity which determines bone calcium release. The combination of low serum phosphate levels (hypophosphatasemia) and increased osteoclast activity results in bone demineralization (11).

In children, severe vitamin D deficiency may cause rickets, a childhood metabolic bone disease caused by under-mineralization of the growing bone. Following the growth plate closure, in older children and adults, the term “osteomalacia” is used to describe the demineralization of bone at sites of bone remodeling (12).

Vitamin D positive effects on the innate immune system are well known since the discovery of its historical beneficial effects on mycobacterium tuberculosis infection (13, 14). Vitamin D modulates monocytes, macrophages, dendritic cell responses, and the production of interleukins (15). Autoimmune diseases (ADs) are caused by an erroneous activation of the immune system, with subsequent destruction of tissues by autoreactive immune cells, which can react against self-antigens (16). Among the causes contributing to the development of ADs, an insufficient vitamin D serum concentration might play a significant role, as proven by epidemiologic findings of higher incidences of ADs among countries with lower sun exposures and high prevalence of vitamin D insufficiency (17, 18).

Recent studies found the vitamin D's involvement in the suppression of T lymphocyte proliferation and adaptive immune system, causing a shift from a Th1 to a Th2 phenotype and a subsequent alteration in the differentiation and maturation of T cells, inducing T regulatory cells function and immune self-tolerance (19, 20). Moreover, B lymphocytes have been found to express vitamin D receptors, which, when activated, can inhibit the differentiation into plasma cells and modulate immunoglobulin production (21). All these

effects could explain the possible connection between variable vitamin D serum levels and the probability to develop an AD (22).

Studies conducted among children with type 1 diabetes (T1D) found a significant difference in the incidence of disease according to the gradient of sun exposure in different countries and the seasonal variability (23, 24). Conflicting evidence has been found about the hypothesis that vitamin D supplementation could reduce the probability to develop T1D in early life, even if a protective correlation between minor incidence and higher serum levels has been found in some studies (25–27). Other studies observed a delay in the progression of beta-cells destruction when vitamin D is administered in an early stage of onset and diagnosis (28–30). Two meta-analyses found that the risk of developing T1D was significantly reduced in children supplemented with vitamin D (27, 31). For these reasons, avoiding a vitamin D insufficiency in patients at high risk for developing T1D is suggested, even if evidence for a specific supplementation in these subjects is lacking (17). Concerning other ADs, low $25(\text{OH})\text{D}$ sera levels have been associated with the development of autoimmune thyroiditis, such as Hashimoto's disease and Grave's disease, both in children and adults (32–34).

Vitamin D also acts as an enhancement of the intestinal defense mechanisms, locally regulating the mucosal immune system and preventing harmful microbial proliferation (35, 36). For instance, an association between lower vitamin D concentrations and an increased risk of developing IBD has been suggested (37–40). This evidence can be strengthened by the reduced vitamin receptors expression found in the colon mucosa of mice affected by IBD when compared to healthy controls, with an increased production of Th1 and Th17 lymphocytes and inflammatory cytokines in the gastrointestinal tract (41, 42). For these reasons, according to recent interventional studies, a vitamin D supplementation can be considered a potential effective and safe therapeutic choice in patients with IBD (43–46).

Emerging evidence from various meta-analyses supposes a plausible role of low vitamin D levels in many other ADs, such as rheumatoid arthritis, systemic lupus erythematosus, and multiple sclerosis, and vitamin D receptors polymorphisms have been associated with higher incidences of several ADs (47–51). However, optimal vitamin D concentrations that could reduce the possible occurrence of ADs are not clear yet, even if levels higher than 20 ng/mL (about 50 nmol/L) should be considered sufficient to maintain the physiologic calcemic and non-calcemic functions of vitamin D (52).

3. Deficiency and insufficiency: Words not to be confused

Vitamin D deficiency has been recognized in a wide range of pathological conditions, from allergic to immune-mediated diseases such as diabetes or chronic inflammatory bowel diseases (25, 27, 53–55). More recently, vitamin D deficiency and its eventual supplementation have been even considered linked with COVID-19 symptoms and prevention, generally without any proof of a cause-and-effect relationship, including reverse causality (56–59).

Although cases of rickets and clinical manifestations of symptomatic vitamin D deficiency are actually rare, many studies worldwide have shown high rates of vitamin D deficiency and insufficiency (measured as the serum concentration of

25-hydroxycholecalciferol, 25(OH)D) in the pediatric population, with rates ranging on average between 40 and 75%, even in developed countries (60–63). The low rates of sunlight exposure in Nordic countries and the limited production in Southern ones, related to the natural protection of dark skin phenotypes toward light together with a diffused poor nutritional status, may represent possible cofactors of this evidence (64–66). Variable percentages of insufficiency/deficiency reported in the literature may be linked also to the variability of the screening methods, which often use improper terminologies and cut-offs. The universal application of unnecessary (and expensive) routine supplementations in a healthy population does not have a scientific rationale. Moreover, there is currently no scientific evidence to recommend vitamin D supplementation in the treatment and prevention of diseases like asthma, allergic, or immune disorders (67).

Consequently, it might be considered if and how a vitamin D deficiency may be responsible for so many different diseases. A meaningful point is represented by the lack of knowledge among clinicians about the current reference values of hypovitaminosis, probably related to the frequent and ambiguous use of terms such as “deficiency,” “sufficiency,” “adequacy,” or “insufficiency” (68, 69). As a consequence, surveys conducted on the general population and based on inappropriate cut-off values have sometimes led to unnecessary supplementations in healthy populations (52, 70, 71).

The threshold value about hypovitaminosis (and therefore “deficiency,” and not “insufficiency”) is debated (72–74), but according to some authorities we suggest considering adequate levels above 30 ng/mL (75 nmol/L). Values included in the range of 20–29 ng/mL (50–74 nmol/L) are then to be considered “insufficient” (Table 1) (75, 76). Furthermore, with the exception of subjects at risk of hypovitaminosis or those who may require supplementation (e.g., inadequate dietary intake), no screening of serum 25(OH)D dosages is recommended, nor an arbitrary or medically unjustified exogenous administration should be generally performed before verifying an effective deficiency/insufficiency (77, 78).

4. Risk factors and current evidence

Several risk factors are associated with vitamin D deficiency in children and may be considered by clinicians upon deciding whether blood serum screening and/or vitamin D supplementation should be started.

The levels of vitamin D may also be influenced by ethnicity, genetic predispositions, and skin types, with darker skin types requiring more sunlight exposure to absorb vitamin D (72, 79–81). Lastly, there is a risk for vitamin D deficiency also for pediatric and adult subjects who are treated with certain medications (e.g., anti-epileptics, and glucocorticoids) and for patients with chronic diseases which prevent vitamin D intestinal absorption, such as celiac disease or cystic fibrosis, but also diseases which impact the

liver, or the kidneys, preventing physiologic vitamin D metabolism (72, 82–85).

Another major risk factor of vitamin D deficiency is the insufficient sunlight exposure, which affects the body's capacity to produce vitamin D (86, 87). Therefore, spending most of the time indoors or living in regions where the weather is mostly cloudy, and cold represents a risk for vitamin D deficiency. Accordingly, other factors such as latitude, and altitude, which directly impact the sun angle and ultraviolet radiations may impact vitamin D status (72).

Another known risk factor for vitamin D deficiency is related to age, with infants being more at risk of developing hypovitaminosis. Under 12 months of age, the risk is even higher for premature babies, who have less vitamin D deposits, and in children who are breastfed (88). Indeed, human breast milk is almost lacking in proper amounts of vitamin D, with concentrations that range from 10 to 80 IU/L in healthy lactating women, depending on the method of measurement (88, 89).

Considering the first 6 months of age, mothers who are lacking in vitamin D, supply even fewer amounts to their infants, while, higher breast milk quantities of vitamin D positively correlate with higher mother 25(OH)D serum levels (90–92). The rapid conversion of cholecalciferol to 25(OH)D in the mother's liver represents another obstacle to a high passage of vitamin D, and it is maybe one of the main reasons for the 0.2 ratio between maternal and breast milk 25(OH)D (93).

The main problem of infants exclusively breastfed by mothers supplemented with 400 IU/day, the typical amount assumed during pregnancy, is the typical deficiency reported in this population (94, 95). Moreover, breastfed infants typically lack in adequate sunlight exposure and the administration could be affected by poor parental compliance (96, 97).

When exclusive breastfeeding is no longer sufficient to meet all the nutritional needs, it is, therefore, necessary to introduce other foods and liquids. This period is known as “complementary feeding” or “weaning,” and should generally be started after 6 months of life, with partial breastfeeding that may continue approximately up to 2 years of age (98).

Low dietary intake of vitamin D remains a common reason for vitamin D deficiency even in older children/adolescents, especially in overweight and obese individuals. Moreover, overweight and obese subjects are more at risk of low blood levels of vitamin D, as adiposity may prevent vitamin D release from the deposits in the fatty tissue and therefore its bioavailability (66, 99).

5. International recommendations

For all the mentioned reasons, most international and national guidelines actually recommend vitamin D prophylaxis to all infants during the first year of life, in order to prevent possible deficiency conditions and in consideration of the frequent, unpredictable, and

TABLE 1 Suggested cut-off values for the definition of vitamin D status based on circulating levels of 25(OH)D (74).

	Severe deficiency	Deficiency	Insufficiency	Sufficiency
Serum	<10 ng/mL	<20 ng/mL	20–29 ng/mL	≥ 30 ng/mL
25(OH)D	(<25 nmol/L)	(<50 nmol/L)	(50–74 nmol/L)	(≥ 75 nmol/L)

often insufficient supply typical of the early infancy (73, 74). It has been estimated that infant formulas are able to provide appropriate amounts of vitamin D (400 IU/day) only once an average intake of at least 1 l of milk per day has been reached, which generally takes place when the baby's body weight is more than 6 kg (100). Moreover, even if cholecalciferol (vitamin D₃) seems to be more effective in raising 25(OH)D levels, there is no proven difference between the administration of ergocalciferol (D₂) or D₃ formulation in preventing possible deficiencies (101, 102). Dosages above 400 IU/day did not show significant differences in vitamin D sufficiency rates and bone health during the first year of life (94). Higher intakes have been suggested only in preterm births; in fact, the European Society of Pediatric Gastroenterology, Nutrition, and Hepatology (ESPGHAN) recommends prophylaxis with 800–1,000 IU/day (avoiding a pro kg dosage) during the first months of the preterm, in order to quickly correct the reduced infants' levels of 25(OH)D, thus reducing the risk of symptomatic deficiencies (103). As for breastfeeding, although some recommendations advise for maternal supplementation of 600 IU per day, some data suggest that this practice does not significantly change the concentration of 25(OH)D in breast milk, which is generally poor in vitamin D (93). For this reason, the American Academy of Pediatrics recommends supplementing all breastfed and partially breastfed infants, regardless of maternal supplementation (88). However, adherence to these recommendations is low (104). Furthermore, due to the poor evidence to assess the benefits of supplementation for improving maternal and infant health outcomes, the World Health Organization (WHO) does not recommend routine vitamin D supplementation in pregnant women (105).

In consideration of the low levels of adherence to a daily administration of vitamin D found in many populations that differed for geographic and socioeconomic conditions, alternative approaches to a daily supplementation based on high doses (up to 6,400 IU/day) given directly to fully breastfeeding mothers have been found to be safe and equally effective in maintaining adequate levels of 25(OH)D, as well as monthly administrations of 50,000 IU given directly to infants (94, 104, 106–110).

After 12 months of life, evidence about pediatric vitamin D supplementation needs is less clear and univocal (111–114). A case-by-case evaluation of the toddler, child, and young adult lifestyle has then been recommended, to correct possible modifiable risk factors when present, particularly in adolescents, by virtue of their increased needs related to major skeletal growth and also the pubertal spurt (99). Any supplementation is therefore only indicated in cases of poor sun exposure or in specific conditions (111). This approach is also supported by WHO, which focuses the indication on vitamin D supplementation more on geographical location and sun exposure than on child age (115). As for the administration of fortified foods in early childhood, the consumption of vitamin D-fortified milk between 2 and 6 years may represent a safe and significantly effective nutritional measure in preventing 25(OH)D insufficiency during periods of reduced sunlight exposure (116–119). On the other hand, other societies, such as the Endocrine Society and the Institute of Medicine, recommend an average vitamin D intake of 600–1,000 IU/d between 1 and 18 years of age (120, 121).

Considering these discrepant recommendations, the inconclusive data on this issue, and that universal screening of 25(OH)D serum

levels cannot represent a feasible solution, new studies should assess if vitamin D evaluation in selected cases would be more appropriate and cost-effective than a routinary, continued, and widespread supplementation.

As was observed 10 years ago in the Consensus statement by the ESPGHAN Nutritional Committee, data on vitamin D concentration and vitamin D deficiency in healthy pediatric subjects are limited, with a lack of consistency in terms of study design and definition of vitamin D deficiency (72). From the studies examined in the statement, it appears that a considerable number of healthy European children and adolescents may be expected to be vitamin D deficient (122–134).

Besides, routine vitamin D screening in healthy children is currently not recommended by experts globally, which partially explains the lack of data and systematization of literature regarding vitamin D status in healthy subjects (73).

Finally, although there are few reports on possible damages from high levels of exogenous administration of vitamin D for example, in cases of mutation of the 24-hydroxylase gene or in sporadic cases of overdoses, possible conditions such as hypercalcemia and hypercalciuria might occur, leading up to acute symptoms such as pain, fever, chills, anorexia, and later to soft tissue calcification, and related chronic pathologies such as nephrocalcinosis in case of prolonged overdoses (135, 136). The issue is still discussed in the hypothesis of either a rare genetic predisposition, or real differences in comparison with the expected spontaneous epidemiological distribution of cases. Cases of vitamin D intoxication have been described only for serum levels above 150 ng/mL (137).

It should be once more stressed that vitamin D levels can significantly vary depending on the lifestyle and overall exposure to ultraviolet B rays, which is affected by factors such as geographic location, age, skin, and family habits (66, 138, 139). In newborns and infants, other factors may well affect vitamin D status such as season of birth, maternal prophylaxis in pregnancy, type of breastfeeding, human milk variable individual composition, and the family socioeconomic status (140, 141). Recently, the rising rate of obesity and the lipophilic nature of vitamin D have suggested the need for higher quantities of vitamin D for these subjects, up to at least 1,000–1,500 IU/day (99, 142).

The 25(OH)D serum dosage should be cautiously considered in clinical practice. The National Institute for Health and Care Excellence (NICE) guidelines recommend dosing 25(OH)D serum only in patients with signs of hypovitaminosis, or in the presence of documented risk factors that justifies their dosage (143). Instead, a 6-month 25(OH)D dosage may be appropriate in supplemented patients to evaluate its effectiveness or to consider whether to suspend it.

In Table 2, we summarize different guidelines and statements for supplementation.

6. Conclusion

All children during the first year of life should receive an oral supplementation of vitamin D. Beyond this age, geographic and cultural variability should always be considered by clinicians and scientific societies in recommending, or not, the need for

TABLE 2 Different guidelines for vitamin D supplementation.

First author, year	Title	Type	Vitamin D status cut-off values considered	Vitamin D toxicity level considered	Population	Vitamin D supplementation
Munns et al., 2016 (73)	Global Consensus Recommendations on Prevention and Management of Nutritional Rickets	Consensus statement from expert member of various international societies	Sufficiency, >50 nmol/L Insufficiency, 30–50 nmol/L Deficiency, <30 nmol/L	>250 nmol/L, with hypercalcemia, hypercalciuria, and suppressed PTH	Children and adults	Infants (0–12 months) 400 IU/day in the first year of life, independent of their mode of feeding. Subject beyond 12 months of age: 600 up to 2000 IU/day (minimum duration 12 weeks) in children with history of symptomatic vitamin D deficiency requiring treatment or children and adults at high risk of vitamin D deficiency Pregnant women 600 IU/d throughout pregnancy
Pludowski et al., 2022 (76)	Clinical Practice in the Prevention, Diagnosis, and Treatment of Vitamin D Deficiency: A Central and Eastern European Expert Consensus Statement	Consensus statement by Eastern European expert	Sufficiency 30–50 ng/mL (75–125 nmol/L) Insufficiency between ≥20 ng/mL (≥50 nmol/L) and <30 ng/mL (<75 nmol/L) Deficiency <20 ng/mL (<50 nmol/L)	>100 ng/mL (250 nmol/L)	Adults	Healthy adults 800 up to 2000 IU/day in: (1) healthy subjects who want to achieve a targeted/measured 25(OH)D concentration, during wintertime (2) subjects >65 years throughout the year (3) Pregnant women or planning a pregnancy Subjects with medical conditions up to 4,000 IU/day
Braegger et al., 2013 (72)	Vitamin D in the healthy European pediatric population	Consensus statement from member of the ESPHGAN Committee of nutrition	Sufficiency >50 nmol/L Severe deficiency <25 nmol/L.	“No agreement on a vitamin D toxicity threshold”	Children	Infants (birth to 12 months) 400 IU/day in the first year of life Beyond 12 months: >600 IU/day supplementation in children from identified risk groups
Saggese et al. 2018 (99)	Vitamin D in pediatric age: consensus of the Italian Pediatric Society and the Italian Society of Preventive and Social Pediatrics, jointly with the Italian Federation of Pediatricians	Consensus statement form national Pediatric societies in Italy	Sufficiency ≥30 ng/mL (≥ 75 nmol/L) Insufficiency 20–29 ng/mL (50–74 nmol/L) Deficiency <20 ng/mL (<50 nmol/L) Severe deficiency <10 ng/mL (<25 nmol/L)	Not reported	Children	Preterm infants: (1) 400–800 IU/day for preterm infants with weight ≥ 1,500 g (2) 200–400 IU/day by enteral feeding in preterm infant with weight < 1,500 g Infants: 400 IU/day in all newborns independent of the type of feeding. Subjects beyond 12 months of age: 600 up to 1,000 IU/day in children and adolescents with risk factors for vitamin D deficiency
Agostoni et al. 2010 (103)	Enteral Nutrient Supply for Preterm Infants: Commentary from the European Society of Paediatric Gastroenterology, Hepatology, and Nutrition Committee on Nutrition	Commentary from ESPHGAN Committee of nutrition	N/A	Not reported	Children	Preterm infants 800 up to 1,000 IU/day during the first months of life

(Continued)

TABLE 2 (Continued)

First author, year	Title	Type	Vitamin D status cut-off values considered	Vitamin D toxicity level considered	Population	Vitamin D supplementation
Wagner et al., 2008 (88)	Prevention of Rickets and Vitamin D Deficiency in Infants, Children, and Adolescents	Guidelines from the American Academy of Pediatrics	"Serum 25-OH-D concentrations in infants and children should be ≥ 50 nmol/L (20 ng/mL)."	Not reported	Children	Infants 400 IU/day in the first year of life in breastfed or partially breastfed infants, and in non-breastfed infants who are ingesting <1,000 mL/day of vitamin D-fortified formula or milk Older children 400 IU/day in case of diet with <1,000 mL/day of vitamin D-fortified formula or milk Adolescents 400 IU/day in case the individual does not obtain 400 IU of vitamin D per day through vitamin D-fortified milk/vitamin D-fortified foods (e.g., cereals) Children/adolescents with risk factors: 400 IU/day supplement despite a food intake of 400 IU/day
Rogers et al., 2012 (105)	Vitamin D supplementation in pregnant women	WHO guidelines	N/A	Not reported	Pregnant women	Supplementation during pregnancy as part of routine antenatal care not recommended (conditional recommendation) In cases of documented deficiency, vitamin D supplements may be given
Holick et al., 2011 (121)	Evaluation, Treatment, and Prevention of Vitamin D Deficiency: an Endocrine Society Clinical Practice Guideline	Clinical practice guidelines by the Endocrine Society	Insufficiency 21–29 ng/mL (525–725 nmol/L) Deficiency <20 ng/mL (50 nmol/L),	Not reported	Children and adults	Infants aged 0–1 year who are vitamin D deficient 2000 IU/day for 6 weeks followed by maintenance therapy of 400–1,000 IU/day Children aged 1–18 years who are vitamin D deficient 2000 IU/day for at least 6 weeks followed by maintenance therapy of 600–1,000 IU/day Adults who are vitamin D deficient 6,000 IU/day for 8 weeks followed by maintenance therapy of 1,500–2000 IU/day

supplementation. Vitamin D status may be closely connected to social inequities and related diseases. Moreover, constant and unjustified monitoring of vitamin D levels has then been considered unnecessary in the general population. Screening of serum 25(OH)D concentration should be carried out only in selected cases.

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EDITED BY

Ranadip Chowdhury,
Society for Applied Studies, India

REVIEWED BY

Gael Janine Mearns,
Auckland University of Technology,
New Zealand
Melissa Young,
Emory University, United States

*CORRESPONDENCE

Martha Irene Kartasurya
✉ marthakartasurya@live.undip.ac.id

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Determinants of length for age Z scores among children aged 6–23 months in Central Java, Indonesia: a path analysis

Martha Irene Kartasurya^{1*}, Ahmad Syauqy², Suyatno Suyatno¹,
Julian Dewantiningrum², Nuryanto Nuryanto², Sunarto Sunarto³,
Mufliah Isnawati³, Yusi Dwi Nurcahyani⁴, Erna Kusuma Wati⁵,
Pramesthi Widya Hapsari⁵, Mohamad Samsudin⁶ and
Noviati Fuada⁷

¹Faculty of Public Health, Universitas Diponegoro, Semarang, Indonesia, ²Faculty of Medicine, Universitas Diponegoro, Semarang, Indonesia, ³Nutrition Department, Poltekkes Kemenkes Semarang, Semarang, Indonesia, ⁴Research Services, Center for Health Research and Development, Magelang, Indonesia, ⁵Faculty of Health, Universitas Jenderal Soedirman, Purwokerto, Indonesia, ⁶Research Center for Public Health and Nutrition, National Research and Innovation Agency (BRIN), Cibinong, Indonesia, ⁷Organization for Health, National Research and Innovation Agency, Jakarta, Indonesia

Introduction: Length for Age Z (LAZ) score determinants are complex and vary among different areas, but it is important for designing effective and efficient strategies to decrease stunting prevalence among children under 2 years. This study aimed to investigate the determinants of LAZ scores among children under 2 years in Central Java, Indonesia.

Methods: This study was conducted on the 2021 Indonesian Nutritional Status Study (INSS) dataset, which was a cross-sectional survey. Data on 3,430 children aged 6–23 months from Central Java province were derived from the 2021 INSS data. After missing data elimination, 3,238 subjects were included in the analysis. Determinant factors included direct and indirect factors. Direct factors were the mother's age, birth weight Z score (BWZ), birth length Z score (BLZ), exclusively breastfed history, dietary diversity scores (DDS), empty calorie drink consumption, unhealthy snacks consumption, and infections. Indirect factors were early initiation of breastfeeding (EIBF) and *posyandu* (integrated health post) utilization. Underlying factors were socioeconomic status (SES) and the mother's education. Bivariate analyses and multiple linear regressions were conducted. A path analysis with a hypothesized model based on the UNICEF conceptual framework was also performed.

Results: Stunting, wasting and underweight proportions among the subjects were 19.1%, 7.6% and 12.3%, respectively. The mean LAZ scores were -0.95 ± 1.22 ; the mother's age was 29.7 ± 5.95 years; BWZ was -0.47 ± 0.97 ; BLZ was -0.55 ± 1.05 ; and DDS was 4.45 ± 1.51 . The infection proportion among the subjects was 28%. BWZ and BLZ were positively correlated to LAZ scores, with $r = 0.267$ ($p < 0.01$) and $r = 0.260$ ($p < 0.01$), respectively. The mother's age was negatively correlated to LAZ scores with $r = -0.041$ ($p < 0.05$). Maternal education was positively correlated to SES but had no direct effect on LAZ scores. LAZ score determinants of BLZ ($p < 0.001$) and SES ($p < 0.001$) showed positive direct associations with LAZ scores, but the mother's age ($p = 0.039$), exclusively breastfed history ($p < 0.001$), and empty calorie drinks consumption ($p < 0.001$) had negative associations with LAZ scores.

Conclusion: To prevent stunting among children aged 6–23 months in Central Java, Indonesia, intervention programs to increase the nutritional status of women at child-bearing age and nutrition education on child feeding practices should be conducted more efficiently and effectively.

KEYWORDS

length for age Z-scores, stunting, under two children, path analysis, Central Java, Indonesia

1. Introduction

Stunting prevalence among children under 5 years in Indonesia is still high, reaching 24.4%, while the prevalence in Central Java is 20.9% (1). Although the prevalence of stunting in Central Java has decreased compared to the prevalence in 2019, it still has to be reduced further because Central Java's dense population of approximately 35 million in 2020 resulted in a big absolute number of stunted children. Central Java is the third populated province on Java Island, which is the most populous island in Indonesia, with 152.4 million inhabitants. Thus, measures should be taken to decrease the prevalence of stunting in this province.

Stunting development can be started in the first 1,000 days of life, from conception until 2 years old. Thus, the problems that occurred during pregnancy, the exclusive breastfeeding period, and the complementary feeding would affect the linear growth (2). The LAZ scores then slow down at 2 to 3 years old with no catch-up period (3). Stunted children are unlikely to catch up to their peers. Thus, possible interventions may only be effective in the first 2 years of life (4). Since 2006, the World Bank recommends focusing on providing nutrition support during the window of the opportunity period, which begins at conception and ends at 2 years of age (5). This period is a critical time when children undergo rapid physical and brain growth and development, so nutrition adequacy is very important (6). Stunting reduction should be more focused on this group through various specific and sensitive interventions so the young population in the future will not be a burden but will be more productive (7–9).

Risk factors of stunting could be different in each area, based on their characteristics. As stunting is the result of linear growth problems, determinants of LAZ scores among children in Central Java should be assessed to have the correct measures in stunting prevention and handling. Determinants of LAZ scores include direct, indirect, and underlying factors. Direct factors consist of nutrition intake, infection, and maternal factors. Indirect factors cover food accessibility, childcare, and environmental health. Underlying factors are social economic status, cultural, and political conditions (10). A previous study showed how diverse the factors were which influenced stunting in each province, regency, and even subdistrict (11). Therefore, the analysis of determinants should use a multilevel method such as path analysis. With path analysis, the pathway of factors and the partial and total effects can be measured.

In this study, the magnitude of direct, indirect, and underlying factors available from the 2021 INSS data in determining LAZ scores was calculated through a path analysis model. Path analysis evaluates associations between a dependent variable and two or more independent variables. With the known magnitude,

preventive measures can be taken more specifically and properly based on local problems. Therefore, this study aimed to investigate the determinants of LAZ scores among children under 2 years in Central Java, Indonesia.

Since 2019, the Indonesian Ministry of Health has started an annual Indonesian Nutritional Status Study (INSS or SSGI), which was conducted in all provinces in Indonesia. This study used the 2021 INSS data, especially data on children aged 6–23 months in Central Java. Data on infants aged 0–6 months old was not used because the analysis include dietary diversity score data, which is only available for infants who were not exclusively breastfed. Therefore, we excluded the infants aged <6 months to prevent selection bias.

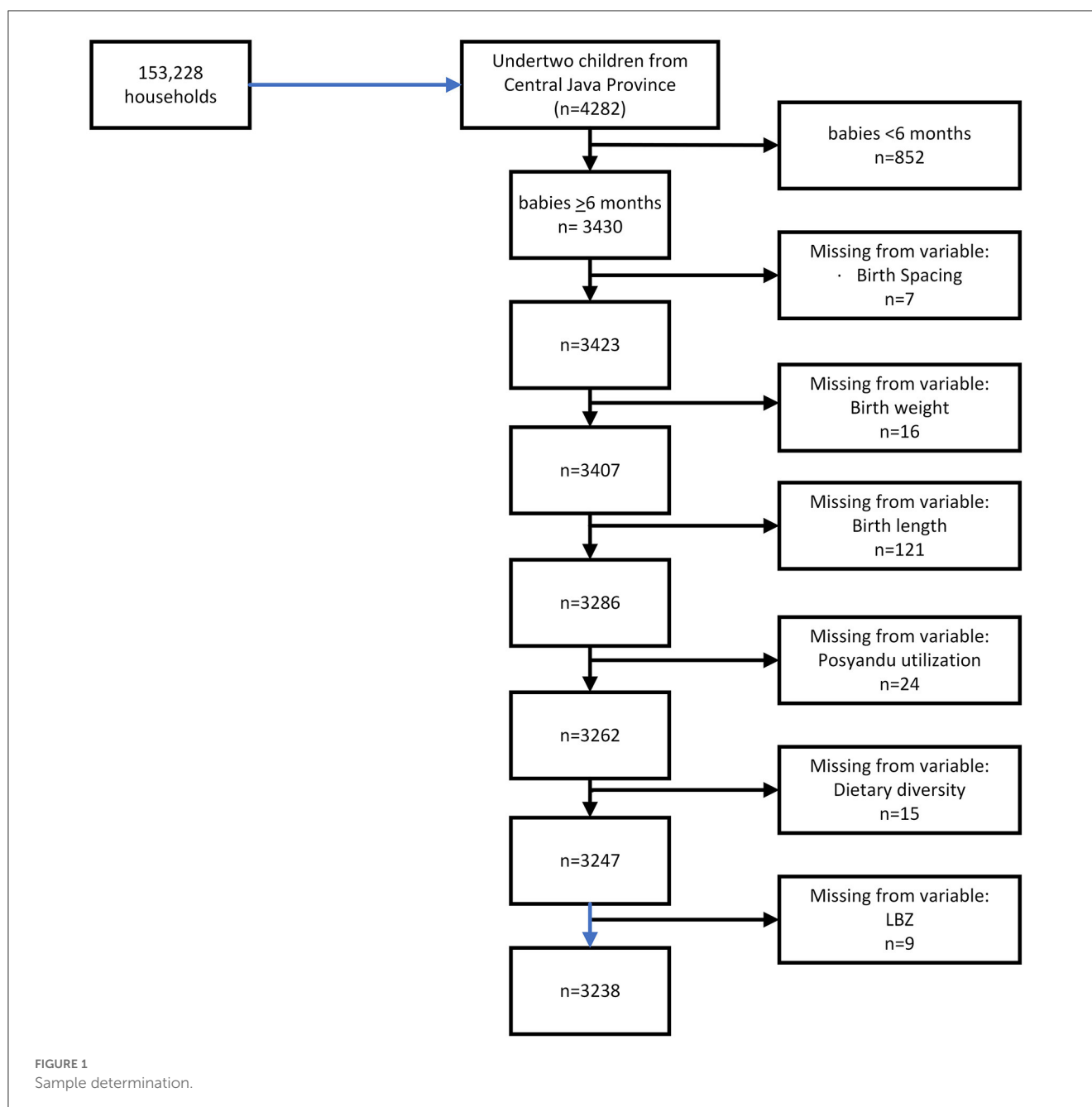
2. Materials and methods

This study was conducted on the 2021 Indonesian Nutritional Status Study (INSS 2021)/SSGBI 2021 data collected annually since 2019 (1). Data were collected in January–December 2021 using two different questionnaires, i.e., household and individual levels. Data collection was done in a cross-sectional survey, using stratified two-stage sampling, with the population of households that had children under 5 years. The samples were children under 5 years in 1,53,228 households from 14,889 census blocks of the 2021 Indonesian National Socio-economic Survey (SUSENAS) in 34 provinces and 514 regencies/cities.

In this study, only data on children aged <2 years from Central Java province were used ($n = 4,282$). Then we chose children aged 6–23 months ($n = 3,430$), and after missing data deletion ($n = 192$), the complete analysis was performed on 3,238 children (Figure 1).

The dependent variable was the LAZ scores which were counted based on the WHO anthropometric calculator on a continuous scale. All extreme values of LAZ > 6.0 and LAZ < −6.0 were excluded. The independent variables were direct, indirect, and underlying determinants of LAZ scores available from the 2021 INSS data. The direct determinants of LAZ scores include those as follows: (1) maternal factor: the mother's age; (2) child factors: birth weight Z scores (BWZ) and birth length Z scores (BLZ); (3) food consumption: dietary diversity score, exclusively breastfed history, unhealthy snack food consumption, and empty calories drink (starch/ sugary water) consumption; and (4) infection. The indirect determinants of LAZ scores include early initiation of breastfeeding (EIBF), *posyandu* utilization, drinking water source, and sanitation. The underlying determinants of LAZ scores include the mother's education and socioeconomic status.

Data on all variables were gathered from the interviews and observations to the records available in the Maternal and Child



Health Handbook, or the other available records. If the record was not available, interviews with the mothers were done based on the subjects' memory. The mother's age was defined as the number of years the mother was alive until the interview time. Birth weight and birth length were measured by the midwives at deliveries and usually were recorded in the Maternal and Child Handbook/other record forms such as the mother's cohort book. At the survey, the birth weight and birth length were observed from the record or mothers'/other family members' memories. Thereafter, birth weight (BWZ) and birth length Z scores (BLZ) were calculated by the researchers based on WHO ANTHRO software.

A dietary diversity score was defined as the number of food groups consumed in the last 24 h by the subjects. The food groups were those as follows: 1. breast milk; 2. grains, roots, tubers,

and plantains; 3. pulses (beans, peas, lentils), nuts, and seeds; 4. dairy products (milk, infant formula, yogurt, and cheese); 5. flesh foods (meat, fish, poultry, and organ meats); 6. eggs; 7. vitamin-A-rich fruits and vegetables; and 8. other fruits and vegetables. The minimum dietary diversity score is 5 (12). Unhealthy snack consumption was defined as the consumption of extrudate snacks (flavored ball puffs of starch, crisps, etc.) in the last 24 h. Empty calorie drink consumption was defined as the consumption of starch water, honey, tea, coffee, sugary water, fruit juice, and milk-flavored sweet thick water in the last 24 h.

Early breastfeeding initiation was defined as the baby directly put on the mother's breast at the 1st h of delivery without any barrier (12). Infants, as mothers reported, who first received food or liquids other than breastmilk after 6 months were categorized

as having exclusively breastfed history (EBF history). Infants, as mothers reported, who first received other food or liquids before 6 months were categorized as having a non-exclusively breastfed history (non-EBF history).

Infection was defined as the existence of at least one of these infections experienced by the subject: diarrhea, upper respiratory tract infection (URTI) in the previous month, or pneumonia, tuberculosis, measles, and worms' infections in the last 6 months. All of the infections were defined based on the health personnel's diagnosis or symptoms experienced by the children which were noticed by their mothers. In the analysis, infection was used as a nominal variable without considering the kind of infection: the existence or no existence of infection.

Posyandu is an integrated health post, which is organized by the local community. *Posyandu* activities include growth monitoring, nutrition education, basic healthcare services such as diarrhea treatment, family planning services, and immunization of children under 5 years. The basic healthcare service is provided by the professional health worker, but for the other services, health cadres from the community serve voluntarily. In general, the level of participation is relatively high, as *posyandu* is the activity by, for, and from the local community (13). *Posyandu* utilization was defined as the mothers' or child caregivers' attendance at the integrated health post. The drinking water source was the source of water for drinking purposes in the household. Proper drinking water was the saved drinking water which includes tap water, public tap water, public hydrant, water terminal, rainwater storage, water springs, protected well, artesian well, or pump well which have a distance of more than 10 m from the garbage storage. Bottled water, water from the mobile vendor, water sold from a water tank, and non-protected water spring/well were not included as proper drinking water (14). Sanitation was the sanitation facilities available, including the availability and type of toilet and the sewage system. The proper sanitation facility was the toilet which fulfills health requirements, completed by goose' neck closet, and the final disposal place was a septic tank or wastewater treatment installation. This facility can be used by the household only or by sharing the facility with other households (15).

The mother's education was defined as the highest level of education which has been passed by the mothers, such as elementary school, junior high school, high school, undergraduate, and postgraduate levels. The group of mothers who had no education at all was combined with the group of mothers who had not completed elementary school as they were only 0.3%. Socioeconomic status was defined as the wealth quintiles based on durable goods possessions, which have been used by the Indonesian National Bureau of Statistics in many national surveys.

For statistical analysis, frequencies and percentages were used to describe the categorical variables, while means and standard deviations were used to describe the continuous variables. LAZ scores, the mother's age, WBZ, LBZ, and dietary diversity score were normally distributed. The other determinant variables were measured as categorical variables. Correlation tests were used to assess the associations between LAZ scores, the mother's age, birth weight Z scores, birth length Z scores, and dietary diversity scores. The results are provided in Table 2. As the correlation between DDS and LAZ was influenced by sex and age, a generalized linear model

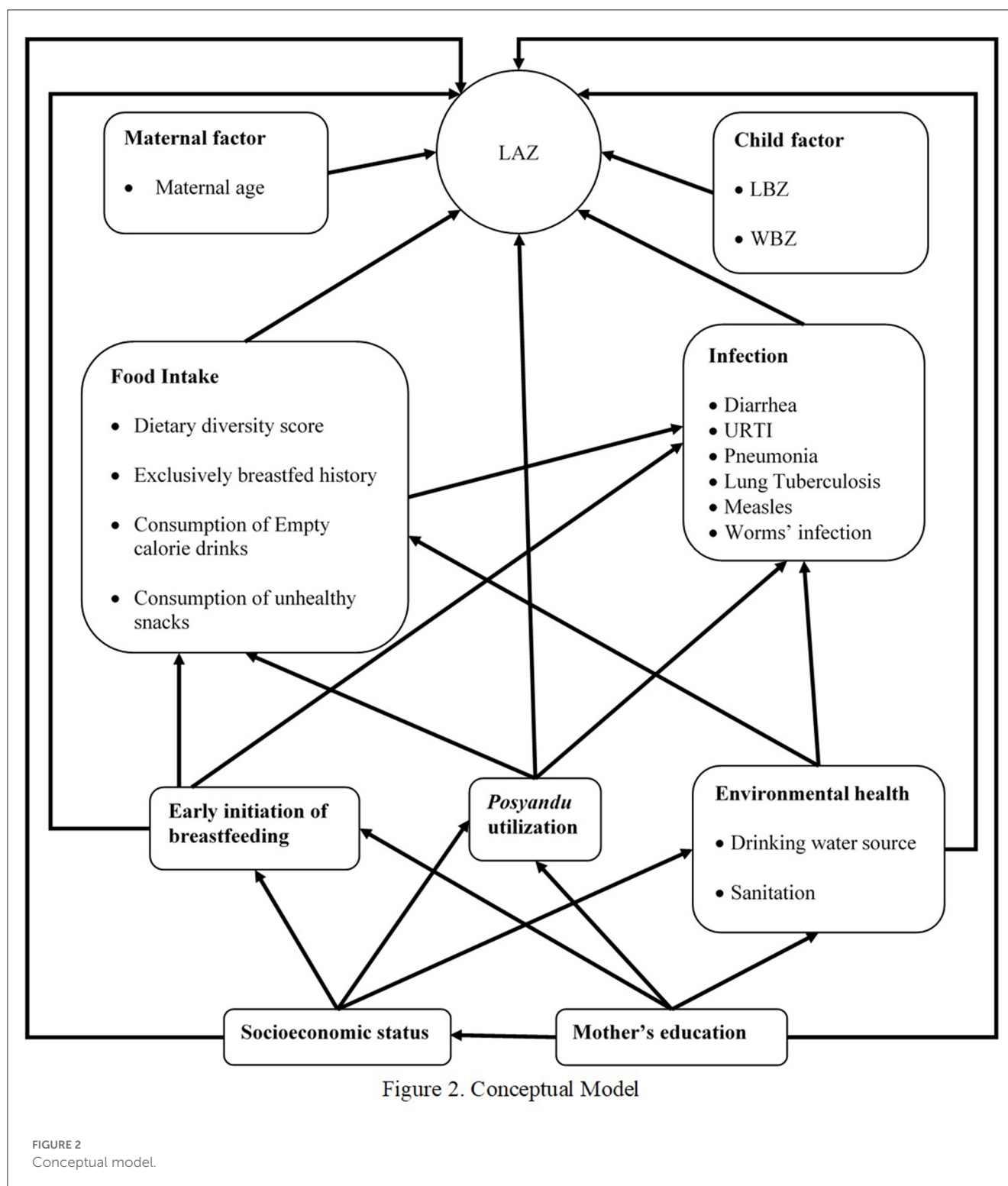
(GLM) which included sex and child's age as the covariates were run. The final GLM model to examine DDS and LAZ correlation was only controlled by the child's age as sex was not a significant covariate. The summary of the result was added as a note in Table 2. We examined the independent associations between each predictor and LAZ scores and dropped any variable that was not associated at $p < 0.05$. The results can be seen in Table 3. As WBZ and LBZ scores were correlated at $r = 0.593$, we decided to include only LBZ scores as the determinants of LAZ scores. In the next step, we included the significant determinants in a multivariate model of each factor group (child factors, food intakes, environmental factors, socioeconomic status, and the mother's education) to predict LAZ scores and dropped any variable that was not associated at $p < 0.05$ (16). The results can be seen in Table 3. All of these processes were performed using IBM SPSS version 25 (SPSS Inc., Chicago, IL, USA).

The analysis was then continued with a path analysis model in SPSS AMOS based on the conceptual model in Figure 2. This figure was based on the UNICEF conceptual framework for undernutrition. In this figure, the direct determinants for LAZ scores were grouped as maternal and child factors, food intake, and infection. The indirect factors included EIBF, *posyandu* utilization, and environmental health, while the underlying factors were socioeconomic status and the mother's education. All of the arrows showed the correlations, which were analyzed, directly to LAZ scores and through the intermediate variables. The analysis using this conceptual model was continued after the previous steps for all of the retained variables. Then, all of the insignificant paths ($p \geq 0.05$) were dropped. The final model can be seen in Figure 3, and this model fulfills all the goodness of fit indicators (NFI-CFI > 0.9 and RMSEA < 0.05).

3. Results

Table 1 shows the descriptions of the characteristics, direct, indirect, and underlying factors of LAZ scores. It is shown that the mean and standard deviation of subjects' LAZ scores were -0.95 ± 1.22 , which means they were in a relatively low stature based on the WHO ANTHRO standard. The proportion of stunted children was 19.1%, wasted 7.6%, and underweight 12.3%. The mean and standard deviation of mothers' age was 29.73 ± 5.95 years; the percentage of mothers aged <20 years was only 2.1%; and those aged >35 years was 18.3%. The mean WBZ and LBZ were -0.47 and -0.55 , respectively. The mean dietary diversity score was 4.45, with the proportion of children who met the minimum dietary diversity was 50.2% (12). All other descriptions of the determinant variables are shown in Table 1. Among the subjects, 6.5% ($n = 210$) were born as low birth weight babies based on the category of $<2,500$ g.

Table 2 shows that the variables correlated with LAZ scores were the mother's age, BWZ, BLZ, and dietary diversity score. The mother's age ($r = -0.041$, $p < 0.05$) and dietary diversity score ($r = -0.036$, $p < 0.05$) were negatively correlated with the LAZ scores, while BWZ and BLZ were positively correlated with the LAZ scores. Then, the correlation between DDS and LAZ scores was controlled for sex and age in a GLM. As child's age was the only significant confounder, this variable was the only covariate included in the



GLM. After adjustment for child's age, the correlation between DDS and LAZ was no longer significant ($p = 0.079$) with a positive parameter estimate of 0.026. In the same model, the child's age negatively correlated to LAZ with a parameter estimate of -0.049 and a $p < 0.001$. The mean LAZ of the children who met the minimum dietary diversity ($DDS \geq 5$) (12) was -0.99 ± 1.198 , while the mean LAZ of the children who did not meet the minimum

dietary diversity (<5) was -0.92 ± 1.258 . The independent t -test results showed no difference in LAZ between the groups, with a p -value of 0.114. BWZ was strongly correlated with BLZ, and dietary diversity score was positively correlated with the mother's age.

Table 3 shows the variable selection results based on the independent association to LAZ scores and adjustment to the other variables in the same category. As BWZ and BLZ were strongly

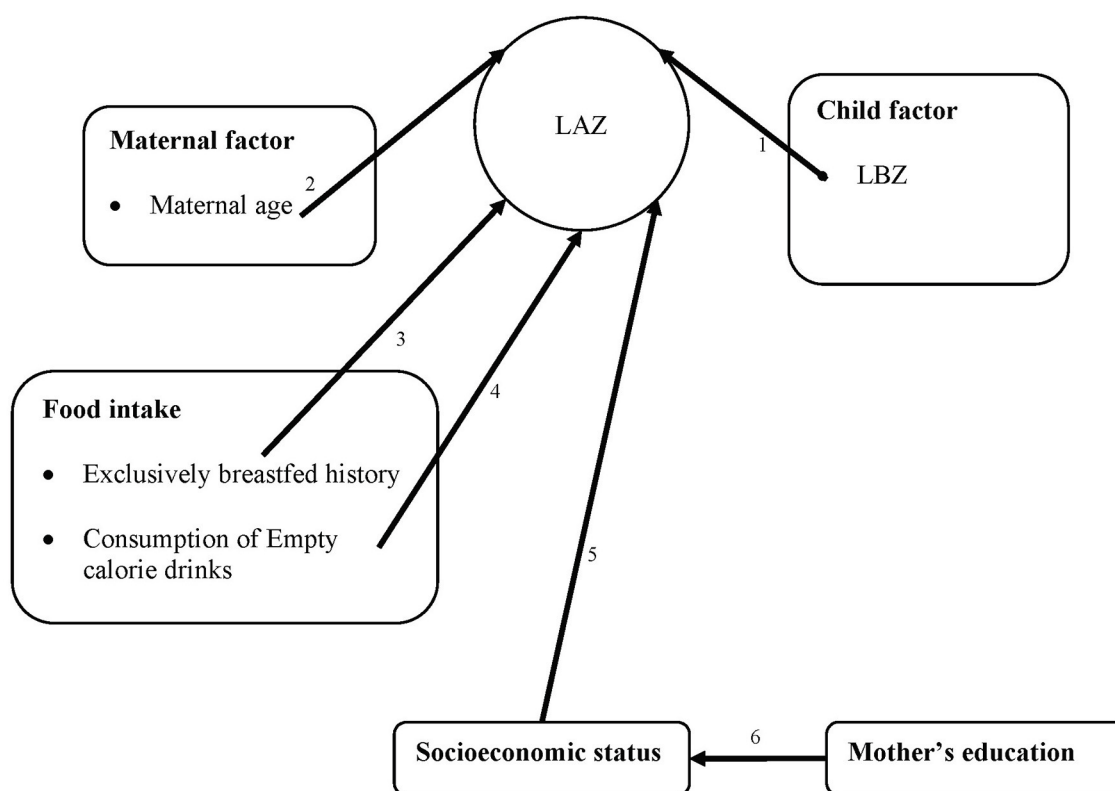


Figure 3. Path Diagram

Estimate (SE); p value:

1: 0.296 (0.020); <0.001

2: -0.007 (0.003); <0.039

3: -0.188 (0.041); <0.001

4: 0.175 (0.045); <0.001

5: 0.090 (0.017); <0.001

6: 0.528 (0.016); <0.001

FIGURE 3
Path diagram.

correlated to each other ($r = 0.593$), we decided to include BLZ only in the model. Based on the $p \geq 0.05$ of the independent correlation to LAZ scores, these variables of unhealthy snack consumption, infection, EIBF, *posyandu* utilization, and drinking water source were dropped from the model. After the adjustment of the other variables in the same category, the dietary diversity score dropped as this variable no longer had a significant effect on LAZ scores.

The conceptual model of the path analysis is shown in Figure 2, and the results of the path analysis model are shown in Figure 3. This figure shows only the significant pathways of determinants. The goodness of fit results of NFI 0.954, RFI 0.913, IFI 0.965, TLI 0.934, CFI 0.965, and RMSEA 0.030 (0.022–0.038) showed that this is a good fit model. There were five direct determinants of LAZ scores: LBZ, the mother's age, exclusively breastfed history, consumption of empty calorie drinks, and socioeconomic status. The mother's education was not a direct determinant of LAZ scores but an indirect determinant through the intermediate factor of socioeconomic status. LBZ and socioeconomic status showed a positive estimate, which means that the subjects with higher LBZ

and socioeconomic status had higher LAZ scores. The mother's age and exclusively breastfed history were negatively associated with LAZ scores, which means that the older mother's age had the lower LAZ scores and the subjects who had exclusively breastfed history had the lower Z scores. The subjects who consumed empty-calorie drinks had lower LAZ scores.

4. Discussion

The prevalence of stunting among children aged 6–23 years old in this study was lower than among children under 5 years old in this 2021 INSS result (24.4%) (1). Thus, many factors still influence the HAZ scores in children after 2 years, resulting in stunting among children under 5 years. However, since the window opportunity for intervention is in the first 1,000 days of life, it is important to set the determinants of LAZ scores among children under 2 years. Few studies had been conducted at this age (17, 18). The determinants of LAZ scores among children under 2

TABLE 1 Descriptions of characteristics, direct, indirect, and underlying factors of LAZ scores among children aged 6–23 months old in Central Java province based on INSS 2021 ($n = 3,238$).

	n	%	Mean	SD
LAZ score			−0.95	1.22
Stunted	617	19.1		
WHZ score			−0.40	1.20
Wasted	248	7.6		
WAZ score			−0.78	1.14
Underweight	398	12.3		
Child Factors				
BLZ scores			−0.55	1.05
Stunted at birth	272	8.4		
BWZ scores			−0.47	0.97
Low birth weight	166	5.1		
Maternal Factors				
Mother's age (years)			29.73	5.95
<20 years	69	2.1		
20–35 years	2,577	79.6		
>35 years	592	18.3		
Food Intake				
Dietary diversity (score)			4.45	1.51
Meet the Minimum Dietary Diversity (MDD)	1,624	50.2		
Exclusively breastfed history				
Yes	1,749	54.0		
Consumption of Empty calorie drinks (starch water, honey, tea, coffee, sugar water, fruit juice, sweetened condensed milk, etc.)				
Yes	984	30.4		
Consumption of unhealthy snacks: extrudates in the forms of puffs, such as cheese flavored balls, crisps, etc.)				
Yes	1,753	54.1		
Infection (experienced at least 1 out of these infections: diarrhea, URTI in the previous month, or pneumonia, tuberculosis, measles, worms' infection in the last 6 months)				
Yes/ having infection	908	28.0		
Early initiation of breastfeeding				
No	1,920	59.3		

(Continued)

TABLE 1 (Continued)

	n	%	Mean	SD
Posyandu utilization				
Not utilized <i>posyandu</i> in the last year	164	5.1		
Environmental Factors				
Drinking water source				
Not proper	1,436	44.3		
Sanitation				
Not proper	421	13.0		
Socioeconomic status				
Lowest 20%	294	9.1		
Low Middle	780	24.1		
Middle	798	24.6		
High Middle	801	24.7		
Top 20%	565	17.4		
Mother's education				
Did not finish Elementary School	57	1.8		
Completed Elementary School (Grade 1–6)	664	20.5		
Completed Middle School (Grade 7–9)	998	30.8		
Completed High School (Grade 10–12)	1,132	35.0		
Completed Diploma 1–3	121	3.7		
Completed Bachelor or master or doctoral degree	266	8.2		

years could differ from the factors for LAZ scores among children under 5 years (19, 20). The results of this study can be used for the prioritization of stunting prevention and alleviation programs based on the total effect of determinants found in this study.

In this study, it was found that the mother's age was related to LAZ scores among children under 2 years. The older the mother, the lower the LAZ scores. Other studies have shown that the mother's age <20 years had a higher risk of having a stunting child (21–23). In this study, only a small percentage of the subjects (2.1% or 69 subjects) were <20 years old while 18.3% were >35 years old. Thus, the mothers who were older than 35 years had more influence on the results. A study in Nepal showed a consistent result with this study (24). Older mothers tended to have a lower nutrient deposit than younger ones as they already had some children.

The child factor of BLZ is strongly related to LAZ scores. An increase in 1 SD in BLZ raised LAZ scores by 0.296. BLZ was the strongest determinant of LAZ scores among children under 2 years in this current study. Birth weight and birth length were interrelated. Logically, the shorter babies will have a lower birth weight. A study in Northern Ghana showed that the low birth weight babies had lower HAZ scores of −0.98 compared to the

TABLE 2 Correlations between continuous variables ($n = 3,238$).

	LAZ scores	Mother's age	Birth length Z scores	Birth weight Z scores	Dietary diversity (score)
LAZ scores	1				
Mother's age	−0.041*	1			
Birth length Z scores	0.260**	−0.029	1		
Birth weight Z scores	0.267**	0.005	0.593**	1	
Dietary diversity (score)	−0.036*	0.035*	0.013	−0.011	1

* $p < 0.05$.** $p < 0.01$.After controlled for the child's age, the correlation between DDS and LAZ was no longer significant ($p = 0.079$).

normal birth weight among children at 6–59 months old (25). Christian et al.'s study in 2013 indicated that low birth weight was associated with 2.5–3.5-fold higher odds of stunting (26). This study also showed that the low birth weight was caused by small for gestational age (SGA), which had a 20% attributable risk for childhood stunting.

After controlling for the child's age, DDS was no longer correlated to LAZ scores. The child's age was negatively correlated to LAZ scores; the older the children, the lower the LAZ scores. This finding was similar to some other studies which showed that the older children had lower Z scores (27, 28). In this study, the older children also consumed more varieties of food; thus, the child's age confounded the correlation between DDS and LAZ scores.

Consumption of sugary water, starch water, and other empty calorie drinks was also related to a lower LAZ, which means that the children who were fed these kinds of drinks had a lower LAZ score of 0.18. Empty-calorie drink consumption replaced the money that should have been used for nutritious food and replaced the food volume in the children's stomachs. By consuming the empty calorie drinks, the children had reached satiety, but the acquired nutrients were very limited (29). Furthermore, the consumption of sugary drinks and foods has a negative effect and causes dental caries, pain, and eating difficulty, resulting in an inadequate intake of nutrients (30, 31).

Surprisingly, in this study, exclusively breastfed history results in lower LAZ scores. The subjects who had a history of exclusively breastfed had 0.19 LAZ scores lower than those who did not. This condition was not related to socioeconomic status as the lower LAZ scores for the children who had a history of exclusively breastfed appeared in all levels of socioeconomic status. This study was performed in a cross-sectional design, and the subjects who had exclusively breastfed history might have continued to be fed by the low quality of complementary food, which then would result in low LAZ scores. Furthermore, by the definition of exclusively

breastfed history (got the first food/drink other than breastmilk at ≥ 6 months), we might have included the subjects who have had prolonged exclusive breastfeeding, which might have resulted in nutrient inadequacy and led to a lower LAZ. Unfortunately, we did not have any data on another variable on the delayed introduction of complementary foods. Thus, the exclusively breastfed history was not the cause of low LAZ but just the history of exclusive breastfeeding will not be enough to prevent stunting in children under 2 years (32). In this study, the children under 2 years who were previously exclusively breastfed have a higher risk of stunting. This fact differs from another study in East Indonesia that showed exclusive breastfeeding is a protective factor against stunting (33).

Data from Central Java health profile 2021 available on the website showed that the prevalence of exclusive breastfeeding was 72.5 %, which increased from 67.3 % in 2020 (34). However, these data were collected not on the children at 6 months but on any age at the time of the children were surveyed. It is possible that after the survey, the children were then given other food/drinks than breastmilk before 6 months. Our results showed that the number of children with a history of exclusive breastfeeding was 54.0%. Thus, our data on EBF history were reasonable.

Another consideration was the influence of the low nutritional status of the mothers, which then might have modestly influenced the breast milk content (35). A study in Indonesia indicated that lactating women had a low intake of micronutrients, which then modestly affected the micronutrient content of breast milk (36). This modestly lowers the content of micronutrients in breast milk that may have affected the micronutrient adequacy of their infants. A study in Bogor Indonesia showed that the lactating mothers' nutritional status was lower than the pre-pregnant women's nutritional status (37). Another study in Indonesia also showed that the nutritional status of lactating women was lower compared to the women who were not lactating (38). Fikawati et al.'s study in Java Island, Indonesia, also showed that the energy consumption of lactating women was low (39). Unfortunately, data on mothers' nutritional status from the 2021 INSS that can explain the results were not available. Thus, this explanation was unlikely to fully explain the finding on the negative correlation between the history of exclusive breastfeeding and LAZ scores.

The other possible explanation of this negative correlation was the reverse causality, in which the children who were having poor growth as a result of poor diet and infections tended to be breastfed or prolonged exclusively breastfed (40). Unfortunately, there was no specific data on children's diet or breastfeeding status after 6 months. Furthermore, data on infection was only cross-sectional. Non-standard definitions of infant feeding practices that were used in this study could also be a potential problem to the finding of this negative correlation between the history of exclusive breastfeeding and LAZ scores.

In this study, it was found that the socioeconomic level had an impact on LAZ scores, with an increase of 0.09 for each level of socioeconomic status which was measured by wealth quintiles. Many studies, such as Darteh et al.'s study in Ghana

TABLE 3 Variable selection results.

	Independent association with LAZ			Adjusted for other variables in the same category		
	Estimate (SE)	P value	Decision	Estimate (SE)	P value	Decision
Child Factors						
LBZ	0.30 (0.02)	<0.0001	Retain	0.30 (0.02)	<0.0001	Retain
Maternal Factors						
Mother's age (years)	−0.008 (0.004)	0.019	Retain	−0.008 (0.004)	0.019	Retain
Food Intake						
Dietary diversity (score)	−0.03 (0.1)	0.040	Retain	−0.01 (0.01)	0.353	Drop
Exclusively breastfed history	−0.16 (0.04)	<0.0001	Retain	−0.16 (0.04)	<0.0001	Retain
Consumption of Empty calorie drinks (starch water, honey, tea, coffee, sugar water, fruit juice, sweetened condensed milk, etc.)	0.18 (0.05)	<0.0001	Retain	0.18 (0.05)	<0.0001	Retain
Consumption of unhealthy snacks: extrudates in the forms of puffs, such as cheese flavored balls, crisps, etc.	0.08 (0.04)	0.060	Drop	-	-	-
Infection	−0.07 (0.05)	0.125	Drop	-	-	-
Early initiation of breastfeeding (EIBF)	0.03 (0.04)	0.532	Drop	-	-	-
Posyandu utilization	−0.11 (0.10)	0.244	Drop	-	-	-
Environmental Factors						
Drinking water source	−0.05 (0.04)	0.238	Drop	-	-	-
Sanitation	0.19 (0.06)	0.003	Retain	0.19 (0.06)	0.003	Retain
Socioeconomic status	0.11 (0.02)	<0.0001	Retain	0.11 (0.02)	<0.0001	Retain
Mother's education	0.08 (0.02)	<0.0001	Retain	0.08 (0.02)	<0.0001	Retain

found that household wealth was related to stunting, where the lowest wealth quintiles had the lowest LAZ scores (41). However, this study was carried out on children under 5 years in Ghana. The underlying cause of low LAZ scores in Central Java among children under 2 years was the socioeconomic status and mother's education.

The implication of the results indicated that the nutritional status of women at child-bearing age has to be improved as studies had shown that macronutrient and food supplementation (42) as well as multiple micronutrient supplementation (43) had decreased low birth weight and increased birth outcomes. Education of the mothers on the feeding practice for their children under 2 years is also an important intervention. Therefore, intervention programs to prevent low birth weight and stunting should be done more effectively and efficiently.

The strength of this study was a relatively large sample size and the use of path analysis to measure the direct and indirect effect size and the total effect size of determinants to LAZ scores. The other benefits of using path analysis are the fact that the effect can be measured according to the conceptual framework. One of the findings in this study is that socioeconomic status was a relatively strong underlying determinant of LAZ scores. Thus, public health actions in the community that have low socioeconomic status to prevent stunting have to be performed, and one of them is through the family empowerment program. The limitation of the

study was the shortness of the available variables in the 2021 ISSN survey. This cross-sectional design of this survey implied that the relations observed in path analysis cannot be taken as casual, and the direction could be reversed.

5. Conclusion

It is concluded that direct determinants of LAZ scores among children aged 6–23 months in Central Java, Indonesia, were birth length Z scores, the mother's age, exclusively breastfed history, and consumption of empty-calorie drinks. The underlying determinants were socioeconomic status and the mother's education. To prevent stunting among children aged 6–23 months in Central Java, Indonesia, intervention programs to increase the nutritional status of women at child-bearing age as well as education on child feeding practices should be conducted more efficiently and effectively.

Data availability statement

The original contributions presented in the study are included in the article/supplementary files, further inquiries can be directed to the corresponding author/s.

Ethics statement

The studies involving human participants were reviewed and approved by Health Research Ethics Committee of Public Health Faculty of Diponegoro University (134/EA/KEPK-FKM/2022). Written informed consent to participate in this study was provided by the participants' legal guardian/next of kin.

Author contributions

MK, AS, SSuy, SSun, MI, NN, YN, JD, EW, MS, PH, and NF were responsible for the conception and design of the study. MK, AS, SSuy, and SSun were responsible for managing and retrieving the data. MK, AS, and SSun performed the statistical analysis and interpretation of data. MK wrote the manuscript. MK and AS did a critical review. All authors have read and approved the manuscript.

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Conflict of interest

The authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

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EDITED BY

Nita Bhandari,
Center for Health Research and Development,
Society for Applied Studies, India

REVIEWED BY

Pabitra Kumar Jena,
Shri Mata Vaishno Devi University, India
Fortunato Leonardo,
Azienda Ospedaliera San Pio di Benevento,
Italy

*CORRESPONDENCE

Virginia Medina Jimenez
✉ virginia.medina@guanajuato.gob.mx

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Universal prenatal screening: a initiative from Guanajuato, Mexico to improve equity in perinatal healthcare

Ma de la Luz Bermudez Rojas¹, Virginia Medina Jimenez^{1*},
Javier Ivan Manzanares Cuadros¹, Daniel Alberto Diaz Martínez²,
Nicolas Padilla Raygoza³ and Elia Lara Lona²

¹State Center for Timely Prenatal Screening, Maternal and Child Hospital of Leon Guanajuato, Maternal-Fetal Unit, Institute of Public Health, Leon, Guanajuato, Mexico, ²Institute of Public Health, Leon, Guanajuato, Mexico, ³Department of Research and Technological Development, Directorate of Teaching and Research Institute of Public Health, Leon, Guanajuato, Mexico

The prenatal approach from a preventive perspective is necessary to reduce perinatal complications. A perinatal care model with a holistic and horizontal approach is required. Mexico is currently considered an emerging market economy with inequality and an economic gap that impacts the accessibility and distribution of healthcare services. Guanajuato is one of the 32 states of Mexico and represents 1.6% of the country's surface. Strategies during the prenatal approach allow prediction, diagnosis, and anticipation of the principal causes of morbidity and mortality. Combining data from maternal characteristics and history with findings of biophysical and biochemical tests at 11 to 13 weeks of gestation can define the patient-specific risk for a large spectrum of complications that include miscarriage and fetal death, preterm delivery, preeclampsia, congenital disorders, and fetal growth abnormalities. We aim to describe the care model designed and implemented in the State Center for Timely Prenatal Screening of the Maternal and Child Hospital of Leon, Guanajuato, Mexico. Previous research showed there is a lack of information for low and middle-income countries regarding how to integrate prenatal screening strategies in the absence of resources to perform cell-free fetal DNA or biochemical serum markers in countries with emergent economies. This care model is carried out through horizontal processes where the screening is provided by trained and certified general practitioners who identify the population at risk in a timely manner for specialized care, and could help guide other Mexican states, and other countries with emergent economies with limited financial, professional, and infrastructural resources to improve prenatal care with a sense of equity, equality, and social inclusion as well as the timely evaluation of specialized perinatal care of high-risk patients.

KEYWORDS

pregnancy, prenatal care, prevention, prenatal diagnosis, congenital abnormalities, preeclampsia, premature birth, pregnancy complications

1. Introduction

An accessible and effective care model for perinatal health under a predictive approach based on identifying obstetric risk factors, characterization of prenatal ultrasonographic parameters, and individualized obstetric follow-up by trained and experienced health personnel is essential to lessen perinatal morbidity and mortality, especially maternal death. Maternal and child indicators are considered parameters that reflect the quality of healthcare provided by health services in a population, such as availability, geographic and economic accessibility, acceptability, and successful coverage based on a structured referral system. Some of the sustainable development goals are to reduce the global maternal mortality ratio to less than 70 per 100,000 live births and abolish preventable deaths of newborns and children under 5 years of age. All countries aim to reduce neonatal mortality to at least as low as 12 per 1,000 live births and under 5 years mortality to at least as low as 25 per 1,000 live births by 2030 (1), currently far from possible for countries with emerging market economies. Previous research showed a lack of information for low and middle-income countries regarding the integration of prenatal screening strategies in the absence of resources to perform cell-free fetal DNA or biochemical serum markers in countries with emergent economies. Such countries should be a priority to improve maternal and child health since they represent the home of 75% of the world's population where 62% of the world is poor (2), they have a high rate of births and morbimortality by implementing cost-effective strategies with high impact and easy access and without economic barriers that allow timely identification of risk situations. Prenatal screenings evaluate the probability of having a healthy fetus and a term of pregnancy in the best conditions. A third of the Latin American population experiences multiple barriers that hinder healthcare (3); the system recommended by PAHO/WHO called SIP (acronym in Spanish for Perinatal Information System) by using indicators to evaluate perinatal health policies, programs, and services, it is a system oriented to public health and not to individual decision-making (4). The SIP is not used in Mexico; prenatal control is based on three guiding documents: The sexual and reproductive health program (5); the NOM (acronym in Spanish for Official Mexican Standard 007) (6) and Clinic Practice Guidelines (7).

The NOM establishes to perform an ultrasound on each trimester of pregnancy by trained personnel to determine maternal and fetal well-being. The first between 11–13.6 weeks to determine gestational age, fetal vitality, and the number of fetuses; the second between 18–22 weeks, and the third between 29–30 weeks which does not contemplate the integration of risk factors and biophysical parameters proposed by other models such as the one proposed by Nicolaides et al. (8–11).

The implementation of universal prenatal screening represents many challenges such as overcoming barriers of accessibility with a lack of economic resources to provide timely attention. Therefore, we aim to describe the care model designed and implemented in CETO (acronym in Spanish for the State Center for Timely Prenatal Screening), currently the chief maternal-fetal reference unit of the Institute of Public Health in the State of Guanajuato, Mexico which provides health care mainly to the population that does not have a formal job. The care model is carried out through horizontal processes where the screening is provided by trained and certified

general practitioners who identify the population at risk in a timely manner for specialized care, shortens waiting times for timely surveillance through an individualized risk estimation for specific entities such as preeclampsia, prematurity, congenital disorders, and fetal growth restriction, applicable to countries with emerging market economies with limited financial, professional, and infrastructural resources.

2. Context

Mexico is considered an emerging market economy (12) with many differences that persist between municipalities within regions (13). The inequality and economic gaps are very evident and impact the accessibility and distribution of healthcare services. Mexico has a fragmented healthcare system; the provision of services is granted with or without social security. Half of the population does not have social security, therefore this health care model was created to provide primary health care and universal access focused especially on those pregnant women who lack a formal job and health insurance.

In Mexico, pregnant women from rural areas with lower socioeconomic levels in marginalized environments and without health insurance, are those with the most deferrals in prenatal care (14) and at an increased risk of maternal and perinatal morbidity and mortality. The calculated maternal death ratio is 30.5 deaths per 100,000 estimated births in Mexico. Our state's maternal death ratio is 38.8 deaths per 100,000 live births (15). The leading causes of death are preeclampsia-eclampsia (18%), obstetric hemorrhage (17.4%), and abortion (7.1%), where the most affected age group is 45 to 49 years (16). On the other hand, in 2020, 22,637 fetal deaths were registered in our country, approximating a rate of 6.7 per 10,000 women of childbearing age. Of all fetal deaths, 82.9% occurred before delivery, 15.6% occurred during delivery, and the cause of 1.5% of fetal deaths is unknown (17). The principal causes of infant mortality in Guanajuato are conditions originating during the perinatal stage. Secondary causes are due to congenital malformations, deformities, and chromosomal abnormalities, with a rate of 4.9 and 3.0 per 1,000 live births, respectively.

Guanajuato is one of the 32 states that constitute the Federal Entities of Mexico, with 6,166,934 inhabitants, which represent 4.9% of the total population of Mexico (18), it has 6,166,934 inhabitants, of which 79% had healthcare coverage; 44.8% of inhabitants were covered by the Institute of Public Health from the State of Guanajuato. In 2021, of 107,409 births, 858 infant deaths under 1 year were reported (19).

According to a national retrospective study in Mexico in 2016, Guanajuato had the highest antenatal coverage (81.6%) of the 32 Mexican states. Heredia P et al. proposed that adequacy in prenatal care consists of four fundamental aspects: (a) Skilled healthcare (antenatal care provided by a nurse or a physician), (b) Timely healthcare (initial antenatal care visit during the first trimester of pregnancy), (c) Sufficient healthcare (at least four antenatal care visits during the pregnancy), and (d) Healthcare appropriate in content (an indicator summarizing the procedures and processes of care provided during antenatal care) (20). According to a national retrospective study in Mexico, antenatal care was appropriate in 71.5% (IC 95% 69.7–73.2) of the cases.

3. Key programmatic elements

A screening test is a medical test or procedure performed on members (subjects) of a defined population to assess the likelihood that its members have a particular disease or outcome and to reduce morbidity or mortality through early detection when treatment may be beneficial (21). CETO model's goal is to screen the population with a holistic, horizontal approach from the first trimester of pregnancy, or as early as possible, to reduce perinatal mortality and morbidity. Its pillars are based on screening in the first, second, and third trimesters using a multiparametric approach based primarily on the Fetal Medicine Foundation. As proposed in the model of the inversion of the prenatal care pyramid proposed by Nicolaides (11), first-trimester screening allows the prediction of entities such as fetal growth restriction, preeclampsia, preterm delivery, and aneuploidy in pregnant women with a window of opportunity corresponding to 11–13.6 weeks of gestational age for referral to prenatal care with a risk-based approach. Second-trimester screening, also termed structural or morphologic sonography, is performed between 18 and 22 weeks of gestational age. Its purpose is to detect congenital anomalies, as well as to predict preeclampsia and preterm delivery. Third-trimester screening allows early detection of late-onset placental diseases and late fetal pathologies for referral after 28 weeks of gestation. In addition, screening for infections for rapid diagnosis and optimal treatment could decrease the likelihood of complications such as preterm delivery, maternal sepsis, etc. This dynamic screening allows to identify of those high-risk patients who are candidates for receiving treatments such as progesterone, cerclage, or pessary to prevent prematurity; acetylsalicylic acid to prevent preeclampsia and/or fetal growth restriction, prompt evaluation by Perinatal Genetics if necessary and/or invasive procedures and fetal surgery in cases of fetal pathology that require it.

At our center, the follow-up of fetal and maternal pathologies is carried out through a specific line of work or clinics by maternal-fetal physicians. Characteristics and mode of operation are detailed below; the care flowchart and risk categorization are shown in Figure 1.

- a) *Extended clinical screening* (first-trimester ultrasound markers including ductus venosus flow and tricuspid regurgitation plus detailed anatomical evaluation).
- b) *Multiple gestations* (first-trimester evaluation for gestational age, chronicity, and risk categorization for the presence of aneuploidy, preeclampsia, and follow-up throughout pregnancy to identify complications, including those requiring intrauterine interventions such as a placental laser).
- c) *Placental disease* (evaluation of high-risk pregnancies with the development of preeclampsia or fetal growth abnormalities, with or without prophylaxis, with acetylsalicylic acid and other abnormalities such as placenta accreta spectrum).
- d) *Prematurity prevention clinic* (evaluation of high-risk pregnancies for spontaneous preterm delivery with ultrasound follow-up, including patients with progesterone, pessary, or cerclage).
- e) *Soft ultrasound markers for aneuploidy* (presence of thickened nuchal fold, pyelectasis, hypoplastic nasal bone, echogenic bowel, limb shortening, choroid plexus cyst, and single umbilical artery, echogenic intracardiac focus (22). Although this marker may be questionable, follow-up of patients with soft markers is justified because performing cell-free fetal DNA is financially unviable. All cases are evaluated and followed up by specialists in maternal-fetal and perinatal genetics).

- f) *Fetal pathology* (if indicated, invasive procedures or fetal surgery with perinatal follow-up).
- g) *Perinatal genetic clinic* (counseling, advice, and follow-up of fetal pathology),
- h) *Pediatric clinic* (with follow-up, coordination, and referral of newborns to different pediatric subspecialties, neurodevelopment, and nutrition).
- i) *Psychology* (mental health assessment of pregnant patients, especially those with a diagnosis of fetal pathology to provide support and coping strategies for perinatal bereavement).
- j) *Second-trimester screening*: Structural evaluation of patients referred from a low-risk screening in the first trimester of peripheral primary unit centers.
- k) *Intrauterine procedures and surgery*: Such as amniocentesis, cordocentesis, chorionic villus biopsy, fetal transfusion, placental laser, etc. performed by a maternal-fetal physician with training in fetal surgery.
- l) *Other fetal subspecialties*: Recently, due to the growing need, two specialized clinics have been created: fetal cardiology, attended by a pediatric cardiologist with training in fetal cardiology, and fetal neurology, with a maternal-fetal physician with training who, in addition to performing advanced fetal neurosonography, determines the performance of fetal MRI scans.

The objectives described in the model are evaluated annually with the following indicators: the proportion of patients screened in the first, second, and third trimesters (high and low-risk classification); the proportion of patients who dropped out of the systematic screening; the proportion of patients reported as high risk in the expanded screening; the proportion of patients that benefited from the diagnostic intervention and preventive treatment described in the care model; the proportion of patients with fetal structural alterations admitted to the model, and, the proportion of patients referred to the Genetics and Psychology clinics and proportion of fetuses with postnatal follow-up.

3.1. Care program development

CETO began in 2014; currently, we have performed 108,331 assessments (including the first, second, and third quarters of 2014 to June 2022). The productivity needed was calculated and derived from an estimate of the population of health jurisdiction VII with 66 medical units and an annual average of 7,540 pregnant women, and health jurisdiction VIII with 51 medical units and an annual average of 6,059 pregnant women.

The consolidation of the center went through different stages. First, the idea of the possibility of providing ultrasound and biochemical screening services for pregnant patients was supported by the state government on July 1, 2012. This model was initially called Project 78 (named after the number of jurisdictions that provided coverage in the State of Guanajuato) and was later renamed CETO. In June 2013, a visit was made by Dr. Kypros Nicolaides for counseling, with a tour of three hospitals where prenatal screening was being implemented. At the end of 2013 and in the first months of 2014, the first stage of Project 78 was implemented. This first stage served as a pilot of the initiative and included the training of a general practitioner who performed the screening in the first trimester of pregnancy at the

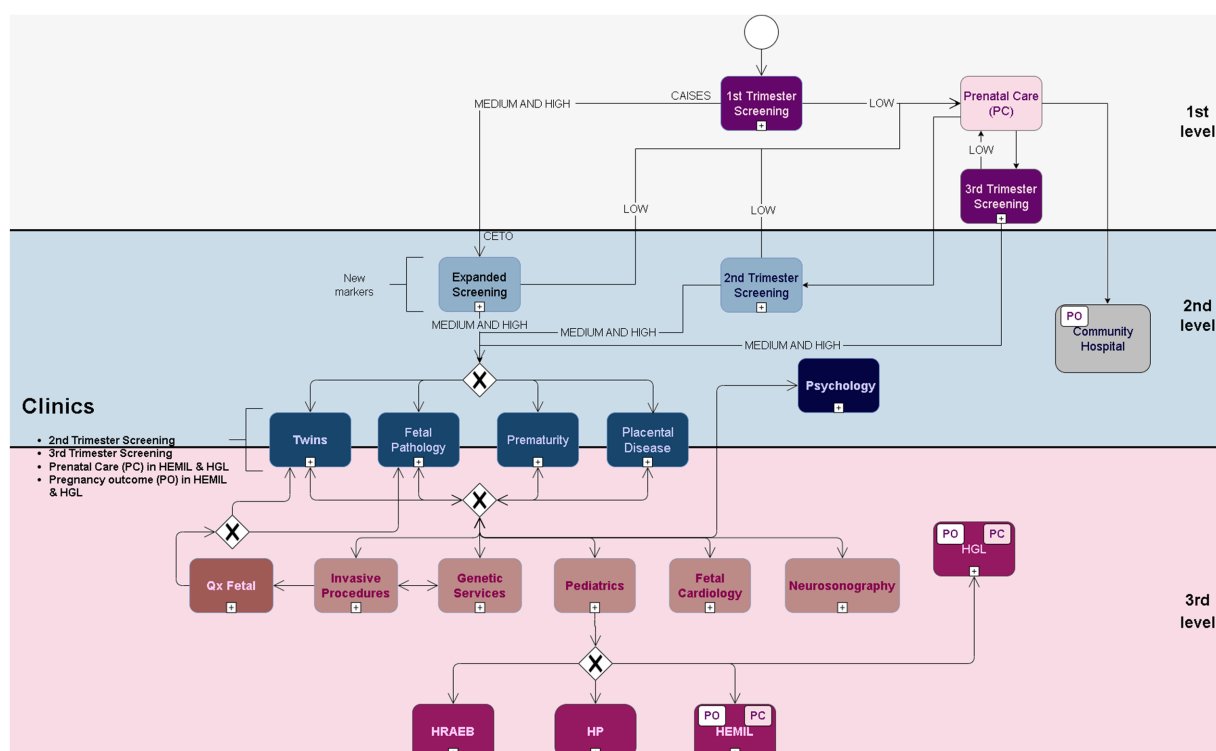


FIGURE 1

Care Flowchart and risk categorization. The model of care process of the State Center for Timely Prenatal Screening is characterized by horizontalizing perinatal care, offering screening to the pregnant population since the first trimester of pregnancy and risk evaluation for the presence of fetal aneuploidy as well as predicting risk for preeclampsia, fetal growth restriction, and preterm birth. Depending on the assigned risk, pregnant women are evaluated and followed up in the corresponding work areas where, if necessary, they are also referred to other hospital centers that belong to the National Institute of Public Health of the State of Guanajuato to continue their postnatal follow-up.

Purísima del Rincón comprehensive care and essential health services center.

In the first half of 2014, 13 ultrasound scanners were acquired to implement and develop Project 78. Management was carried out through program Q06681, strengthening health units for surveillance and pregnancy control. In July 2014, the budget request was submitted.

From February to May, the second stage was executed. The main objective was to train general practitioners to perform first-trimester screening and triage of the population. In addition, second-trimester screenings were initiated under the supervision of an Ultrasonography specialist. All the above was carried out in the HEMIL (an acronym for Hospital Materno Infantil de León, Guanajuato) facilities.

The third stage consisted of implementing the care model proposed in the initiative. In this stage, previously trained personnel were assigned to six first-level care units (four in jurisdiction VII and two in jurisdiction VIII).

In the fourth stage, the care model was strengthened by expanding staff. Nurses, specialists, social workers, and administrative and IT personnel were hired. Two computer systems were acquired to store and generate medical reports. Also, during the fourth and fifth stages, inter-institutional collaborations were created with third-level health units (specialties) in other states, for example, the Women's and Children's Hospital of Querétaro, which offered surgical services.

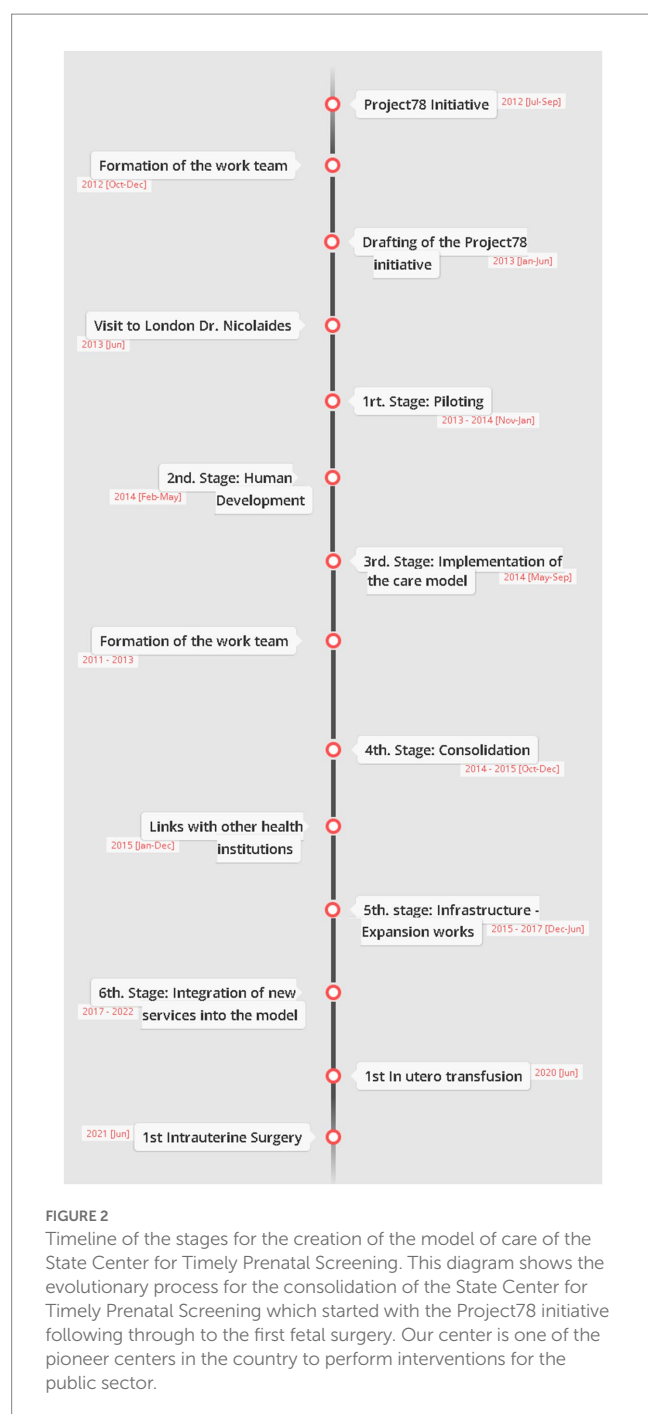
In the fifth stage, the expansion of the Center was carried out with the management of its building and the necessary technological

equipment. This building is in the HEMIL facilities. In addition, treatments for some diagnoses were incorporated into the model. The sixth stage was characterized by the expansion of the care model by adding new services.

The timeline of stages for the creation of the State Center for Timely Prenatal Screening care model is shown in Figure 2.

3.2. Operability

This multicentric center is made up of primary healthcare units with general practitioners certified by The Fetal Medicine Foundation that evaluate pregnant women from the sanitary jurisdictions VII (Casa Blanca, Las Trojes, Miguel Aleman and Floresta) and VIII (Purísima and San Francisco del Rincón) who are under continuous supervision and leadership by specialists in Obstetrics and Gynecology and Maternal-Fetal specialists from the central unit (CETO) in order to identify patients at high risk for preeclampsia, fetal growth restriction, preterm delivery, aneuploidies, birth defects, abnormal placentation, fetal infections and/or maternal comorbidities. The practitioners comprehensively protocolize the type of genetic or structural condition detected from the number of weeks of gestation, which allow an early and multidisciplinary approach in coordinated care regarding the optimal place and time of birth determined by a prompt evaluation in the Central Unit (CETO), located in the Maternal and Child Hospital of León, Guanajuato, Mexico. Here, there are specialists in gynecology and



obstetrics, subspecialists in maternal-fetal medicine, a perinatal geneticist, a pediatrician, a fetal cardiologist, a fetal neurosonographer, a fetal surgeon, as well as psychology nurses, social workers, and administrative staff with a multidisciplinary approach.

Since biochemical markers are not available, we created a strategy with greater control to increase the detection rate during the first-trimester evaluation by incorporating the rest of the first-trimester ultrasound markers in addition to nuchal translucency (nasal bone, tricuspid flow, venous ductus flow, doppler of uterine arteries and cervical length), as well as a complementary fetal anatomical evaluation through expanded screening by a maternal-fetal subspecialist. If the patient is at low risk, she is incorporated into the low-risk patient care

consultation scheme. If the patient is not at low risk, she is referred to specific care consultations; prematurity, placental pathology, soft markers of aneuploidy, fetal pathology, and perinatal genetics, except in the case of multiple pregnancy, which is evaluated by a maternal-fetal subspecialist from the onset of pregnancy to term. Simultaneously, psychologists evaluate patients in all clinics. Low-risk patients receive their prenatal check-ups in the primary care units, and their second-trimester screening at 18–22 weeks of gestation is performed in the central unit by specialized obstetrician-gynecologists. In the absence of structural anomalies and low risk for preeclampsia, and preterm delivery, patients continue their prenatal check-ups in the primary care units.

All patients categorized as high-risk pregnancies in the primary care units are evaluated in the central unit where more detailed screening is performed to assign the line of work or clinic that will provide the patient with follow-up consultations during pregnancy (multiple pregnancies, soft markers, fetal pathology including neurosonography and fetal cardiology when indicated; prevention of prematurity and placental disease). Simultaneously, a prenatal control consultation is scheduled for high-risk pregnancies to guarantee follow-up around the time of delivery at the Maternal and Child Hospital of Leon, Guanajuato (Second Level Hospital). In addition, high-risk and low-risk patients receive orientation for nutritional support, vaccinations, cervicovaginal cytology, and pregnancy education at their corresponding units.

3.3. Infrastructure

The center has 13 high-resolution General Electric Voluson General ultrasound units. We also have a software Viewpoint that allows us to link the ultrasound information to a clinical record to exchange medical information about the patient thereby integrating a final report of the evaluation that allows us to have a follow-up of each patient to regulate therapeutic behaviors promptly. On the other hand, we have an electronic agenda that allows us to schedule patient appointments and obtain general and individual productivity indicators for each evaluator, percentage of absences, and other healthcare quality indicators, with the added convenience of scheduling appointments by phone for the patient, or between the different interconnected units without the need of the patient to travel, making her care process more accessible and comfortable.

The interconnection between the different levels of care is achieved through the Institution's referral. In this way, effective communication is ensured, and patients at high risk of maternal mortality or near-miss are notified to facilitate early recognition and to anticipate the optimal time and place of delivery. Fetuses with congenital anomalies are seen in a weekly face-to-face or virtual multidisciplinary session composed of pediatric subspecialists (neonatologists, cardiologists, pediatric surgeons, pediatric endocrinologists, pediatric hematologists, perinatal geneticists, among others), social workers, pediatricians, and gynecologists to identify and optimize resources around the time of delivery. Newborns and infants have follow-up visits by the pediatric hospital, the general hospital, and the high specialty hospital of Leon, Guanajuato. Newborns evaluated prenatally at our center receive follow-up, early stimulation, and neurodevelopmental evaluation at the primary care units. Newborns prenatally identified with high-risk factors for

TABLE 1 Productivity by work lines or clinics.

Work lines	2018	2019	2020	Total 2018–2020
First-trimester scan	848	688	383	1919
Second-trimester scan	1965	3,910	2,730	8,605
Third-trimester scan	886	1,049	1,148	3,083
Complementary scan (High-risk first-trimester scan)	1,142	1,109	660	2,911
Preterm prevention	1,604	2,552	1,617	5,773
Placental disease	662	655	488	1805
Multiple pregnancies	546	451	461	1,458
Soft markers	459	603	345	1,407
Fetal pathology	545	524	391	1,460
Invasive procedures (Amniocentesis, Cordocentesis, or Chorionic villus biopsy)	52	86	175	313
Pathological Uterine Arteries	836	792	621	2,249
Complementary scan (High-risk second-trimester scan)	-	24	72	96
Total of prenatal screenings	5,846	6,798	5,049	17,693

TABLE 2 Coverage of the main perinatal outcomes.

Period	Preeclampsia	Coverage %	Fetal growth restriction	Coverage %	Prematurity	Coverage %	Birth defects	Coverage %
2011	489	0.9%	482	0.9%	352	0.7%	471	0.9%
2012	551	1.0%	374	0.7%	266	0.5%	456	0.8%
2013	633	1.2%	307	0.6%	221	0.4%	453	0.8%
2014	645	1.2%	292	0.5%	218	0.4%	514	1.0%
2015	538	1.0%	308	0.6%	204	0.4%	325	0.6%
2016	720	1.3%	341	0.6%	257	0.5%	352	0.7%
2017	788	1.5%	292	0.5%	195	0.4%	368	0.7%
2018	904	1.7%	234	0.4%	181	0.3%	332	0.6%
2019	1,000	1.9%	173	0.3%	141	0.3%	314	0.6%

neurodevelopmental disorders such as fetal anemia, twin-to-twin transfusion, polycythemia sequence due to twin anemia, fetal growth restriction, central nervous system anomalies, congenital infections with brain tropism such as cytomegalovirus, toxoplasmosis, etc. are referred for a specialized neurodevelopmental evaluation and assessment of the possibility of neurorehabilitation and follow-up for at least the first three to 6 years of life. This is performed by the pediatrician assigned at CETO who establishes the connection between the different pediatric subspecialties and related medical areas: psychology, neurodevelopment, early stimulation, and individualized follow-up of the child's health during infancy.

3.4. Casuistry

From January 2018 to December 2020, we performed 50 screenings per day, 300 screenings per week, and 1,200 screenings per month, with a total of 17,693 prenatal screenings, representing the coverage of 43.3% of the entire population (considering 40,797 pregnancies between 2018–2020 of). According to the World Health Organization, health services should be provided to 100% of the

population. In our country, healthcare is divided into the public and private sectors. Our center belongs to the Public Health Institute of the State of Guanajuato, which excludes other governmental institutions. A percentage of pregnant women who do not attend complete follow-ups, either due to early loss, premature delivery, or migration to other geographic areas, is expected (20). Productivity by work areas or clinics is shown in Table 1. The coverage of the main outcomes such as preeclampsia, preterm birth, birth defects, and fetal growth restriction is shown in Table 2. The tendency of the main perinatal outcomes is shown in Figure 3.

4. Discussion

Strategies carried out with a prenatal approach allow for prediction, diagnosis, and anticipation of the principal causes of mortality in pregnancy. According to a study conducted in India by Yadav A et al., female education, mass media exposure, women's autonomy, and economic status were significantly associated with the need for maternal healthcare services (23). As reported by Yadav A et al., income and education are the most significant contributors to women's

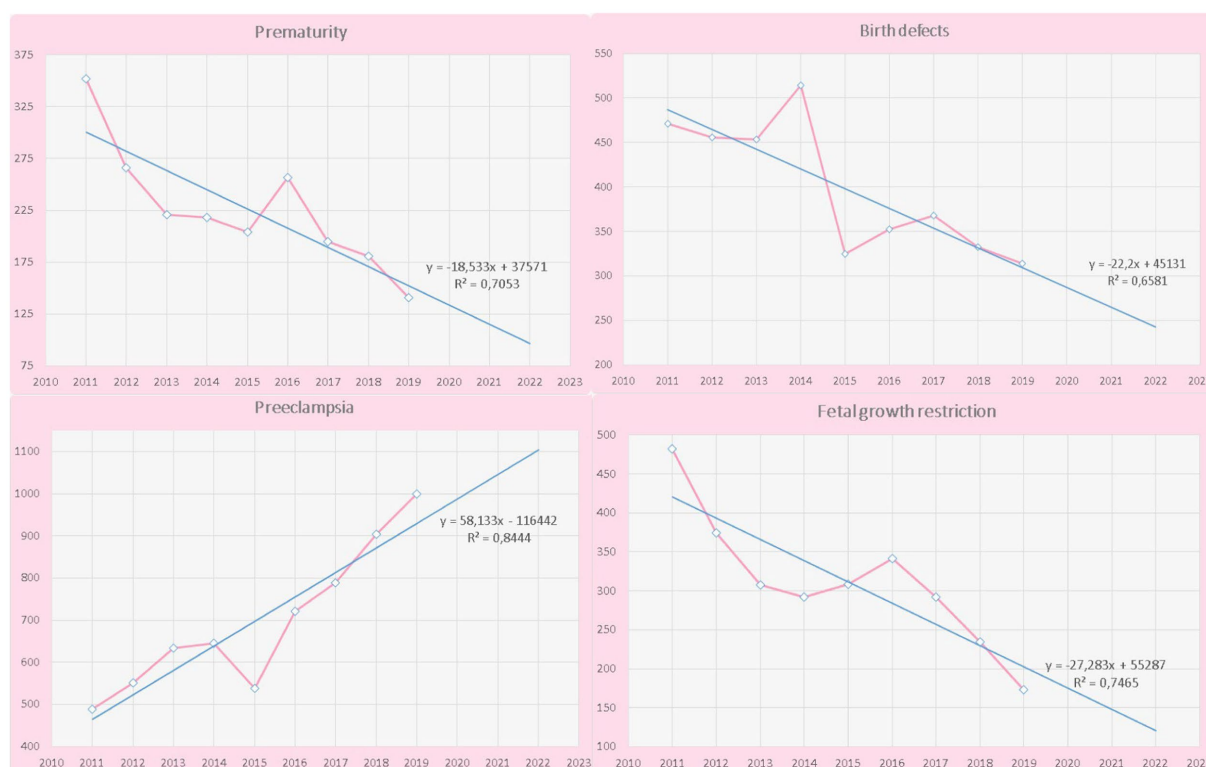


FIGURE 3
Indicators of the care model over time.

employment of maternal healthcare services, followed by the availability of water facilities at home and in geographical regions (24). Our initiative links the most effective strategies reported in studies. From 11 to 13 weeks, the combination of maternal characteristics and historical data with the findings of biophysical and biochemical tests can define the patient's specific risk for a broad spectrum of complications including abortion and fetal death, preterm delivery, preeclampsia, congenital disorders, and fetal growth abnormalities (11). There are a few studies published in our country regarding first-trimester screening, one of which is a study published by Oviedo-Cruz H et al. that reported an estimated detection rate of 85% and a false positive rate of 3.9%. However, the authors used biochemical and ultrasonographic markers in a Mexican population assisted by private medicine that does not resemble our population which is evaluated in the public health sector. In our case, the evaluations outnumber the tests we can perform on biochemical markers, which exemplifies the vast economic disparity that exists in our country (25). The importance of screening in the first trimester to detect congenital anomalies was demonstrated in a Mexican study by Nuñez-Sánchez G et al. The authors reported a detection rate of 83.6%, further increased to 90% by adding screening in the second trimester. The highest detection rates were obtained by screening for abdominal wall defects, nervous system alterations, cardiac defects, and skeletal anomalies (26). Early identification of patients at risk for hypertensive disorders in pregnancy, including preeclampsia and eclampsia, is advantageous to prescribe pharmacological interventions (acetylsalicylic acid) and to establish specific follow-up until obstetric outcome, a strategy validated in Mexico (8, 27–30). Lakshmy et al. defined that screening for preeclampsia by combining maternal history and biophysical or

biochemical parameters, as feasible, could prevent patients from developing the complications of preeclampsia, even in low-resource settings (31).

The most frequent cause of obstetric hemorrhage is uterine atony (32). Identification of the factors that cause uterine overdistension can help to anticipate this complication. Additionally, prenatal evaluation of the placenta in high-risk patients can help to suspect the spectrum of placenta accreta which is the cause of severe postpartum hemorrhage (33). On the other hand, since 1990, most infant deaths in Mexico were due to conditions or difficulties during pregnancy, delivery, or the first month after birth, as well as congenital problems. The lethality and morbidity of congenital anomalies require early diagnosis during prenatal care (34). Screening for fetal aneuploidy at 11 to 13 weeks is possible using maternal age and fetal nuchal translucency assessed by ultrasound with a detection rate of 80% and a false positive rate of 5%, acceptable in developing countries such as Mexico, where biomarkers are not always available for financial reasons (10). Prematurity is the most unresolved problem in perinatal medicine worldwide. Premature births are responsible for 70% of neonatal deaths and 36% of infant deaths, and 25–50% of long-term neurological impairment cases in children (35). Early identification of the high-risk group for preterm spontaneous delivery before 34 weeks may be determined by an algorithm combining maternal characteristics and obstetric history with cervical length measurement to decide which patients require effective interventions such as progesterone, cerclage, or pessary (as a heroic alternative in patients refractory to progesterone and who due to gestational age are not candidates for cerclage) (11, 36). This also allows for the patient follow-up to identify the occurrence of

prenatal infections that may lead to inflammation and preterm delivery to treat them promptly and may help decrease the probability of fetal brain injury (37).

To our knowledge, no previous studies have examined how to integrate all prenatal screening strategies into a single care model in Latin American countries or other middle-income countries.

The strength of our project is the horizontalization of perinatal care from an interdisciplinary approach that simultaneously includes the three levels of care, allowing other states of our country and other countries with emerging economies to replicate the broad care coverage.

Likewise, the involvement of the first level of care and specifically general practitioners guarantees greater coverage, accessibility, and cost-effectiveness of care for pregnant women; coupled with an early evaluation of the risk for a potentially developing pathology that could be prevented or reversed. This itself could be a weakness of our project, however, they are continuously trained, certified, and supervised. Additionally, gynecologist-obstetricians with master's degrees in prenatal ultrasonography and maternal-fetal specialists evaluate the patients identified as potentially at high risk which decreases the possibility of making mistakes around perinatal care. Another weakness is that we do not yet have biochemical markers for the first trimester nor cell-free fetal DNA. However, given that our center has been equipped and strengthened over time, we do not rule out the possibility of obtaining these markers henceforth. Subsequent studies will verify the results of our care model, and this publication will serve as a precedent for the implementation and operation of this perinatal care model.

5. Conclusion

A fundamental part of care models is guaranteeing a care network with which the population can move effortlessly from one service to another (38). Having a horizontal model of prenatal screening makes it possible to reduce waiting times for care, as well as to provide a comprehensive approach to the mother-baby binomial, reducing delays in care, and thus reducing perinatal morbidity and mortality. CETO's horizontal perinatal care model may serve as a guide for other Mexican states and other countries with emerging economies, with a sense of equity, equality, and social inclusion, as well as providing a timely evaluation of specialized perinatal care for high-risk patients. Other Mexican states and developing countries may replicate this care model to improve perinatal care seizing the opportunity offered by the first level of care, with regard to recruitment, accessibility, and equal conditions for pregnant women, triggering systematized screening that allows a real sense of prenatal control with a risk approach perspective.

Data availability statement

The raw data supporting the conclusions of this article will be made available by the authors, without undue reservation.

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Author contributions

MB and VM: conceptualization. MB created and developed the model of care previously described and established in the CETO. MB and EL: methodology. JM: data analysis, design of figures, and tables. VM: writing-original draft preparation. MB, EL, DD, NP, and VM: writing-review and editing. All authors contributed to the article and approved the submitted version.

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Conflict of interest

The authors declare that the research was conducted in the absence of any commercial or financial relationships that may be construed as a potential conflict of interest.

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EDITED BY

Ravi Prakash Upadhyay,
Center for Health Research and Development,
Society for Applied Studies, India

REVIEWED BY

Saurabh Sharma,
National Institute of Medical Statistics (ICMR),
India
Rukman Manapurath,
Center for Health Research and Development,
Society for Applied Studies, India

*CORRESPONDENCE

Melissa F. Young
✉ melissa.young@emory.edu

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Maternal preconception BMI and gestational weight gain are associated with weight retention and maternal and child body fat at 6–7years postpartum in the PRECONCEPT cohort

Melissa F. Young^{1,2*}, Phuong Hong Nguyen^{3,4}, Lan Mai Tran^{1,2},
Long Quynh Khuong⁵, Sara Hendrix¹, Reynaldo Martorell^{1,2} and
Usha Ramakrishnan^{1,2}

¹Hubert Department of Global Health, Emory University, Atlanta, GA, United States, ²Doctoral Program in Nutrition and Health Sciences, Laney Graduate School, Emory University, Atlanta, GA, United States, ³Poverty, Health and Nutrition Division, International Food Policy Research Institute (IFPRI), Washington, DC, United States, ⁴Thai Nguyen University of Pharmacy and Medicine, Thai Nguyen, Vietnam, ⁵Hanoi School of Public Health, Hanoi, Vietnam

Background: There is limited evidence from prospective cohorts in low-resource settings on the long-term impact of pre-pregnancy body mass index (PPBMI) and gestational weight gain (GWG) on postpartum weight retention (PPWR) and maternal and child body composition.

Objectives: We examined the associations between PBPBM and timing of GWG on PPWR at 1, 2, and 6–7years and maternal and child percent body fat at 6–7years.

Methods: We used data from the PRECONCEPT study (NCT01665378) that included prospectively collected data on 864 mother–child pairs from preconception through 6–7years postpartum. The key outcomes were PPWR at 1, 2, and 6–7years, and maternal and child percent body fat at 6–7years that was measured using bioelectric impedance. Maternal conditional GWG (CGWG) was defined as window-specific weight gains (< 20wk, 21–29wk, and ≥30wk), uncorrelated with PBPBM and all prior body weights. PBPBM and CGWG were calculated as standardized z-scores to allow for relative comparisons of a 1 standard deviation (SD) increase in weight gain for each window. We used multivariable linear regressions to examine the associations, adjusting for baseline demographic characteristics, intervention, breastfeeding practices, diet and physical activity.

Results: Mean (SD) PBPBM and GWG were 19.7 (2.1) kg/m² and 10.2 (4.0) kg, respectively. Average PPWR at 1, 2, and 6–7years was 1.1, 1.5 and 4.3kg, respectively. A one SD increase in PBPBM was associated with a decrease in PPWR at 1 year (β [95% CI]: –0.21 [–0.37, –0.04]) and 2 years (–0.20 [–0.39, –0.01]); while a one SD in total CGWG was associated with an increase in PPWR at 1 year (1.01 [0.85, 1.18]), 2 years (0.95 [0.76, 1.15]) and 6–7 years (1.05 [0.76, 1.34]). Early CGWG (< 20weeks) had the greatest association with PPWR at each time point as well as with maternal (0.67 [0.07, 0.87]) and child (0.42 [0.15, 0.69]) percent body fat at 6–7years.

Conclusion: Maternal nutrition before and during pregnancy may have long-term implications for PPWR and body composition. Interventions should consider targeting women preconception and early in pregnancy to optimize maternal and child health outcomes.

KEYWORDS

maternal nutrition, BMI, gestational weight gain, body composition, child body composition, postpartum weight retention

Introduction

Maternal nutrition before and during pregnancy is a critical window of opportunity for optimizing maternal and child health outcomes (1–3). Women who enter pregnancy with a healthy body mass index (BMI between 18.5 and 24.9 kg/m²) are at a lower risk for adverse pregnancy outcomes such as pre-eclampsia, gestational diabetes, large or small for gestational age (LGA or SGA), and stillbirths (4–7). Poor maternal nutrition also has long-term implications for the offspring health by placing them at increased risk of diabetes, hypertension, hypercholesterolemia and heart disease later in life (8–12).

Excessive or inadequate gestational weight gain (GWG) during pregnancy has likewise been associated with increased risk adverse birth outcomes such as SGA, LGA, preterm birth and gestational diabetes (13–15). Prior work from the Women First Trial including over 2000 women from the Democratic Republic of Congo, Guatemala, India and Pakistan reported that women's pre-conception BMI (PPBMI), early GWG from preconception to 12 weeks and from 12 to 32 weeks were independently associated with birth length and weight (16).

However, the long-term impact of GWG on maternal and child health outcomes is less well established. In a systematic review, excess GWG above the Institute of Medicine (IOM) recommendations was associated with an additional post-partum weight retention (PPWR) of 3 kg and 4.7 kg at 3 and 15 years postpartum, respectively, compared to those who gained within IOM recommendations (17). Women who gained below IOM recommendations had a 3 kg less of weight retention at 6 months postpartum; however, there was no long-term associations at 15 years (17). PPBMI was reported to have a negative association with PPWR, though GWG was considered the key driver of short and long term PPWR (18). However, these conclusions were based on limited data primarily from high income settings with inadequate adjustment for confounding factors (such as breastfeeding and physical activity, for example). Furthermore, there was imprecise measurement of key exposures as pre-pregnancy weight that was often based on retrospective self-report data and may be prone to reporting bias (19, 20). The measures of GWG also do not permit the examination of the possible effects of differences in the timing and/or patterns of weight gain across pregnancy. Thus, there remain questions on the relative contributions of maternal nutrition before and during pregnancy on weight retention and long-term health outcomes.

We have previously examined the relative role of maternal nutrition before and during pregnancy from the PRECONCEPT study and reported similar and independent associations of maternal PPBMI and GWG with infant size at birth (21). In addition, ultrasound data on fetal growth were used to pinpoint critical periods for GWG that were most influential on child growth. Early GWG in the first 20 weeks had 3 times the influence on birthweight compared to GWG $\geq$ 30 weeks (22); however, the long-term impacts remain unclear. Thus, our current objective was to examine the associations

between PPBMI and timing of GWG on PPWR at 1, 2 and 6–7 years and maternal and child percent body fat and BMIZ at 6–7 years, using a prospective cohort of Vietnamese mothers and their children.

Methods

Data sources

We used prospectively collected data from mothers and their offspring who participated in the PRECONCEPT study, a randomized controlled trial (RCT) to evaluate the effects of preconception micronutrient supplementation on maternal and child health outcomes in Thai Nguyen province in Vietnam (NCT: 01665378) (23–26). The original aim of PRECONCEPT was conducted in 2011–2014 to evaluate impact on birth outcomes, with subsequent follow-up at 1, 2, and 6–7 years.

Study population

Details of the PRECONCEPT study have been published previously (23). Briefly, the study included 5,011 women of reproductive age who were randomly assigned to receive weekly supplements containing either 2,800 µg folic acid (FA), 60 mg iron and 2,800 µg FA (IFA), or multiple micronutrients (MM) containing the same amount of IFA, from baseline until conception, followed by daily prenatal supplements containing 60 mg iron and 400 µg FA until delivery. Study participants were enrolled from 20 communes located in Thai Nguyen province, the gateway to Vietnam's northeastern region. Study sites were selected based on location, availability of health services, and comparability in malnutrition and other public health problems to surrounding provinces and national average (23, 27, 28). All women were followed prospectively to identify pregnancies and evaluate primary RCT outcomes at birth (26). All offspring ($n = 1,599$ livebirths) and their mothers have also been followed up through ages 2 years and at 6–7 years (24, 25). In order to maximize sample size we used two analytic samples with the following inclusion criteria: (1) maternal outcome sample: all women who had live singleton births, were not pregnant at the time of follow-up, and had PPWR measurements available at 1, 2, and 6–7 years ($n = 864$) and (2) child outcome sample: included data from all women who had live singleton births and whose children had percent body fat measured 6–7 years ($n = 1,381$). Details on study sample inclusion and loss to follow up are provide in [Supplementary Figure 1](#).

Outcome measurements

The outcomes of this study included PPWR at 1 year, 2 years, 6–7 years, and maternal and child percent body fat at age 6–7 years.

The PPWR (kg) is a continuous variable calculated by subtracting the pre-pregnancy weight from the weight at specific time (i.e., 1, 2, and 6–7 years).

Maternal and child percent body fat at 6–7 years was measured by trained field staff using a Seca mBCA 525 multifrequency BIA among fasted participants (Seca Corporation, Hanover, MD, USA). Child percent body fat was calculated from child characteristics (age, sex), weight, raw values of total body resistance, and reactance at 50 kHz and using Vietnamese specific formulas (29). Maternal and child weight and height were measured by trained and standardized field staff using standard methods (30). All measurements were taken in duplicate, and a third measurement was obtained if the first two were significantly different using standard trigger limits. All field staff participated in rigorous, in-depth training sessions that were conducted at various time-points and included: training on standard operating procedures, quality control by study investigators, as well as demonstrations and practice both in-class and in field settings. All measurement procedures were checked and standardized with a wide range of participants in local settings. Refresher trainings were conducted for each follow-up period. In addition, all anthropometric equipment were regularly calibrated. Horizontal level of the scales and height board were regularly checked with a spirit level. For quality control, field directors and supervisors regularly checked the measurement procedures, participant posture, and the accuracy of reading and recording results. Child body-mass-index-for-age z-scores (BMIZ) were calculated using 2006 WHO child growth standards (31).

Predictor variables

Pre-pregnancy BMI (PPBMI)

Maternal pre-pregnancy weight and height were measured at enrollment in Community Health Centers by trained staff using standard procedures (30). PPBMI was calculated as $\text{weight}/\text{height}^2$ (kg/m^2) and then was standardized to z-scores allow for relative comparisons of a 1 standard deviation (SD) average change. The PPBMI z-score was also categorized into tertiles, with a higher tertile indicating greater PPBMI.

Conditional gestational weight gain (CGWG)

GWG was determined as the difference between pregnancy weight and pre-pregnancy weight. CGWG is a derived variable and computed as the standardized residuals from linear regressions of weight gain during pregnancy on PPBMI. The CGWG can be interpreted as weight gain deviation from previous nutrition status, thus is an indicator the speed of weight gains during pregnancy and independent of pre-pregnancy nutrition status. The tertiles of CGWG and window-specific CGWG at <20w, 21–29w, and ≥ 30 w were also calculated.

Potential confounders

Potential confounding variables included maternal age, education, parity, socio-economic status (SES), minority status, treatment intervention, gestational age, exclusive breastfeeding at 3 months, breastfeeding at 12 months, dietary diversity and physical activity. Variables were selected *a priori* based on previous studies and

theoretical framework (17, 18). Household SES was calculated using a principal components analysis of assets and services, including house and land ownership, housing quality, access to services (electricity, gas, water, and sanitation services), and household assets (productive assets, durable goods, animals, and livestock). The first component derived from component scores were used to divide household SES into tertiles. Gestational age was calculated as the number of days between the day of delivery and the first day of the last menstrual period which was obtained prospectively by village health workers during their biweekly home visits. Maternal physical activity was measured using the Global Physical Activity Questionnaire (GPAQ) scale, which consists of 16 items on three aspects as well as sedentary behavior: activity at work, travel to and from places, recreational activities. The GPAQ has been translated and validated in the Vietnamese population (32).

Statistical analysis

Descriptive statistics were used to describe the characteristics of the study population, with frequency and percentage for categorical variables; mean and SD for continuous variables. Multivariable linear regressions were used to assess the association between PPBMI and CGWG with PPWR at 1, 2, 6–7 years, maternal, and child percent body fat at age 6–7 years. The models were fitted using full-information maximum likelihood for estimation while accounting for missing data among the controlled variables under the assumption of missing at random and without having to do imputation. We investigated this relationship in three models: Model 1 included PPBMI z-score and CGWG z-score as predictors; Model 2 included PPBMI z-score and CGWG z-score at <20w, 21–29w, and ≥ 30 w; and Model 3 consisted of PPBMI z-score tertiles and CGWG z-score tertiles. Note, we have previously compared GWG to IOM recommendations (22); however, for the purposes of this analysis we focused on continuous CGWG and CGWG z-score tertiles as intent of analyses to was to examine relative differences within our cohort. All models were adjusted for maternal age, education, parity, household SES, minority status, treatment intervention, gestational age, exclusive breastfeeding at 3 months, breastfeeding at 12 months, dietary diversity and physical activity.

A significance level of 0.05 was used for all statistical tests. All analyses were carried out using Stata v16 (StataCorp, College Station, TX, USA).

Ethical approval

The study was approved by the Ethical Committee of Institute of Social and Medicine Studies in Vietnam and Emory University's Institutional Review Board, Atlanta, Georgia, USA. The trial was registered in the US Clinical Trials registry (identification number NCT01665378). Written informed consent was obtained from all study participants.

Results

The baseline maternal and household characteristics, birth outcomes, and feeding practices were similar in our final analytic

TABLE 1 Comparison of maternal baseline characteristics, birth outcomes and child feeding practices by data availability.¹

Variable	Dataset with complete maternal outcome data (n = 864)	Dataset with complete child outcome data (n = 1,381)
Maternal characteristics at preconception enrollment		
Age, year – mean ± SD*	26.4 ± 4.4	25.9 ± 4.3
Minority ethnic, n (%)	434 (50.2)	688 (49.8)
Education Level, n (%)		
Primary school	64 (7.4)	100 (7.2)
Secondary school	463 (53.6)	768 (55.6)
High school	217 (25.1)	354 (25.6)
College or higher	120 (13.9)	159 (11.5)
Work as farmers, n (%)	676 (78.2)	1,117 (80.9)
Number of children ≥1, n (%)	706 (94.6)	1,106 (94.4)
Household characteristics		
Socio-economic status, n (%)		
Low	295 (34.2)	477 (34.6)
Average	273 (31.6)	454 (32.9)
High	295 (34.2)	449 (32.5)
Food security, n (%)	627 (72.6)	1,006 (72.8)
Child characteristics		
Gestational age, week – mean ± SD	39.2 ± 2.1	39.2 ± 2.0
C-section, n (%)	263 (31.3)	397 (28.9)
Preterm, n (%)	84 (10.1)	128 (9.4)
Having another child at follow up, n (%)	158 (18.3)	182 (20.4)
Exclusive breastfeeding, n (%)	463 (60.2)	737 (60.1)
Breastfeeding at 12 months, n (%)	679 (95.9)	1,096 (95.5)
Breastfeeding at 24 months, n (%)	28 (4.1)	45 (4.1)
Number of food groups consumed at 6–7 years – mean ± SD	5.1 ± 1.2	5.1 ± 1.2
Physical activity at 6–7 years, n (%)		
Low	54 (6.3)	55 (6.2)
Average	794 (91.9)	821 (91.9)
High	16 (1.9)	17 (1.9)

¹There were no significant differences in characteristics of the analytic datasets, with the exception of maternal age with $p < 0.05$.

samples for maternal (n = 864) and child health (n = 1,381) outcomes [Table 1](#). In brief, women were on average 26 years of age at preconception enrollment and nearly 80% worked as farmers. Around 10% of the infants were born preterm. Approximately 60% of infants were exclusively breastfeed, with the majority continuing to provide breastmilk for the first year (>95%) but not for the full 2 years (<5%).

TABLE 2 Maternal weight, gestational weight gain (GWG) and percent body fat through 6–7 years postpartum¹.

Variable	Dataset with complete maternal outcome data N = 864	Dataset with complete child outcome data N = 1,381
Maternal weight, kg		
Preconception	45.9 ± 5.7	45.8 ± 5.5
At delivery	56.1 ± 6.7	55.8 ± 6.5
At 1 year post-partum	47.0 ± 6.1	46.9 ± 6.0
At 2 years post-partum	47.6 ± 6.2	47.5 ± 6.0
At 6–7 years post-partum	50.2 ± 7.1	50.4 ± 7.3
GWG, kg	10.2 ± 4.0	10.0 ± 4.0
GWG <20w	1.7 ± 2.2	1.8 ± 2.4
GWG 20–29w	4.8 ± 2.6	4.8 ± 2.5
GWG ≥30w	4.3 ± 2.8	4.2 ± 2.9
Maternal BMI, g/kg²		
Preconception	19.7 ± 2.1	19.6 ± 2.0
At 1 year post-partum	20.1 ± 2.3	20.1 ± 2.3
At 2 years post-partum	20.4 ± 2.4	20.3 ± 2.3
At 6–7 years post-partum	21.6 ± 2.7	21.6 ± 2.8
Maternal weight retention, kg		
At 1 year post-partum	1.1 ± 2.9	1.1 ± 2.9
At 2 years post-partum	1.5 ± 2.9	1.4 ± 3.0
At 6–7 years post-partum	4.3 ± 4.1	4.3 ± 4.1
Maternal percent fat at 6–7 years, %	28.2 ± 6.2	28.1 ± 6.2
Child percent fat at age 6–7 years, %	27.2 ± 4.5	27.1 ± 4.4
Child BMI-Z at age 6–7 years	−0.70 ± 1.14	−0.73 ± 1.13

¹There were no significant differences in characteristics of the analytic datasets, BMI: body mass index, GWG: gestational weight gain.

At the 6–7 years follow-up visit, children received on average 5 different food groups and had reported average physical activity levels. There were no significant differences in the analytic samples, with the exception of slight differences in maternal age at enrollment.

Average maternal BMI was 19.7 kg/m² at preconception with an average total GWG of 10.2 kg ([Table 2](#)). There was a steady increase in weight gain throughout pregnancy with an average weight gain per period of 1.7 kg (<20 weeks), 4.8 kg (20–29 weeks) and 4.3 (≥ 30 weeks). Women retained on average 1.1 kg, 1.5 kg and 4.3 kg at the 1, 2, and 6–7 years follow-up visits, respectively. At the 6–7 years follow-up visit, maternal percent body fat was 28.2 ± 6.2% and child percent body fat was 27.2 ± 4.5%.

We examined the relative association of maternal PPBMI and total CGWG z-scores with PPWR at 1, 2, and 6–7 years ([Table 3](#)). A one SD increase in PPBMI was associated with a decrease in PPWR at 1 (−0.21 [−0.37, −0.04]) and 2 years (−0.20 [−0.39, −0.01]) while a one SD increase in total CGWG was associated with an increase in PPWR at 1 (1.01 [0.85, 1.18]), 2 (0.95 [0.76, 1.15]), and 6–7 years (1.05 [0.76, 1.34]). Additionally, early maternal CGWG in the first window (≤ 20 weeks) had the greatest association with PPWR at each time point:

TABLE 3 Association between maternal PPBMI and CGWG with PPWR at 1, 2, and 6–7 years¹.

Outcomes (z-scores)	PPWR at 1 years		PPWR at 2 years		PPWR at 6–7 years	
	(n = 1,251)		(n = 963)		(n = 864)	
	β [95% CI]		β [95% CI]		β [95% CI]	
	Crude	Adjusted	Crude	Adjusted	Crude	Adjusted
Model 1						
PPBMI z-score	−0.19* [−0.35, −0.03]	−0.21* [−0.37, −0.04]	−0.18 [−0.37, 0.01]	−0.20* [−0.39, −0.01]	−0.11 [−0.36, 0.15]	−0.10 [−0.36, 0.15]
CGWG z-score	1.05*** [0.88, 1.21]	1.01*** [0.85, 1.18]	0.96*** [0.77, 1.15]	0.95*** [0.76, 1.15]	1.01*** [0.72, 1.29]	1.05* [0.76, 1.34]
Model 2						
PPBMI z-score	−0.16 [−0.32, 0.01]	−0.19* [−0.35, −0.02]	−0.15 [−0.34, 0.05]	−0.18 [−0.38, 0.01]	−0.12 [−0.37, 0.14]	−0.13 [−0.39, 0.12]
CGWG <20	0.85*** [0.68, 1.02]	0.85*** [0.68, 1.02]	0.70*** [0.49, 0.91]	0.71*** [0.49, 0.93]	0.99*** [0.69, 1.29]	1.03*** [0.73, 1.33]
CGWG <20–29	0.55*** [0.34, 0.76]	0.58*** [0.37, 0.80]	0.47*** [0.22, 0.72]	0.50*** [0.24, 0.77]	0.20 [−0.13, 0.54]	0.21 [−0.15, 0.56]
CGWG ≥30	0.14 [−0.07, 0.35]	0.15 [−0.06, 0.37]	0.19 [−0.06, 0.43]	0.20 [−0.04, 0.45]	0.12 [−0.24, 0.48]	0.13 [−0.23, 0.50]

¹Model adjusted for maternal age, education, parity, having other children after the index child, household SES, minority status, treatment intervention, gestational age, EBF at 3 months, breastfeeding at 12 months, physical activity, dietary diversity scores. Conditional gestational weight gain during pregnancy: each window is independent of pre-pregnancy BMI and independent of weight gain in any prior window. Units are in standardized z-scores to allow for relative comparisons of a 1 SD average increase in weight gain for each window. CI, Confident interval; CGWG, Conditional gestational weight gain; PPBMI, Pre-pregnancy body mass index; PPWR, postpartum weight retention. * $p < 0.05$, *** $p < 0.001$.

1 (0.85 [0.68, 1.02]), 2 0.71 [0.49, 0.93]), and 6–7 years (1.03 [0.73, 1.33]). Maternal CGWG in the second window (<21–29 weeks) was also associated with PPBMI at the 1 year and 2- years time points (0.58 [0.37, 0.80] and 0.50 [0.24, 0.77] respectively), but to a lesser degree. Later CGWG (≥30 weeks); however, was not significantly associated with PPWR at any of the time periods.

Maternal PPBMI and CGWG was also associated with maternal and child percent body fat at 6–7 years postpartum (Table 4). A one SD increase in both PPBMI and total CGWG were associated with an increase of maternal percent body fat at 6–7 years (3.19 [2.85, 3.53] and 0.81 [0.43, 1.19] respectively). A one SD in PPBMI was also associated with an increase of child percent body fat at 6–7 years (0.79 [0.55, 1.02]). While total CGWG was not significantly associated with child percent body fat, when separated by timing of GWG, greater early (<20 weeks) and mid (20–29 weeks) CGWG was significantly associated with an increase in child percent body fat (0.42 [0.15, 0.69], 0.42 [0.09, 0.74], respectively). Furthermore, a one SD increase of PPBMI and total GWG were positively associated with child BMI z-score at 6–7 years (0.27 [0.21, 0.33] and 0.11 [0.04, 0.17] respectively). For child BMIZ, CGWG in mid-pregnancy (<20–29 weeks) appeared to the most influential time period.

To examine these relationships further, we also divided participants into PPBMI and conditional GWG tertiles. As show in Figure 1, women in PPBMI tertile 3 (the largest PPBMI) had significantly lower PPWR at 1 year (−0.55 [−0.94, −0.15]) and 2 years (−0.55 [−1.01, −0.09]) but not at 6–7 years compared to women in PPBMI tertile 1 (the smallest PPBMI). Women with the largest CGWG (tertile 3) had significantly greater PPWR at 1 year (2.18 [1.76, 2.60]), 2 years (2.29 [1.80, 2.73]), and 6–7 years (2.57 [1.88, 3.27]) compared to women who gained the least amount of weight (tertile 1). Likewise, greater PPBMI (tertile 3) was positively associated with

both maternal (7.03 [6.13, 7.93]) and child (1.24 [0.67, 1.81]) percent body fat at 6–7 years compared to PPBMI tertile 1 (Figure 2). Greater maternal CGWG was associated with significantly higher maternal (2.23 [1.26, 3.20]) but not child percent body fat.

Discussion

In our prospective Vietnamese cohort, maternal nutrition before and during pregnancy had long-term implications for PPWR and maternal and child body composition. Maternal PPBMI was negatively associated with PPWR at 1 and 2 years but not at 6–7 years; in contrast, maternal PPBMI remained a significant predictor of both maternal and child percent body fat at 6–7 years. Total CGWG was positively associated with PPWR at 1, 2, and 6–7 years as well as maternal percent body fat and child BMIZ at 6–7 years and most notably CGWG in both the early (<20 weeks) and mid (20–29 week) periods were positively associated with child percent body fat at 6–7 years. Early CGWG (<20 weeks) also had the strongest relative associations with PPWR at all time points compared to later weight gain, signaling that not only the total amount of weight gained during pregnancy but also the timing of weight gain may be an important consideration for future programs to address.

Our findings corroborate the findings from previous studies that showed positive associations between GWG and PPWR and negative associations between PPBMI and PPWR (17, 18) but were done mainly in high-income countries. An exception is a recent previous study among Vietnamese women, that reports that women with an underweight PPBMI had a significantly higher PPWR at 1 year compared to women with a normal PPBMI (adjusted mean PPWR of 3.7 kg vs. 2.34 kg, respectively) (33). Likewise, women with excessive

TABLE 4 Association between PPBMI, GWG with maternal and child percent fat, and child BMIZ¹.

Outcomes	Maternal percent fat at 6–7 years		Child percent fat at 6–7 years		Child BMIZ at 6–7 years	
	(n = 827)		(n = 1,381)		(n = 1,406)	
	β [95% CI]		β [95% CI]		β [95% CI]	
	Crude	Adjusted	Crude	Adjusted	Crude	Adjusted
Model 1						
PPBMI z-score	3.24*** [2.90,3.58]	3.19*** [2.85,3.53]	0.79*** [0.56,1.02]	0.79*** [0.55,1.02]	0.27*** [0.21,0.33]	0.27*** [0.21,0.33]
CGWG z-score	0.90*** [0.53,1.27]	0.81*** [0.43,1.19]	0.24 [−0.00,0.47]	0.20 [−0.04,0.44]	0.11*** [0.05,0.17]	0.11*** [0.04,0.17]
Model 2						
PPBMI z-score	3.26*** [2.91,3.60]	3.19*** [2.85,3.54]	0.80*** [0.56,1.03]	0.79*** [0.55,1.02]	0.27*** [0.21,0.33]	0.27*** [0.21,0.33]
CGWG <20	0.54** [0.15,0.93]	0.67* [0.07,0.87]	0.43** [0.16,0.70]	0.42** [0.15,0.69]	0.06 [−0.01,0.13]	0.06 [−0.01,0.13]
CGWG <20–29	0.41 [−0.03,0.85]	0.37 [−0.09,0.84]	0.50** [0.19,0.81]	0.42* [0.09,0.74]	0.15*** [0.07,0.23]	0.12** [0.04,0.20]
CGWG ≥30	0.35 [−0.12,0.82]	0.27 [−0.21,0.76]	0.05 [−0.27,0.37]	0.01 [−0.32,0.33]	0.03 [−0.05,0.11]	0.03 [−0.05,0.11]

¹Model adjusted for maternal age, education, parity, having other children after the index child, household SES, minority status, treatment intervention, gestational age, EBF at 3 months, breastfeeding at 12 months, physical activity, dietary diversity scores. Conditional gestational weight gain during pregnancy: each window is independent of pre-pregnancy BMI and independent of weight gain in any prior window. Units are in standardized z-scores to allow for relative comparisons of a 1 SD average increase in weight gain for each window. CI, Confident interval; CGWG, Conditional gestational weight gain; PPBMI, Pre-pregnancy body mass index; PPWR, postpartum weight retention. * $p < 0.05$, ** $p < 0.01$, *** $p < 0.001$.

PPWR at 1 year

Pre-pregnancy BMI z-score- tertile 2	-0.37 (-0.76, 0.02)
Pre-pregnancy BMI z-score- tertile 3	-0.55 (-0.94, -0.15)
Conditional GWG z-score- tertile 2	0.79 (0.38, 1.21)
Conditional GWG z-score- tertile 3	2.18 (1.76, 2.60)

PPWR at 2 years

Pre-pregnancy BMI z-score- tertile 2	-0.18 (-0.64, 0.28)
Pre-pregnancy BMI z-score- tertile 3	-0.55 (-1.01, -0.09)
Conditional GWG z-score- tertile 2	1.10 (0.63, 1.58)
Conditional GWG z-score- tertile 3	2.29 (1.80, 2.77)

PPWR at 6–7 years

Pre-pregnancy BMI z-score- tertile 2	-0.55 (-1.19, 0.10)
Pre-pregnancy BMI z-score- tertile 3	-0.47 (-1.11, 0.18)
Conditional GWG z-score- tertile 2	1.06 (0.37, 1.75)
Conditional GWG z-score- tertile 3	2.57 (1.88, 3.27)

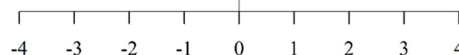


FIGURE 1

Association between pre-pregnancy body mass index (PPBMI), gestational weight gain (GWG) with postpartum weight retention (PPWR) at 1, 2, 6–7 years.

GWG had a significantly higher PPWR at 1 year compared to those with adequate GWG (adjusted mean PPWR of 5.1 kg vs. 2.9 kg, respectively) (33). Our findings expand upon this work to utilize an

advanced analytic approach that allowed us to examine the independent effects of maternal nutrition before and during pregnancy and compare the relative strength of associations using

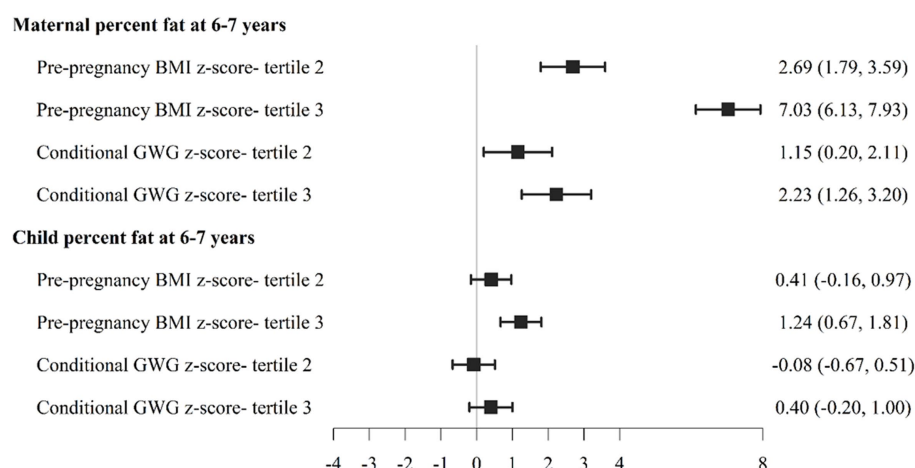


FIGURE 2

Association between pre-pregnancy body mass index (PPBMI) and gestational weight gain (GWG) with maternal and child percent body fat at 6-7 years.

standardized z-scores. In our cohort of Vietnamese women, a one SD increase in total CGWG had nearly a 5-fold greater influence on PPWR compared to PPBMI.

A novel aspect of our study was the ability to further examine the unique and independent influence of the role of timing of GWG on PPWR. While growing evidence has indicated the potential importance of timing of GWG on infant size at birth (16, 22, 34, 35), to our knowledge, this is the first study to prospectively follow women from preconception throughout early childhood to examine the long-term associations with PPWR in a middle-income country. In our cohort early CGWG (<20 wk) had a 6 to 7-fold greater association with PPWR compared with later CGWG (≥ 30 wk). The mechanisms underlying these associations with early weight gain are unclear. One possible explanation is that the anabolic metabolic adaptations during early pregnancy may be related to increases in insulin sensitivity and/or increased maternal fat stores (36). In contrast, later pregnancy is a catabolic state that is associated with increased insulin resistance to facilitate nutrient transfer and fetal growth (36).

Another major contribution of our study is the examination of long-term associations with maternal and child body composition. In our cohort of Vietnamese women, PPBMI had nearly a 4-fold stronger relative association with maternal and child percent body fat at 6–7 years compared with total CGWG. We furthermore report new findings that early CGWG (<20 wks) had the strongest relative association with both maternal and child percent body fat, indicating the importance of early maternal nutrition for long-term body composition. While prior research has indicated that excessive GWG is associated greater gains in fat mass during pregnancy, few studies have tracked the long-term impact on body composition (37–39). In a prospective cohort of African American and Dominican mothers from New York, excessive GWG was associated with higher percent body fat and PPWR at 7 years among women who were underweight, normal and some overweight but not obese prior to pregnancy (39). The evidence on the role of timing of GWG on later body composition has been mixed. In the Avon Longitudinal Study of Parents and Children, among normal weight women, mid-pregnancy (19–28 wks) GWG was more strongly related to maternal adiposity and blood pressure at 16 years postpartum (40). In contrast, in a Boston

pregnancy cohort, first trimester specific weight gain compared to later weight gain was most strongly associated with higher weight retention, maternal waist circumference and blood pressure (41). Even less is known on the long-term associations with child body composition, though greater GWG in the first trimester was associated with increased offspring overweight and obesity, higher waist circumference, skin fold thickness and blood pressure at 4 years in a prospective cohort from Greece (42). Further work is needed to understand context and timing specific findings.

Key strengths of our cohort include the prospective cohort design, accurate assessment of gestational age and maternal body size measurements from pre-pregnancy through pregnancy and postpartum. Most of the research to date estimate PPBMI based on maternal recall or measurements that are made at the first antenatal care visit when some women may have already started gaining weight. This is an important limitation particularly in light of the current findings on the importance of early GWG. Given the study design, i.e., longitudinal follow-up of a birth cohort, the results are subject to a number of biases related to attrition, non-response bias, representativeness of the sample. Although we had low loss to follow-up for the children and the final sample was comparable to those lost to follow-up. Our findings may not be generalizable to other settings with a greater prevalence of preconception obesity or excessive GWG, as in our context nearly a third of women entered pregnancy underweight and over two thirds gained below IOM recommendations (22). Nevertheless, our study provides valuable insights for similar low-resource settings undergoing nutrition transition with dual burdens of under and over nutrition (43). Most notably, we present novel data on maternal and child percent body fat at 6–7 years. While there are inherent limitations of the using BIA for assessing body composition (including potential role of hydration status, food intake, and previous physical exercise); the use of validated population-specific prediction equations strengthens our findings (44, 45). However, the lack of data on changes in maternal body composition or in the patterns of fat deposition during pregnancy limits our ability to examine how GWG is associated with changes in body composition and how this may be influenced by the timing of weight gain. Maternal fat accretion accounts for a substantial portion of GWG and consists

of mammary tissue expansion, visceral adipose tissue, and subcutaneous adipose tissue (46–48). Visceral adipose fat surrounds intra-abdominal solid organs (49) and produces more pro-inflammatory adipokines and cytokines than subcutaneous adipose tissue (50–52) and is also associated with increased gestational metabolic disease including gestational diabetes and hypertension (53–56). A deeper understanding on the patterns of fat deposition could help explain underlying mechanisms of maternal nutrition and obesity and chronic disease risk. Furthermore, additional research with more detailed dietary intake data would be valuable to understand the role of both maternal and child diet.

In summary, we present novel findings on the long-term associations of maternal nutrition before and during pregnancy on PPWR as well as maternal and child body composition at 6–7 years in a study setting that is experiencing the nutrition transition represented by the dual burden of under and overnutrition and associated changes in diet quality and lifestyle (57). This work has important implications for targeting women of reproductive age as early GWG may represent a critical window when modifying maternal nutrition can have long-term consequences for maternal and child nutrition and be part of the strategies required to address the burden of non-communicable diseases like diabetes and cardiovascular disease that are the leading causes of morbidity and mortality globally (58, 59). Further research and replication of the unique analytic approach to examine the independent time effects of GWG in other settings may be merited and will help inform future revisions of GWG recommendations for different populations.

Data availability statement

The data analyzed in this study is subject to the following licenses/restrictions: Data available upon request and approval of study team. Requests to access these datasets should be directed to UR, uramakr@emory.edu and PN, P.H.Nguyen@cgiar.org.

Ethics statement

The studies involving human participants were reviewed and approved by Ethical Committee of Institute of Social and Medicine Studies in Vietnam and Emory University's Institutional Review Board, Atlanta, Georgia, USA. Written informed consent to participate

in this study was provided by the participants' legal guardian/next of kin.

Author contributions

MY, PN, RM, and UR: designed the research. PN, LT, and LK: conducted the field research. MY, LT, LK, and PN: analyzed data. MY, PN, SH, and UR: wrote the manuscript. MY: had primary responsibility for the final content of the manuscript. All authors reviewed and provided critical feedback.

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Conflict of interest

The authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

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Supplementary material

The Supplementary material for this article can be found online at: <https://www.frontiersin.org/articles/10.3389/fnut.2023.1114815/full#supplementary-material>

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EDITED BY

Nita Bhandari,
Society for Applied Studies, India

REVIEWED BY

Tarun Shankar Choudhary,
University of Bergen, Norway
Ranadip Chowdhury,
Society for Applied Studies, India

*CORRESPONDENCE

M. Jeeva Sankar
✉ jeevasankar@gmail.com

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Probiotics for the prevention of mortality and sepsis in preterm very low birth weight neonates from low- and middle-income countries: a Bayesian network meta-analysis

Deena Thomas¹, Akash Sharma² and M. Jeeva Sankar^{3*}

¹Department of Pediatrics, Muthoot Hospitals, Kozhancherry, Kerala, India, ²Department of Pediatrics, Sir Padampat Institute of Neonatology and Pediatric Health (SPINPH), SMS Medical College, Jaipur, India,

³Department of Pediatrics, All India Institute of Medical Sciences, New Delhi, India

Background: Probiotics have been shown to reduce the risk of mortality and necrotizing enterocolitis (NEC) in very low birth weight (VLBW) neonates. The probiotic species with the maximal benefits in neonates from low- and middle-income countries are unknown.

Objective: To identify the strain of probiotics with the maximum benefit in preventing neonatal mortality, sepsis, and NEC using the Bayesian network meta-analysis.

Search methods: We searched Medline via PubMed, Embase, and Cochrane Central Register of Controlled Trials (CENTRAL). We also hand-searched reference lists of previous systematic reviews to identify eligible studies.

Selection criteria: Randomized controlled trials (RCTs) from LMICs comparing enteral supplementation of one or more probiotics with another probiotic species or placebo were included.

Data collection and analysis: Two authors screened the studies, extracted the data, and examined the risk of bias using the Cochrane risk of bias 2 (RoB 2) tools. Bayesian network meta-analysis was performed using the “BUGSnet” package in R and RStudio (version 1.4.1103). The confidence in the findings was assessed using the Confidence in Network Meta-analysis (CINeMA) web application.

Results: Twenty-nine RCTs enrolling 4,906 neonates and evaluating 24 probiotics were included. Only 11 (38%) studies had a low risk of bias. All the studies compared the probiotics with a placebo; none had a head-to-head comparison of different probiotic species. Also, only one study each had evaluated most probiotic regimens. When compared to placebo, the combination of *B longum*, *B bifidum*, *B infantis*, and *L acidophilus* may reduce the risk of mortality (relative risk [RR] 0.26; 95% credible interval [CrI] 0.07 to 0.72), sepsis (RR 0.47; 95% CrI 0.25 to 0.83), and NEC (RR 0.31; 95% CrI 0.10 to 0.78) but the evidence is very uncertain. There is low certainty evidence that the single probiotic species, *B lactis*, could reduce the risk of mortality (RR 0.21; 0.05 to 0.66) and NEC (RR 0.09; 0.01 to 0.32).

Conclusion: Given the low to very low certainty of evidence for the efficacy of the two probiotics found to reduce mortality and necrotizing enterocolitis, no firm conclusions can be made on the optimal probiotics for use in preterm neonates in low- and middle-income countries.

Systematic review registration: https://www.crd.york.ac.uk/prospero/display_record.php?ID=CRD42022353242, identifier: CRD42022353242.

KEYWORDS

network meta-analysis, neonate, very low birth weight, probiotics, enterocolitis, necrotizing, neonatal sepsis, neonatal mortality

Introduction

Globally, about 5 million children die before reaching their fifth birthday every year. Roughly half of these under-five child deaths occur during the neonatal period—the first 28 days of life. The risk of neonatal deaths is not uniform across the countries—it varies from 1 per 1,000 live births to 44 per 1,000 live births. The mortality rate is highest in the countries from sub-Saharan Africa and Southern Asia region; a child born in sub-Saharan Africa is about ten times more likely to die during the neonatal period than a child born in a high-income country (1).

The two most common causes of neonatal deaths in low- and middle-income countries (LMIC) are preterm birth complications and neonatal sepsis (2). Various interventions, including antenatal corticosteroids (3) and kangaroo mother care (4, 5), have been shown to reduce neonatal mortality and sepsis in preterm neonates. Increased coverage of the proven interventions during labor, birth, and postnatal period would avert up to 70% of neonatal deaths in LMICs (6). Efforts are underway to address the coverage of interventions and improve the quality of care in the facility-based care of neonates in LMIC settings. Concurrently, it is critical to identify other evidence-based interventions to reduce neonatal mortality secondary to prematurity and sepsis.

Probiotics have emerged as a promising intervention to prevent necrotizing enterocolitis (NEC) and mortality in preterm very low birth weight (VLBW) neonates. The Cochrane Review (2020), which included 56 trials involving 10,812 neonates, concluded that probiotics might reduce the risk of NEC, mortality, and sepsis. However, the sensitivity analysis of 16 studies at low risk of bias did not show any effect on mortality or sepsis (7). Another meta-analysis assessing the efficacy and safety of probiotics in LMICs in 2017 showed a reduction in all-cause mortality, sepsis, and NEC among 2000 enrolled neonates (8). Around 2,000 additional neonates have been enrolled in probiotic trials in LMICs in the last 5 years, which mandates an update of the available evidence.

While the beneficial effects of probiotics—as a group—are known, it is still unclear which probiotic species, alone or in combination, provides the maximum benefits in reducing mortality or NEC. A few network meta-analyses involving studies from high-income countries and LMICs have examined this issue. But they have predominantly evaluated the probiotics' effect at the genus level, not at the species/strain level. Assessing the impact of individual species/strains of probiotics is critical in LMICs, given the potentially different maternal and neonatal microbiomes in these settings (9, 10). Differences in maternal gut microbiota, environmental flora, and nature of antibiotic use in mothers and neonates could substantially affect the effects of the individual probiotic species in LMIC settings. We, therefore, conducted this Bayesian species-specific network meta-analysis to examine the

efficacy of different probiotic species on (1) all-cause mortality, (2) culture-positive sepsis, and (3) NEC in very low birth weight neonates or neonates <32 weeks of gestational age at birth.

Methods

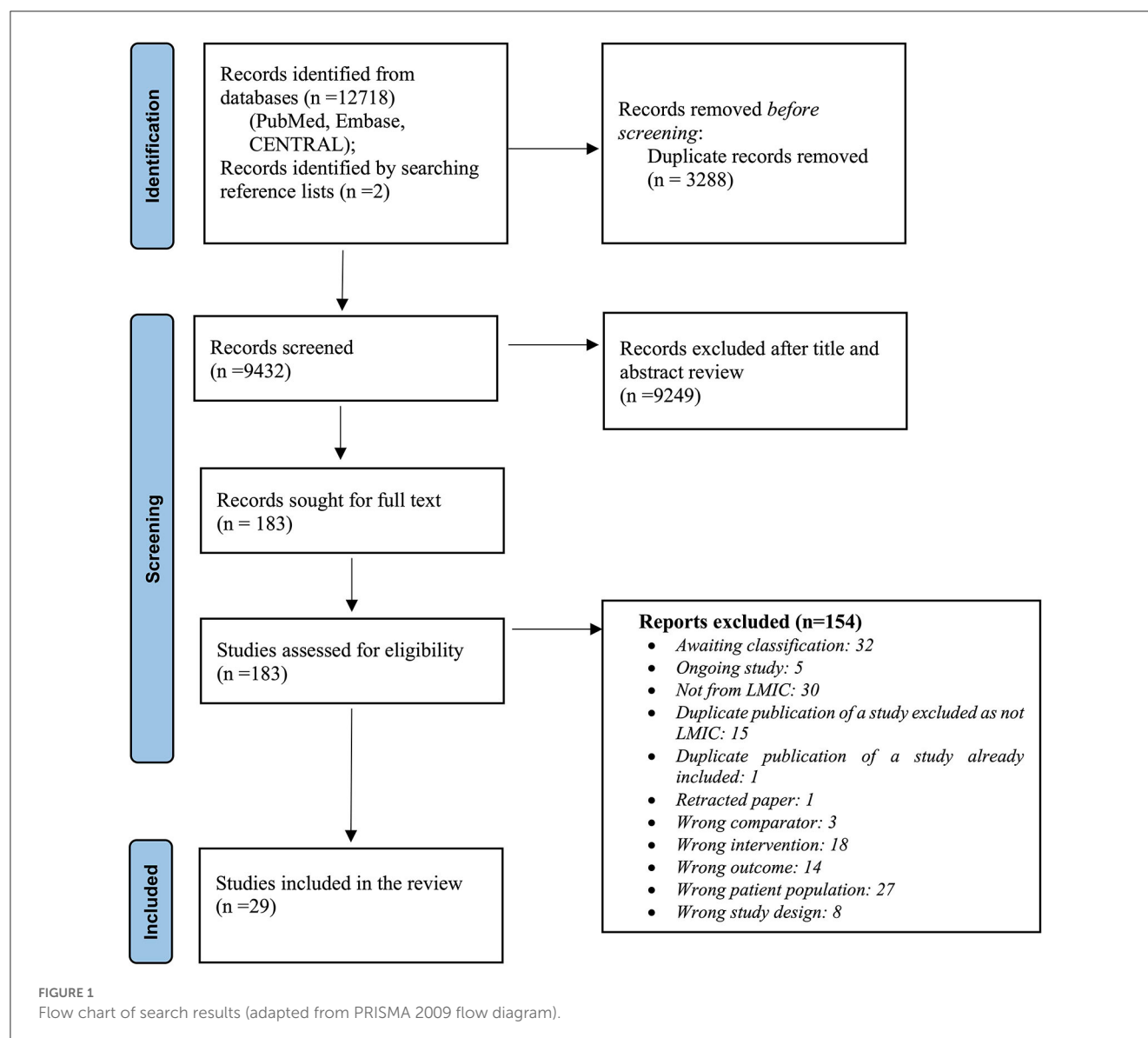
Search strategy

We followed the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) (11) statements and Cochrane Handbook for Systematic Reviews of Interventions (12). The study protocol was prospectively registered with PROSPERO (CRD42022353242). Deviations from the published protocol have been mentioned in [Supplementary Table 1](#).

We searched MEDLINE (via PubMed), Cochrane Central Register of Controlled Trials (CENTRAL), and Embase from inception to July 31, 2022. The search strategy was developed by two reviewers (DT and AS) and finalized by the third reviewer (MJS). The following keywords were used to build our search strategy: intervention and control—*probiotic*/prebiotic*/synbiotic*/placebo*; population—*infant, newborn, OR preterm*; study design—*randomized controlled trials*. In addition, we also searched the references of previous systematic reviews and meta-analyses. No language restrictions were used during the literature search. Only studies from low- and middle-income countries (13) were identified and included in the final analysis. The detailed search strategy has been described in [Supplementary Table 2](#).

Study selection

Randomized controlled trials (RCT) or quasi-RCT comparing (1) enteral supplementation of one or more species of probiotics with another probiotic species/genera and (2) supplementation of any probiotics with placebo or no probiotics in very low birth weight (VLBW) neonates were considered eligible for this review (14). Two researchers (DT and AS) independently conducted the title and abstract screening—using the Covidence web application (14)—followed by full-text screening to determine eligibility. The disagreements were resolved by mutual discussion or discussion with the third author (MJS). Studies that met the following criteria were finally included: (i) *population*: birthweight of enrolled neonates <1,500 g or gestation <32 weeks. Studies that enrolled more mature or heavier neonates were also included if the mean gestation of the neonates was <32 weeks or birth weight was <1.5 kg. If the gestation/birthweight data was unavailable, at least 50% of neonates must have been born before 32 weeks or have a birth weight of <1.5 kg to be eligible; (ii) *intervention*: one or



more species of probiotics; (iii) *comparator*: a different species of probiotics or placebo or no probiotics; (iv) *outcome*: neonatal mortality, sepsis/severe infection, and necrotizing enterocolitis stage 2 or more as per modified Bell's staging (15); and (v) *others*: conducted in LMICs wherein LMIC was defined as per world bank data as countries with gross national income per capita less than \$4,256 (13). We excluded cross-over trials and studies that employed prebiotics or synbiotics as cointerventions (along with the probiotics) or had not reported at least one of the three primary outcomes.

Primary and secondary outcomes

Primary outcomes were all-cause neonatal mortality and sepsis/severe infection at discharge or 28 days or the latest follow-up. Sepsis was identified by a positive culture of bacteria or fungus

from blood, cerebrospinal fluid, urine, or from a normally sterile body space or as defined by the authors of the individual studies. The secondary outcome was necrotizing enterocolitis (NEC)—stage 2 or more as per modified Bell's staging (15).

Data extraction

Two reviewers (DT and AS) extracted the data of key demographic characteristics and outcomes from the included studies and collated them in a predesigned master spreadsheet. Data collected included general article information (author, study ID, and language of trial), trial information (type, location, setting, size sample, treatment arms, and randomization), demographic information of participants (gestation and birth weight), characteristics of interventions (number of treatment arms, intervention and control groups, and timing, dose, and route

of administration), outcomes (primary and secondary outcomes), and risk of bias (sequence generation, allocation concealment, blinding, selective reporting, and incomplete data). The third reviewer (MJS) checked the master spreadsheet for the accuracy of extracted data.

Risk of bias and certainty of evidence

Two reviewers (DT and AS) independently assessed the risk of bias of each study using Cochrane's "Risk-of-bias" 2.0 (RoB 2) tool (16); any discrepancy was resolved by discussion with the third reviewer (MJS). The "robvis" package in R (17) was used to create the summary and traffic-light plots of the risk-of-bias summary assessment for each outcome. We used the CINeMA (Confidence in Network Meta-Analysis) web application to examine the confidence in the findings from the network meta-analysis (18, 19). CINeMA considers six domains: within-study bias, reporting bias, indirectness, imprecision, heterogeneity, and incoherence. We first evaluated the direct evidence from pairwise comparisons on these domains. Then we intended to assess the certainty of indirect evidence from the lowest quality of direct evidence (of pairwise comparisons) from the first-order loops. The certainty of the evidence was ranked as high, moderate, low, and very low based on the presence or absence of "major concerns" in 0, 1, 2, or 3 (or more), respectively, of the six domains mentioned above.

Statistical analysis

We used Stata version 15.1 (StataCorp, College Station, TX) for data preparation and analysis. For each outcome, we conducted a Bayesian network meta-analysis (NMA) by fitting a generalized linear model with a complementary log-log link function and binomial likelihood function using the "BUGSnet" (Bayesian inference Using Gibbs Sampling to conduct a Network meta-analysis) package (20) in R and RStudio (version 1.4.1103). We performed the Bayesian analysis with Markov chain Monte Carlo simulation using vague priors. We specified a burn-in of 50,000 iterations followed by 100,000 iterations with 10,000 adaptations, consistent with the NICE-DSU technical support document (21). Leverage plots, total residual deviance, and deviance information criterion were employed to assess the model fit. Gelman-Rubin and trace and density plots were inspected for model convergence. We intended to use the node-splitting and inconsistency model method to look for any inconsistency between the direct and indirect evidence (22).

Network diagrams were generated for each outcome wherein the node size and the line width represent the number of neonates and the number of trials for different comparisons, respectively. Posterior medians of relative risks (RR) and 95% credible intervals (CrI) were used to express the effect size. Forest and league plots were used to depict the network estimates of different comparisons. We calculated the mean surface under the cumulative ranking (SUCRA) curve for each intervention arm. In addition, we planned to do a subgroup analysis on the effect of probiotics on the

two primary outcomes based on the type of feeding—exclusive breastmilk feeds, exclusive formula feeding, or mixed feeding.

Results

Study selection

Figure 1 depicts the process of screening and selection of eligible studies. Of the 183 full-text articles assessed for eligibility, 29 randomized and quasi-randomized studies from low- and middle-income countries enrolling 4,906 neonates were included in the review (Table 1). A detailed list of the excluded studies, those awaiting classification, and ongoing studies have been provided in Supplementary Tables 3–5, respectively.

Summary of the included studies

The characteristics of included studies have been summarized in Table 1 (23–51). About 60% of the studies were conducted in India, Turkey, Mexico, and China. The sample size ranged from 30 to 500 in the included studies. The mean gestation of enrolled neonates varied from 28 to 33 weeks, while the mean birth weight varied from 945 to 1,445 g. Almost all the studies initiated the intervention in the first week of life; most only stopped the intervention at discharge. A total of 24 different probiotics—alone or in combination—were evaluated in the included studies (Supplementary Table 6). While 12 studies evaluated a single probiotic species (mainly from the *Lactobacillus* genus), the others used two or more species in combination (mainly from the *Lactobacillus* and *Bifidobacterium* genera). The probiotic dosage varied from 10×10^6 to $50,000 \times 10^6$ colony-forming units (CFU). Among the studies that reported the type of milk received by the neonates, the exclusive breast milk feeding proportion varied from 13 to 100%.

Risk of bias assessment

The risk of bias assessment of the included studies is shown in Supplementary Figure 1A. More than half of the studies had an unclear or high risk of bias arising from the randomization process; about 30% of the included studies had a high risk of bias due to deviations from the intended intervention (Supplementary Figures 1A, B). Only 11 studies (38%) had a low risk of bias (Supplementary Figure 1B).

Outcomes

Mortality

A total of 26 studies involving 3,863 neonates provided information on all-cause mortality. Six studies had zero events in at least one of the treatment arms and were dropped in the final analysis. The remaining 20 studies had enrolled 3,527 neonates, of whom 267 (7.6%) died. Figure 2A illustrates the network plot—each intervention arm has been compared with the standard reference arm (placebo) but not among themselves,

TABLE 1 Baseline characteristics of included studies.

S No.	References	Country	Inclusion criteria	Gestation, weeks; mean (SD)		Birthweight, grams; mean (SD)		Sample size	Intervention			Control	Postnatal age randomization (days)		Proportion of infants on exclusive breastmilk feeding		Critical outcomes reported	Mode of feeding	Duration of follow up
				P	C	P	C		Probiotic species	Duration of treatment	Dosage		P	C	P	C			
1.	Braga et al. (23)	Brazil	750–1,500 g	29.5 (2.5)	29.2 (2.6)	1,195 (206)	1,151 (225)	231	<i>B breve</i> + <i>L casei</i> (n = 119)	Till 30 days of life/diagnosis of NEC/discharge or death, whichever occurred earlier	35×10^6 to 3500×10^6 CFU OD	None (n = 112)	2	2			Mortality, sepsis, NEC	Both HM and F	30 days
2.	Chandrashekar et al. (24)	India	Clinically stable ≤ 34 weeks	-	-	-	-	140	<i>B longum</i> + <i>L acidophilus</i> + <i>L rhamnosus</i> + <i>Sa boulardii</i> (n = 70)	Minimum of 7 days or till 35 weeks of gestation	1250×10^6 CFU OD	None (n = 70)			74.3	81.4	Mortality, sepsis, NEC	Both HM and F	Duration of hospital stay: 15 days for probiotic and 23 days for control
3.	Chowdhury et al. (25)	Bangladesh	<33 weeks; <1,500 g; age >48 h	31.4 (0.9)	31.7 (0.8)	1,311 (110)	1,338 (98)	119	<i>B bifidum</i> + <i>B longum</i> + <i>B infantis</i> + <i>L rhamnosus</i> + <i>L paracasei</i> + <i>L casei</i> + <i>L acidophilus</i> + <i>L lactis</i> (n = 60)	Till discharge (minimum 10 days)	3000×10^6 CFU OD	None (n = 59)	3.3	3.4			Mortality, NEC	Both HM and F	Duration of stay: 16 days in study grp vs 19 days in control group

(Continued)

TABLE 1 (Continued)

S No.	References	Country	Inclusion criteria	Gestation, weeks; mean (SD)		Birthweight, grams; mean (SD)		Sample size	Intervention			Control	Postnatal age at randomization (days)		Proportion of infants on exclusive breastmilk feeding		Critical outcomes reported	Mode of feeding	Duration of follow up
				P	C	P	C		Probiotic species	Duration of treatment	Dosage		P	C	P	C			
4.	Dashti et al. (26)	Iran	700–1,800 g; stable and able to have enteral feeding	31.1 (2.68)	31.4 (2.6)	1,373 (279)	1,441 (253)	136	<i>B longum</i> + <i>B breve</i> + <i>L acidophilus</i> + <i>L rhamnosus</i> + <i>L bulgaricus</i> + <i>L casei</i> + <i>S thermophilus</i> (<i>n</i> = 69)	Information not available	750 × 10 ⁶ CFU OD; birthweight < 1000 g; 500 × 10 ⁶ CFU OD	Placebo (<i>n</i> = 67)	4.5 (3.4)	4.2 (2.9)	42.6	27.3	Mortality, sepsis, NEC	Both HM and F	Duration of stay 27–28 days
5.	Demirel et al. (27)	Turkey	≤32 weeks and ≤1,500 g who survived to start enteral feeds	29.4 (2.3)	29.2 (2.5)	1,164 (261)	1,131 (284)	271	<i>S boulardii</i> (<i>n</i> = 135)	Till discharge	5000 × 10 ⁶ CFU OD	None (<i>n</i> = 136)					Mortality, sepsis, NEC	Both HM and F	Duration of stay: 43 to 47 days
6.	Dilli et al. (28)	Turkey	<32 weeks and <1,500 g or transferred to NICU within first 7 days and fed enterally	28.8 (1.9)	28.2 (2.2)	1,236 (212)	1,147 (271)	200	<i>B lactis</i> (<i>n</i> = 100)	Till discharge or max of 8 weeks	5000 × 10 ⁶ CFU	Placebo (<i>n</i> = 100)	3 (3–4)*	2 (2–4)*	53.0	48.0	Mortality, sepsis, NEC	Both HM and F	Duration of stay: 37 days in probiotic and 50 days in placebo

(Continued)

TABLE 1 (Continued)

S No.	References	Country	Inclusion criteria	Gestation, weeks; mean (SD)		Birthweight, grams; mean (SD)		Sample size	Intervention			Control	Postnatal age at randomization (days)		Proportion of infants on exclusive breastmilk feeding		Critical outcomes reported	Mode of feeding	Duration of follow up
				P	C	P	C		Probiotic species	Duration of treatment	Dosage		P	C	P	C			
7.	Dutta et al. (29)	India	27 to 33 weeks; age <96 h; feeds of at least 15 mL/kg/day	Grp A 30.6 (1.6); grp B 31.1 (1.9) Grp C 30.9 (2.0)	30.8 (1.7)	Grp A 1,286 (265), Grp B 1,286 (265), Grp C 1,413 (296)	1,252 (309)	149	<i>B longum</i> + <i>L helveticus</i> + <i>L rhamnosus</i> + <i>Sa boulardii</i> (n = 114)	21 days	Grp A: 10 ¹⁰ CFU 12 hourly for 21 days; Grp B: 10 ¹⁰ CFU 12 hourly for 14 days; Grp C: 10 ⁹ CFU 12 hourly for 21 days	Placebo (n = 35)	72 (48, 92); 72 (54, 90); 93.5 (72, 96)* h	81 (67.5, 96)* h	88.6	97.1	Mortality, sepsis, NEC	Both HM and F	28 days
8.	Fernández-Carrocerá et al. (30)	Mexico	<1,500 g	31.2 (26–35.4)\$	31 (27–36)\$	1,090 (580–1,495)\$	1,170 (540–1,492)\$	150	<i>B infantis</i> + <i>L casei</i> + <i>L rhamnosus</i> + <i>L plantarum</i> + <i>L acidophilus</i> + <i>S thermophilus</i> (n = 75)	-	<i>L acidophilus</i> : 1 × 10 ⁹ CFU/g; <i>L rhamnosus</i> 440 × 10 ⁶ CFU/g; <i>L casei</i> 1 × 10 ⁹ CFU/g; <i>L plantarum</i> 176 × 10 ⁶ CFU/g; <i>B infantis</i> 27.6 × 10 ⁶ CFU/g; <i>S thermophilus</i> 0.66 × 10 ⁶ CFU/g	Placebo (n = 75)	5 (1–23)\$	4 (1–15)\$	21.3	14.7	Mortality, sepsis, NEC	Both HM and F	36–38 days

(Continued)

TABLE 1 (Continued)

S No.	References	Country	Inclusion criteria	Gestation, weeks; mean (SD)		Birthweight, grams; mean (SD)		Sample size	Intervention			Control	Postnatal age randomization (days)		Proportion of infants on exclusive breastmilk feeding		Critical outcomes reported	Mode of feeding	Duration of follow up
				P	C	P	C		Probiotic species	Duration of treatment	Dosage		P	C	P	C			
9.	Gomez Rodriguez et al. (31)	Mexico	<33 weeks; 700 to 1,500 g	Grp A: 30.3 (1.83); Grp B: 31.3 (2.3)	-	Grp A: 1,175 (21); Grp B: 1,214 (24)		90	Grp A: <i>L. acidophilus</i> (45); Grp B: <i>B. infantis</i> + <i>L. rhamnosus</i> + <i>L. casei</i> + <i>L. plantarum</i> + <i>L. acidophilus</i> + <i>S. thermophilus</i> (n = 45)	21 days	1000 × 10 ⁶ CFU	None (n = 45)	5	5	Grp A:60.0; Grp:80.0		Mortality, sepsis, NEC	Both HM and F	26–28 days
10.	Hariharan et al. (32)	India	Birth weight <1,250 g; gestation <32 weeks	28.7	29.3	945	972	196	<i>B. bifidum</i> + <i>L. acidophilus</i> + <i>Sa. boulardii</i> (n = 93)	42 days	2500 × 10 ⁶ CFU	None (n = 103)					Mortality, sepsis, NEC	Both HM and F	NA
11.	Hernandez-Enriquez et al. (33)	Mexico	<34 weeks; <1,500 g					44	<i>L. reuteri</i> (n = 24)	10 days	100 × 10 ⁶ CFU	Placebo (n = 20)					Mortality, sepsis, NEC	Both HM and F	Duration of stay: 39 days for study group vs 50 days for control group

(Continued)

TABLE 1 (Continued)

S No.	References	Country	Inclusion criteria	Gestation, weeks; mean (SD)		Birthweight, grams; mean (SD)		Sample size	Intervention			Control	Postnatal age at randomization (days)		Proportion of infants on exclusive breastmilk feeding		Critical outcomes reported	Mode of feeding	Duration of follow up
				P	C	P	C		Probiotic species	Duration of treatment	Dosage		P	C	P	C			
12.	Huang et al. (34)	China	<1,500 g					183	<i>B. adolescentis</i> (n = 95)	Till discharge		Placebo (n = 88)					NEC	Both HM and F	NA
13.	Li et al. (35)	China	≤34 weeks and <1,500 g	29.3 (1.3)	30.4 (1.6)	1,176 (164)	1,326 (193)	30	<i>B. longum</i> + <i>B. bifidum</i> + <i>L. plantarum</i> (n = 16)	36 weeks' PMA	50,000 × 10 ⁶ CFU	Placebo (n = 14)			0	0	Mortality, sepsis	Both HM and F	28 days
14.	Matin et al. (36)	Iran	1,000–1,500 g	31.7 (2.2)	30.8 (2.3)	1,396 (139)	1,362 (143)	52	<i>L. paracasei</i> (n = 26)	28 days	1,500 × 10 ⁶ CFU	Placebo (n = 26)					Mortality, sepsis, NEC	Both HM and F	28 days
15.	Oncel et al. (37)	Turkey	≤ 32 weeks, <1,500 g	28.2 (2.4)	27.9 (2.5)	1,071 (274)	1,048 (298)	400	<i>L. reuteri</i> (n = 200)	Till discharge or death	100 × 10 ⁶ CFU	Placebo (n = 200)	1 (1–5) ^s	1 (1–5) ^s	17.0	13.0	Mortality, sepsis, NEC	Both HM and F	Duration of stay: 38 days in study group and 49 days in control
16.	Zahed Pasha et al. (38)	Iran	<1,500 g	30.24 (1.57)	30.4 (2.65)	1,245 (176)	1,223 (206)	60	<i>B. infantis</i> + <i>L. reuteri</i> + <i>L. rhamnosus</i> (n = 30)	Till full feeds achieved	2,000 × 10 ⁶ CFU	None (n = 30)					Mortality, NEC	Both HM and F	Duration of stay: 32 days in study. 41 days in control

(Continued)

TABLE 1 (Continued)

S No.	References	Country	Inclusion criteria	Gestation, weeks; mean (SD)		Birthweight, grams; mean (SD)		Sample size	Intervention			Control	Postnatal age at randomization (days)		Proportion of infants on exclusive breastmilk feeding		Critical outcomes reported	Mode of feeding	Duration of follow up
				P	C	P	C		Probiotic species	Duration of treatment	Dosage		P	C	P	C			
17.	Rehman et al. (39)	Pakistan	27–36 weeks; 7 days of age; <1,500 g	32.5 (2.2)		1,320 (170)		146	Bifidobacterium - species + <i>L. acidophilus</i> + <i>S. thermophilus</i> + <i>L. debraukii</i> (<i>n</i> = 73)			None (<i>n</i> = 73)					Mortality, NEC, sepsis	Both HM and F	NA
18.	Rojas et al. (40)	Columbia	<2,000 g; <48 h old					360	<i>L. reuteri</i> (<i>n</i> = 176)	Till discharge or death	100 × 10 ⁶ CFU	Placebo (<i>n</i> = 184)					NEC, Sepsis	Both HM and F	Duration of stay: 32 days in study, 37 days in control
19.	Roy et al. (41)	India	Feeding within 72 h; <37 weeks; <2,500 g; <2 weeks' postnatal age	32 (2)	32.2 (2)	1,192 (341)	1,069 (365)	112	<i>B. longum</i> + <i>B. bifidum</i> + <i>B. lactis</i> + <i>L. acidophilus</i> (<i>n</i> = 56)	Till discharge or 6 weeks	6,000 × 10 ⁶ CFU	Placebo (<i>n</i> = 56)					Mortality, sepsis, NEC	HM only	Duration of stay: 29 days in probiotic and 34 days in control
20.	Saengtawesin et al. (42)	Thailand	≤34 weeks; ≤1,500 g	31 (1.8)	30.6 (1.8)	1,250 (179)	1,208 (199)	60	<i>B. bifidum</i> + <i>L. acidophilus</i> (<i>n</i> = 31)	Till discharge or till 6 weeks	1,000 × 10 ⁶ CFU each OD	None (<i>n</i> = 29)			38.7	37.9	Mortality, sepsis, NEC	Both HM and F	Duration of stay: 60 days in probiotic, 57 days in control.

(Continued)

TABLE 1 (Continued)

S No.	References	Country	Inclusion criteria	Gestation, weeks; mean (SD)		Birthweight, grams; mean (SD)		Sample size	Intervention			Control	Postnatal age randomization (days)		Proportion of infants on exclusive breastmilk feeding		Critical outcomes reported	Mode of feeding	Duration of follow up
				P	C	P	C		Probiotic species	Duration of treatment	Dosage		P	C	P	C			
21.	Samanta et al. (43)	India	<32 weeks; <1,500 g	30.1 (1.6)	30.1 (1.6)	1,172 (143)	1,210 (143)	186	<i>B longum</i> + <i>B bifidum</i> + <i>B infantis</i> + <i>L acidophilus</i> (n = 91)	Till discharge	2,500 × 10 ⁶ CFU each OD	None (n = 95)	6.0 (1.4)	5.4 (1.3)			Mortality, sepsis, NEC	HM only	Duration of stay: 17 days vs. 24 days
22.	Sari et al. (44)	Turkey	<33 weeks; <1,500 g	29.5 (2.4)	29.7 (2.4)	1,231 (262)	1,278 (282)	221	<i>L sporogenes</i> (n = 110)	Till discharge	350 × 10 ⁶ CFU each OD	None (n = 111)	2	2	23.8	32.8	Mortality, NEC	Both HM and F	Duration of stay: 34 days in study, 30 days in control
23.	Serce et al. (45)	Turkey	≤32 weeks; ≤1,500g	28.8 (2.2)	28.7 (2.1)	1,126 (232)	1,162 (216)	208	<i>Saccharomyces boulardii</i> (n = 104)	Till discharge	500 × 10 ⁶ cells/kg/dose BD	Placebo (n = 104)	2 (1)	1.8 (1.1)	-	-	Mortality, NEC, sepsis	Both HM and F	Duration of stay: 39 days in study, 43 days in control
24.	Shadkam et al. (46)	Iran	28–34 weeks; 1,000–1,800 g	30.9 (1.9)	31 (1.9)	1,396 (234)	1,418 (328)	60	<i>L reuteri</i> (n = 30)	Till 120 mL/kg/day enteral feeds		Placebo (n = 30)			100	100	Mortality, NEC, sepsis	HM only	NA
25.	Shashidhar et al. (47)	India	750–1,499 g	31.2 (2.1)	31 (2.1)	1,256 (185)	1,190 (208)	98	<i>L acidophilus</i> + <i>L rhamnosus</i> + <i>B longum</i> + <i>S boulardii</i> (n = 49)	Till discharge	1,250 × 10 ⁶ CFU OD	None (n = 49)					Mortality, NEC, sepsis	HM only	Duration of stay: 28 days in study, 31 days in control group

(Continued)

TABLE 1 (Continued)

S No.	References	Country	Inclusion criteria	Gestation, weeks; mean (SD)		Birthweight, grams; mean (SD)		Sample size	Intervention			Control	Postnatal age at randomization (days)		Proportion of infants on exclusive breastmilk feeding		Critical outcomes reported	Mode of feeding	Duration of follow up
				P	C	P	C		Probiotic species	Duration of treatment	Dosage		P	C	P	C			
26.	Sowden et al. (48)	South Africa	750–1,500 g; <37 weeks	29 (0.5)	30 (0.4)	1,174 (226)	1,150 (230)	200	<i>L acidophilus</i> + <i>B bifidum</i> + <i>B infantis</i> (n = 100)		2,000 × 10 ⁶ CFU/day	Placebo (n = 100)					Mortality, NEC	Both HM and F	NA
27.	Tewari et al. (49)	India	<34 weeks					120	<i>B clausii</i> (n = 59)	6 wk or discharge or death or LOS	2,400 × 10 ⁶ CFU	Placebo (n = 61)					Mortality, sepsis, NEC	HM only	NA
28.	Van Niekerk et al. (50)	South Africa	<34 weeks and <1,250 g	28.7		987 (160)		184	<i>B infantis</i> + <i>L rhamnosus</i> (n = 91)		1,000 × 10 ⁶ CFU OD	Placebo (n = 93)					Mortality, sepsis, NEC	HM only	28 days
29.	Wu et al. (51)	China	28–34 weeks; <1,500 g; admission within 12 hrs of birth	32.0 (2.6)	31.3 (2.8)	1,240 (180)	1,235 (164)	500	<i>B longum</i> + <i>L acidophilus</i> + <i>E faecalis</i> (n = 250)	Till TPN was given	10 × 10 ⁶ CFU/g	None (n = 250)			0	0	Sepsis, NEC	F only	14–16 days

P, Probiotic arm; C, Control arm; CFU, colony forming unit; SGA, Small-for-gestational age; IUGR, Intrauterine growth restriction; TPN, total parenteral nutrition; OD, once daily; BD, twice daily. Data represented as mean (SD); [§]Data represented as median (range);

*Data represented as median (IQR); HM Human milk; F, Formula.

thereby precluding the formation of any closed loop in the network. Based on the visual examination of the leverage plots and comparison of the DIC values of the fixed- and random-effects model (Supplementary Figures 2A, B), we chose the fixed-effect model for estimating the effect size and credible intervals. The trace and density plots demonstrated good convergence of the model (Supplementary Figure 3A).

When compared with the placebo, three probiotic arms, namely, *B. lactis* alone (“B lac”; RR 0.21; 95% CrI 0.05 to 0.66; low certainty of evidence); the combination of *B. longum*, *B. bifidum*, *B. infantis*, and *L. acidophilus* (“B3iL”; RR 0.26, 95% CrI 0.07 to 0.72; very low certainty of evidence); and that of *B. infantis*, *L. rhamnosus*, *L. casei*, *L. plantarum*, *L. acidophilus*, and *S. thermophilus* (“BinL4S”; RR 0.09, 95% CrI 0.003 to 0.576; low certainty of evidence) may reduce the risk of mortality (Figure 3A, Supplementary Table 8). SUCRA values ranked “BinL4S” (SUCRA 0.92), “BL2aSa” (combination of *B. longum*, *L. acidophilus*, *L. rhamnosus*, and *Sa. boulardii*; SUCRA 0.84), “B lac” (SUCRA 0.84), and “B3iL” (SUCRA 0.80; Figure 4A) as the most beneficial interventions. The league plot (Supplementary Figure 4A) of the network estimates confirmed the findings of the SUCRA plot. The split between direct and indirect evidence could not be checked because of the absence of closed loops in the network. However, the deviance contribution plot (Supplementary Figure 5A) showed most points near or above the line of equality, suggesting a lack of critical inconsistency.

Sepsis

Twenty-four studies involving 4,314 neonates reported on the incidence of sepsis. All but two studies (23, 42) had documented culture-positive sepsis. Three studies had zero events in at least one arm and were dropped in the final analysis. The remaining 21 studies enrolled 4,112 neonates, of whom 825 (20.1%) were diagnosed with sepsis. Figure 2B illustrates the network plot—each probiotic arm has been compared with the standard reference arm (placebo) but not among themselves. The fixed-effect model was used to estimate the effect size and credible intervals after examining the leverage plots and comparing the DIC values of the fixed- and random-effects models (Supplementary Figures 2C, D).

When compared with the placebo, two probiotic arms, namely, the combinations of *B. longum*, *B. bifidum*, *B. infantis*, and *L. acidophilus* (“B3iL”; RR 0.47, 95% CrI 0.25 to 0.83; very low certainty of evidence) and *B. longum*, *B. bifidum*, *B. lactis*, and *L. acidophilus* (“B3L”; RR 0.73; 95% CrI 0.54 to 0.96; low certainty of evidence) may result in a reduction in the incidence of sepsis (Figure 3B, Supplementary Table 9). SUCRA values ranked “B3iL” (SUCRA 0.88), “BL2Sa” (combination of *B. longum*, *L. helveticus*, *L. rhamnosus*, and *Sa. boulardii*; SUCRA 0.76), and “B lac” (*B. lactis*; SUCRA 0.75; Figure 4B) as the most beneficial interventions. The league plot (Supplementary Figure 4B) of the network estimates confirmed the findings of the SUCRA plot. The split between direct and indirect evidence could not be checked. The deviance contribution plot (Supplementary Figure 5B) did not suggest any critical inconsistency.

Necrotizing enterocolitis

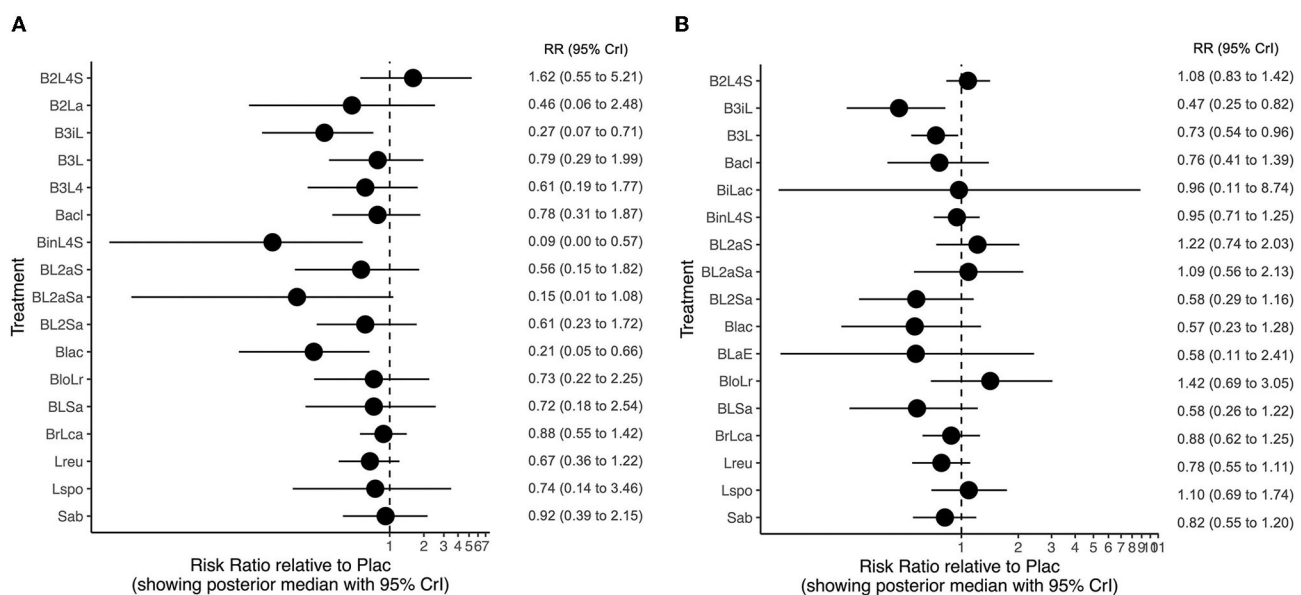
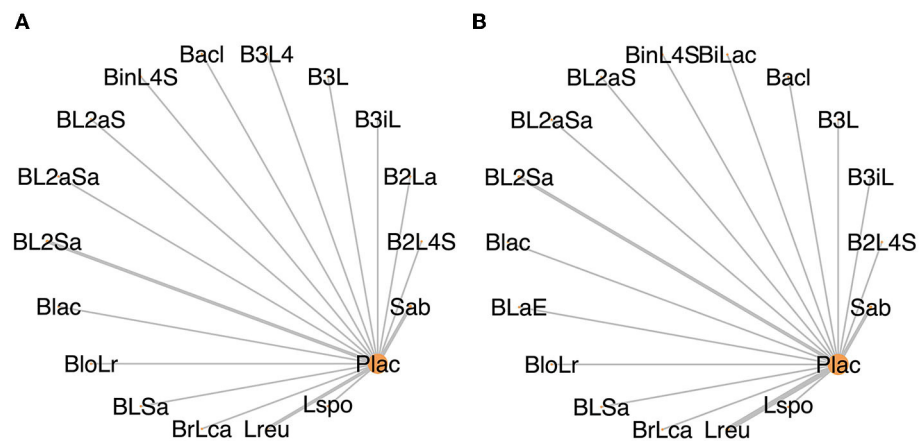
A total of 28 studies involving 4,876 neonates reported the incidence of NEC. All but two studies provided the risk of NEC stage 2 or more; two studies Rehman et al. (39) and Roy et al. (41)—did not mention the stage of NEC. Nine studies with zero events in at least one study arm were dropped from the analysis. The remaining 19 studies enrolled 3,527 neonates, of whom 65 (1.8%) had NEC. Supplementary Figure 6 illustrates the network plot wherein each probiotic arm has been compared with the standard reference arm (placebo) but not among themselves. The fixed-effect model was used to estimate the effect size and credible intervals after examining the leverage plots and comparing the DIC values of the fixed- and random-effects models (Supplementary Figures 2E, F). The trace and density plots demonstrated good convergence of the model (Supplementary Figure 3B).

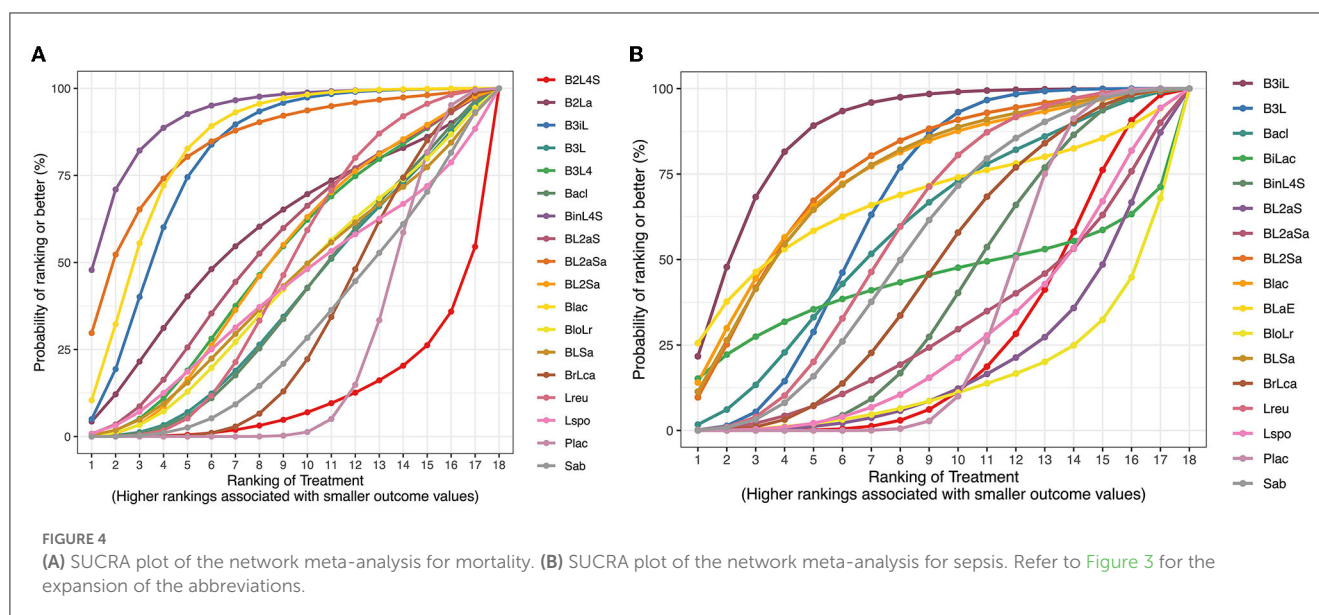
Six probiotic regimens, namely *B. lactis* (“B lac”; RR 0.09, 95% CrI 0.01–0.32; low certainty of evidence), *L. reuteri* (“Lreu”; RR 0.40, 95% CrI 0.23–0.68; low certainty of evidence), and the combinations of *B. bifidum*, *B. longum*, *B. infantis*, *L. rhamnosus*, *L. paracasei*, *L. casei*, *L. acidophilus*, and *L. lactis* (“B3L4”; RR 0.10, 95% CrI 0.003–0.66; very low certainty of evidence), *B. longum*, *L. acidophilus*, and *E. fecalis* (“BLaE”; RR 0.13, 95% CrI 0.01–0.51; low certainty of evidence), *Bifidobacterium* spp., *L. acidophilus*, *S. thermophilus*, and *L. delbrueckii* (“BL2aS”; RR 0.19, 95% CrI 0.02–0.78; low certainty of evidence), *B. longum*, *B. bifidum*, *B. infantis*, and *L. acidophilus* (“B3iL”; RR 0.31; 95% CrI 0.10–0.78; very low certainty of evidence) may result in a reduction in the incidence of NEC (Supplementary Figure 7). SUCRA values ranked “B lac” (SUCRA 0.88), “B3L4” (SUCRA 0.82), and “BLaE” (SUCRA 0.80; Supplementary Figure 8) as the most beneficial interventions. The league plot (Supplementary Figure 4C) of the network estimates confirmed the findings of the SUCRA plot.

Safety outcomes and subgroup analyses

Fifteen studies that evaluated the risk of probiotic-related sepsis as a safety outcome found no incidence of culture-positive sepsis attributable to the probiotic administered in any of the arms (27–31, 36, 37, 40, 42–45, 47, 49, 50).

On subgroup analyses by the type of milk received by the enrolled neonates, two probiotic arms, namely, *B. lactis* alone (“B lac”; RR 0.21; 95% CrI 0.05 to 0.66; low certainty of evidence) and that of *B. infantis*, *L. rhamnosus*, *L. casei*, *L. plantarum*, *L. acidophilus*, and *S. thermophilus* (“BinL4S”; RR 0.09, 95% CrI 0.003 to 0.58) possibly reduced the risk of mortality (Supplementary Figure 9A) among those receiving either breastmilk or formula feeds. In contrast, the combination of *B. longum*, *B. bifidum*, *B. infantis*, and *L. acidophilus* (“B3iL”; RR 0.26; 95% CrI 0.07 to 0.71) may reduce the mortality risk in exclusively breastmilk-fed neonates (Supplementary Figure 9B). None of the probiotics reduced the incidence of sepsis among neonates receiving breastmilk or formula feeds (Supplementary Figure 10A); however, among those receiving only breastmilk, two probiotic combinations, namely, *B. longum*, *B. bifidum*, *B. infantis*, and *L. acidophilus* (“B3iL”; RR 0.47, 95% CrI 0.25 to 0.82) and *B. longum*, *B. bifidum*, *B. lactis*, and *L.*





precision of the result. In addition to “B3iL” and *B lactis*, four more probiotic combinations may reduce the incidence of NEC. The certainty of the evidence was, however, low.

The review findings are concordant with that of the previous network meta-analysis by van den Akker et al., which reported that the probiotic combination of *B longum*, *B bifidum*, *B infantis*, and *L acidophilus* (“B3iL”) reduced the incidence of mortality and late-onset sepsis while the single probiotic species *B lactis* reduced the risk of NEC (52). However, the other probiotic combinations found to reduce the incidence of NEC—*L rhamnosus* GG or the combination of *B infantis* and *L acidophilus*—were not shown to be beneficial in the current study. The other network meta-analysis by Morgan et al. found the combinations of *Lactobacillus spp.* and *Bifidobacterium spp.* (mainly, *L rhamnosus* GG and *B longum* subsp *infantis*; *Lactobacillus casei* and *B breve*) to be among the most effective regimens in reducing the incidence of all-cause mortality and NEC (53); it did not find any probiotic species to be beneficial in reducing the risk of culture-proven sepsis.

The discrepancy in results wasn’t unexpected given the focus of the current review on *only* the studies from low- and middle-income countries (cf. previous reviews that included all studies irrespective of the settings). The other reviews did not provide the subgroup analyses of the studies from LMICs, which precludes direct head-to-head comparison with the current review. Notwithstanding these issues, the discordant results could be because of the differences in the maternal genital tract and gut microbiome, exposure to broad-spectrum antibiotics in the antenatal and postnatal periods, resistant environmental flora in the delivery areas and neonatal units, mode of delivery, rates of intrauterine growth restriction, exclusive breastfeeding rates, and use of fortifiers. The predominance of Gram-negative pathogens among neonates with early-onset sepsis in LMICs, as opposed to that by group B streptococci in neonates from high-income countries (HIC), could indicate a qualitatively different vaginal flora and gut microbiome among mothers from the two settings

(54, 55). The mode of delivery and breastfeeding rates have been demonstrated to influence the gut microbiome of preterm neonates (56, 57). Together, these factors underscore the potential problems in extrapolating the results of probiotic studies from HICs to LMIC settings.

The clinical practice and public health implications of the current network meta-analysis’s results are unknown. There is uncertain evidence on the effects of the probiotic combination of *B longum*, *B bifidum*, *B infantis*, and *L acidophilus*, the only regimen found to be beneficial in reducing the incidence of all three outcomes. Only one study involving 186 neonates evaluated its efficacy. The ESPGHAN Working Group for Probiotics and Prebiotics (52), which chose a minimum number of 247 infants per group to be studied before making recommendations, did not consider the said probiotic combination because of the small numbers enrolled (52). Moreover, the ESPGHAN group has cautioned against using probiotic strains that produce D-lactate because of the lack of safety data in preterm neonates. *L acidophilus* is a partially D-lactate-producing strain. On the other hand, the Working Group has conditionally recommended using *L rhamnosus* GG to reduce the risk of NEC in preterm neonates. None of the studies included in the review have evaluated its efficacy in neonates from LMICs. The recent WHO guidelines for the care of preterm and low-birth-weight infants also did not make any recommendations on the type, formulation, dose, timing, or duration of probiotics due to a lack of sufficient evidence (58).

Our review suggested that the single probiotic species *B lactis* may reduce the risk of mortality and NEC. Unfortunately, it is not commonly available in India and possibly other LMICs (Supplementary Table 9). There is an urgent need to examine (a) the efficacy of *B lactis*, *L rhamnosus* GG, or their combinations to identify the optimal probiotic species for use in LMIC settings and (b) the safety of probiotic combinations containing *L reuteri* or *L acidophilus* that produce D-lactate in preterm neonates from LMICs.

The current review is arguably the first species-specific network meta-analysis involving studies from LMICs. The overarching goal was to identify the optimal probiotic species that provides the maximal benefits in reducing the risks of mortality and sepsis in preterm neonates from these settings, which would not have been possible with the traditional pair-wise meta-analyses comparing any probiotics with placebo. However, none of the included studies compared one probiotic species with another, thus precluding obtaining direct and network estimates for each comparison and checking the consistency between the direct and indirect estimates. Therefore, we did not use or interpret the estimates from indirect comparisons among the probiotic regimens. The other critical limitation of the review was that all the trials were relatively small, and only one study each had evaluated almost all probiotic regimens. Finally, we had to drop studies with zero events from the analysis to avoid convergence issues and prevent getting spurious estimates.

To conclude, no firm conclusions can be made on the optimal probiotic species to be used in preterm very low birth weight neonates in LMICs because of the lack of direct comparisons between different probiotics and the low to very low certainty of the evidence for the efficacy of the two probiotics found to reduce mortality and necrotizing enterocolitis. Future studies should evaluate the efficacy of *B. lactis*, *L. rhamnosus* GG, or their combinations to guide clinical practice and policymaking in these settings.

Data availability statement

The original contributions presented in the study are included in the article/Supplementary material, further inquiries can be directed to the corresponding author.

Author contributions

MS: had full access to all of the data in the study and takes responsibility for the integrity of the data and the accuracy of the data analysis, administrative, technical, or material support, and supervision. DT, AS, and MS: concept, design, acquisition, analysis, and interpretation of data. DT and AS: drafting of the manuscript and statistical analysis. All authors: critical revision of the manuscript for important intellectual content.

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Conflict of interest

The authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

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Supplementary material

The Supplementary Material for this article can be found online at: <https://www.frontiersin.org/articles/10.3389/fnut.2023.1133293/full#supplementary-material>

SUPPLEMENTARY FIGURE 1

Risk of bias of the included studies: (A) overall plot and (B) traffic light plot.

SUPPLEMENTARY FIGURE 2

Fixed effect model of the network meta-analysis for (A) Mortality, (C) Sepsis, and (E) NEC and random effect model for (B) Mortality, (D) Sepsis, and (F) NEC.

SUPPLEMENTARY FIGURE 3

Trace and density plot for (A) Mortality and (B) Sepsis.

SUPPLEMENTARY FIGURE 4

League table heatmap of the network meta-analysis for (A) Mortality, (B) Sepsis, and (C) NEC. The decoding of the probiotics has been given in Supplementary Table 6. The values in each cell represent the relative risk (and 95% credible intervals) of the treatment on the top, compared to the treatment on the left. A double asterisk indicates statistical significance.

SUPPLEMENTARY FIGURE 5

Deviance contribution plots of the network meta-analysis for (A) Mortality, (B) Sepsis, and (C) NEC.

SUPPLEMENTARY FIGURE 6

Network plot depicting the studies included for the secondary outcome- NEC.

SUPPLEMENTARY FIGURE 7

Forest plot depicting the relative risks of different probiotic species compared with placebo for the secondary outcome- NEC.

SUPPLEMENTARY FIGURE 8

SUCRA plot of the network meta-analysis for the secondary outcome- NEC. The decoding of the probiotics has been given in Supplementary Table 6.

SUPPLEMENTARY FIGURE 9

Forest plot depicting the relative risks of different probiotic species compared with placebo for mortality among patients fed (A) Both human milk and formula (B) Human milk only

SUPPLEMENTARY FIGURE 10

Forest plot depicting the relative risks of different probiotic species compared with placebo for sepsis among patients fed (A) Both human milk and formula (B) Human milk only.

SUPPLEMENTARY TABLE 1

Deviations in the protocol.

SUPPLEMENTARY TABLE 2

Search strategy from electronic databases.

SUPPLEMENTARY TABLE 3

Excluded studies after full-text screening.

SUPPLEMENTARY TABLE 4

Studies awaiting classification.

SUPPLEMENTARY TABLE 5

Characteristics of ongoing studies.

SUPPLEMENTARY TABLE 6

Coding of probiotics used alone or in combination used in the study.

SUPPLEMENTARY TABLE 7

Summary of confidence rating of various probiotic interventions compared to placebo for mortality.

SUPPLEMENTARY TABLE 8

Summary of confidence rating of various probiotic interventions compared to placebo for sepsis.

SUPPLEMENTARY TABLE 9

Commonly used probiotic preparations for neonatal use in India.

SUPPLEMENTARY TABLE 10

PRISMA-NMA checklist.

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EDITED BY

Nita Bhandari,
Center for Health Research and Development,
Society for Applied Studies, India

REVIEWED BY

Ravi Prakash Upadhyay,
Center for Health Research and Development,
Society for Applied Studies, India
Beena Koshy,
Christian Medical College & Hospital, India

*CORRESPONDENCE

Betty R. Kirkwood
✉ betty.kirkwood@lshtm.ac.uk

[†]These authors share first authorship

[†]These authors share senior authorship

[‡]These authors share last authorship

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Effect of the SPRING home visits intervention on early child development and growth in rural India and Pakistan: parallel cluster randomised controlled trials

Betty R. Kirkwood^{1*†}, Siham Sikander^{2,3†}, Reetabrata Roy^{1,4†}, Seyi Soremekun⁵, Sunil S. Bhopal^{1,6}, Bilal Avan⁵, Raghu Lingam⁷, Lu Gram⁸, Seeba Amenga-Etego⁹, Bushra Khan¹⁰, Sarmad Aziz¹¹, Divya Kumar⁴, Deepali Verma⁴, Kamal Kant Sharma⁴, Satya Narayan Panchal⁴, Shamsa Zafar¹², Jolene Skordis⁸, Neha Batura⁸, Assad Hafeez¹³, Zelee Hill⁸, Gauri Divan^{4‡§} and Atif Rahman^{2‡§}

¹Department of Population Health, Faculty of Epidemiology & Population Health, London School of Hygiene & Tropical Medicine, London, United Kingdom, ²Department of Primary Care and Mental Health, University of Liverpool, Liverpool, United Kingdom, ³Global Institute of Human Development, Shifa Tameer-e-Millat University, Islamabad, Pakistan, ⁴Child Development Group, Sangath, New Delhi, India, ⁵Department of Infection Biology, Faculty of Clinical Research, London School of Hygiene and Tropical Medicine, London, United Kingdom, ⁶Population Health Sciences Institute, Newcastle University, Newcastle upon Tyne, United Kingdom, ⁷Population Child Health Research Group, School of Clinical Medicine, University of New South Wales, Randwick, NSW, Australia, ⁸Institute for Global Health, University College London, London, United Kingdom, ⁹Kintampo Health Research Centre, Ghana Health Service, Kintampo, Ghana, ¹⁰Department of Psychology, University of Karachi, Karachi, Sindh, Pakistan, ¹¹Department of Anthropology, University College London, London, United Kingdom, ¹²Fazaia Medical College, Air University, Islamabad, Pakistan, ¹³World Health Organization, Kuwait City, Kuwait

Introduction: Almost 250 million children fail to achieve their full growth or developmental potential, trapping them in a cycle of continuing disadvantage. Strong evidence exists that parent-focussed face to face interventions can improve developmental outcomes; the challenge is delivering these on a wide scale. SPRING (Sustainable Programme Incorporating Nutrition and Games) aimed to address this by developing a feasible affordable programme of monthly home visits by community-based workers (CWs) and testing two different delivery models at scale in a programmatic setting. In Pakistan, SPRING was embedded into existing monthly home visits of Lady Health Workers (LHWs). In India, it was delivered by a civil society/non-governmental organisation (CSO/NGO) that trained a new cadre of CWs.

Methods: The SPRING interventions were evaluated through parallel cluster randomised trials. In Pakistan, clusters were 20 Union Councils (UCs), and in India, the catchment areas of 24 health sub-centres. Trial participants were mother-baby dyads of live born babies recruited through surveillance systems of 2 monthly home visits. Primary outcomes were BSID-III composite scores for psychomotor, cognitive and language development plus height for age z-score (HAZ), assessed at 18 months of age. Analyses were by intention to treat.

Results: 1,443 children in India were assessed at age 18 months and 1,016 in Pakistan. There was no impact in either setting on ECD outcomes or growth.

The percentage of children in the SPRING intervention group who were receiving diets at 12 months of age that met the WHO minimum acceptable criteria was 35% higher in India (95% CI: 4–75%, $p = 0.023$) and 45% higher in Pakistan (95% CI: 15–83%, $p = 0.002$) compared to children in the control groups.

Discussion: The lack of impact is explained by shortcomings in implementation factors. Important lessons were learnt. Integrating additional tasks into the already overloaded workload of CWs is unlikely to be successful without additional resources and re-organisation of their goals to include the new tasks. The NGO model is the most likely for scale-up as few countries have established infrastructures like the LHW programme. It will require careful attention to the establishment of strong administrative and management systems to support its implementation.

KEYWORDS

early child development (ECD), child growth and nutrition, home visits, nurturing care, cluster randomised control trial, community health worker (CHW), India, Pakistan

Introduction

Early childhood development (ECD) has risen exponentially in policy importance over the last 10 years (1). It is embedded in several of the Sustainable Development Goals (2), is explicit in the new vision of the UN Secretary-General's Global Strategy for Women's, Children's and Adolescents' Health 2016–2030 with the objectives of Survive, Thrive and Transform (3), and has been prioritised in the work programmes of several global institutions, including UNICEF, the World Bank, UNESCO and the World Health Organization (4). This culminated in the launch of the Nurturing Care Framework (NCF) for ECD during the 71st World Health Assembly in May 2018 (5), where it was argued that “Investing in ECD is one of the best investments a country can make to boost economic growth, promote peaceful and sustainable societies, and eliminate extreme poverty and inequality.” The NCF and this statement are underpinned by considerable advancements in science over the last 30 years (6–10).

The Lancet Series on ECD estimated that almost 250 million children under the age of 5 years who live in low- and middle-income countries (LMICs) are at high risk of not reaching their developmental potential (11). Many are likely to do poorly in school and subsequently as adults many will have poor health, high fertility, and provide poor health care, nutrition, and stimulation to their own children, thus contributing to the intergenerational transmission of disadvantage (12). The loss of human potential that this represents is also associated with more than a 20% deficit in adult income and will have negative implications for national development (13, 14).

The NCF is a road map for action built around five components: good health; adequate nutrition; responsive caregiving; security and safety; and opportunities for early learning. It focusses on the critical period from pregnancy to age 3, during which neuroplasticity is at its peak with new neural synaptic connections made in response to interactions with the environment, providing the foundation for healthy physical and mental health throughout the life course (6).

Strong evidence exists from several randomised controlled trials that parent-focussed face to face interventions can improve child development outcomes and can allow children to compensate for delays in their development due to diverse risks, such as malnutrition

and poverty (15–17). This evidence is summarised in a World Health Organization ECD guideline which recommends supporting responsive care and early learning activities for all young children, providing such support in conjunction with nutrition interventions, and promoting maternal mental health. The guideline outlines that the challenge now is understanding how to deliver such interventions effectively at scale across diverse contexts (5, 18).

The Wellcome Trust SPRING programme in India and Pakistan was designed to address this challenge. Both countries featured in the 2016 Lancet ECD Series list of the top 10 countries in 2010 with the largest number of children at risk of impaired cognitive and social-emotional development, as a result of stunting or extreme poverty (11). These countries were, in order of numbers affected, India, China, Nigeria, Bangladesh, Indonesia, Pakistan, Ethiopia, DR Congo, Tanzania, and the Philippines. The 2021 UNICEF ECD country profiles give 2015 estimates of 45% for India and 54% for Pakistan (19), while the WHO 2022 World Health Statistics report give estimates of the percentage of children stunted as 30.9% for India and 36.7% for Pakistan, both estimates from 2020 (20).

SPRING stands for Sustainable Programme Incorporating Nutrition and Games. The aim was to develop an integrated nutrition and child development intervention package to support families to give their children the best start in life, that was designed from the outset to be feasible, affordable and appropriate for delivery at scale, and to test this through cluster randomised controlled trials in two settings, using two different delivery models for scale-up using community-based workers (CWs). In Pakistan, the SPRING intervention was embedded into the existing monthly home visits of the Lady Health Workers (LHWs). In India, home visits were implemented by a civil society/non-governmental organisation (CSO/NGO) that trained a new cadre of CWs, called Kilkaari Workers (KW) to work alongside the existing maternal and child health community services provided by ASHAs and Anganwadi workers (21).

The primary objectives were: (1) To design the SPRING integrated nutrition and child development intervention, based on extensive formative research and best practise guidelines; (2) To test the SPRING intervention through parallel cluster randomised controlled trials in India and Pakistan; (3) To evaluate the impact of SPRING on

early child growth and development, and on intermediate outcomes that lie on the hypothesised change pathway including quality of the home environment, infant feeding practises and maternal psychosocial distress; (4) To evaluate and monitor all aspects of the SPRING intervention process and implementation; and (5) To cost the delivery of the SPRING intervention and assess its cost effectiveness.

In this paper we present the impact of SPRING on early child development and growth in the first 18 months of life. A companion paper in this supplement presents findings from the process evaluation together with lessons learned for delivering community based ECD interventions at scale (22).

Methods

Trial design

The SPRING intervention was evaluated through parallel cluster randomised trials carried out in Rawalpindi District in Pakistan and Rewari district in the south of Haryana in India. Clusters were chosen to be supervisory zones of the CWs to minimise any chance of contamination. In Pakistan, clusters were 20 Union Councils (UCs), which cover populations of about 22,000 and which are the supervisory zones of the LHWs. There are approximately 15–20 LHWs in a UC. Each LHW is a local resident of the community she serves, covering a population of 1,200–1700 and approximately 250–275 households. They are paid by the government, have a minimum 8–10 years of education, and are trained for 15 months to carry out monthly home visits to provide preventive maternal and child health services along with other duties (23). Each UC has one LHW supervisor (LHS) responsible for holding monthly group supervisory meetings and carrying out one to one field supervision of LHWs. LHWs in 10 of the UCs chosen at random were trained to deliver the SPRING intervention alongside their other activities.

In India, clusters were the catchment areas of 24 health sub-centres with functional Auxiliary Nurse Midwives and covering a population of at least 8,000. They were the supervisory zones of the ASHAs, a comparable cadre to the project appointed Kilkaari Workers (KWs) who were recruited in 12 of the clusters chosen at random to deliver the SPRING intervention through monthly home visits. Each intervention cluster had 3–6 KWs each serving a maximum of a hundred homes with eligible families. If the potential workload in a single cluster did not justify a full-time appointment the KW covered two clusters. KWs were recruited by the implementing NGO using similar criteria as those used for ASHA workers in that they were: Married, educated till 8th grade or above, lived in the community they served – or in the adjacent community, and had good communication skills.

Surveillance system

The trials were supported by surveillance systems of regular 2-monthly visits by trained fieldworkers to identify pregnant women and newborns. There was one resident fieldworker (FW) in each cluster, making a total of 24 in India and 20 in Pakistan with one field supervisor per 5 FWs and a head of FW in each site. Training consisted of 3 phases of 3–5 days length covering: mapping of the study area; baseline survey; and the two-monthly surveillance visits. In India the surveillance system covered all households in the trial clusters. In Pakistan the surveillance system covered all households within

sub-areas designated as evaluation zones within each cluster (Union Councils). These evaluation zones were chosen to be comparable in population size to the clusters in India and comprised 7 LHW catchment areas, out of the 15 LHW areas in each Union Council. Each zone was defined by selecting one LHW area at random and then adding the 6 nearest LHW areas to form a contiguous evaluation zone. This selection was carried out by the SPRING statistician who had no knowledge of the areas.

All women of reproductive age were enrolled into the surveillance system at the first household visit if they were aged less than 50 years, married, not sterilised and whose husbands were not sterilised. Additional women were enrolled at subsequent visits if they met the criteria, for example if a woman became married or if an eligible woman moved into a cluster. Visits took place every 8 weeks in India and every 10 weeks in Pakistan.

Participants

Mother-baby dyads of all live born babies identified by the surveillance system in trial clusters who were born on or after the date of full implementation of SPRING were enrolled into the SPRING trial. This was 2 May 2014 in Pakistan and 18 June 2015 in India allowing for a 2–3 month embedding period. Exclusion criteria were babies with major congenital malformations, babies whose mothers died and mothers who were incapable of answering questions. Socio-economic and birth data were collected at enrolment. Data on contact with maternal and child health and community workers and on breastfeeding and complementary feeding practises were collected at all subsequent home visits up to 30 April 2016 in Pakistan and 01 July 2017 in India, when primary outcome data collection was completed.

The first mother-baby dyads identified were recruited in the child development assessment (CDA) subsample for assessments of primary outcomes when children reached 12 months of age and again at 18 months of age; these assessments were carried out by specialist outcome assessment teams. CDA recruitment continued until sample size requirements were met. Additional mothers were recruited for assessment of maternal mental and social wellbeing, family support and maternal efficacy at the 12-month assessment as these intermediate outcomes required a larger sample size; they are not included in this paper.

Interventions

Spring intervention

In India, SPRING was branded “Kilkaari,” the happy gurgling of a small child, and delivered by CWs called Kilkaari workers (KWs), a new cadre of CWs, specifically recruited by SANGATH, the implementing NGO, to only deliver the SPRING intervention. They were recruited to have characteristics similar to government frontline workers, and received similar remuneration. KWs were resident in the community, had a minimum of 8th grade education, were married and had good communication skills. Each served a maximum of 100 eligible households. They were asked to engage with the existing maternal and child health community services provided by ASHAs and Anganwadi workers and attend local community events such as Village Health Days to identify new pregnancies and mothers with young children.

In Pakistan, SPRING was branded “Roshan Kal,” a bright tomorrow. It was embedded in the government Lady Health Worker (LHW) monthly home visit programme which was established in 1994 (23). The LHW role comprises over 20 maternal and child health services including health education on breastfeeding and complementary feeding, child growth monitoring, immunisations, family planning and basic curative care. Within the government programme LHWs receive 15 months training, are aged 18–45 years, resident in the community they serve, have a minimum 8 years of education, are preferably married and are acceptable to the community. Each Union Council has 15–20 LHWs, each serving 150–200 households. LHWs conduct approximately 7 home visits per day and the SPRING content was integrated into these home visits.

The SPRING intervention targeted infant/young child feeding and interaction and play with the aim of improving child growth and development. It was guided by the conceptual framework & change pathway shown in Figure 1, which was used both during the development of the intervention and to guide the intermediate outcome data collected in the evaluation. The content was based on formative research into existing behaviours, and into barriers to and facilitators for adopting desired ECD and feeding practises (24). The desired behaviours for play were adapted from the WHO/UNICEF Care for Development curriculum (25), and those for complementary feeding from WHO/UNICEF infant and young child feeding guidelines (26).

It was delivered through monthly home visits by the CWs to mothers starting in pregnancy and continuing through the first 2 years of a child's life (Table 1). Home visits in pregnancy focused on maternal health and sensitisation about breastfeeding. Postnatal visits focused on breastfeeding, complementary and responsive

feeding, and play activities, with new messages introduced each month dependent on the age of the child. The CWs were trained to engage with and include other family members in the visits as appropriate.

The CWs used a counselling approach based on cognitive behaviour therapy (CBT) that had successfully been used with LHWs in a previous study in Pakistan (27). The approach comprises 6 key principles: family support; guided discovery using pictures; behavioural activation; empathic listening; problem-solving; and praise. The child development component included practical coaching of families on stimulation activities, where CWs explained the child stimulation activities and demonstrated if needed and then coached families on key elements such as praising the child and scaffolding new activities as appropriate. This practical component aimed to enhance caregiver self-efficacy, skills and recall. CWs were trained to use counselling cards, which included culturally appropriate illustrations for the family to look at and instructions and key messages for the CW to deliver, that were simple to use and easy to understand. In Pakistan, CWs also gave families pictorial Roshan Kal calendars, which comprised reminder messages and a space for families to tick if they had been able to follow the behaviours discussed.

Training

In both sites the CWs were trained by SPRING supervisors who were female social science graduates overseen by senior project staff. Training was divided into two phases of 5 and 3 days, to ensure the quantity of material covered was manageable for the CWs, and to maximise experiential learning. Maximum group size was 29. The first training phase focused on ensuring the CWs had the core knowledge and competencies required to counsel and problem solve with families, as well as covering the background to child development and

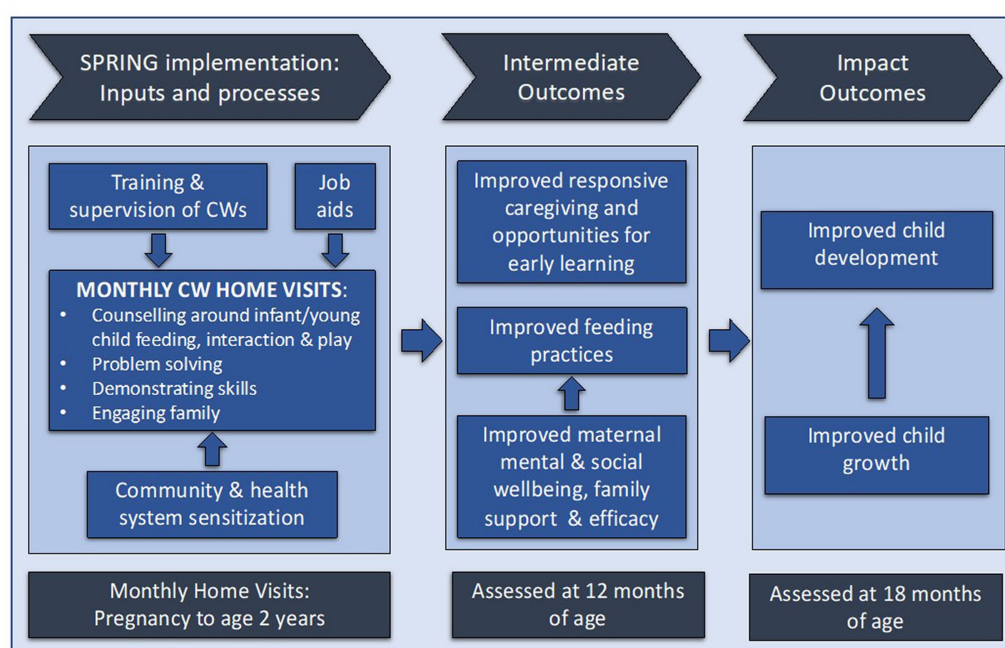


FIGURE 1
SPRING conceptual framework and change pathway.

TABLE 1 SPRING intervention – content of CW monthly home visits.

Age at visit	Nutrition related	Play and stimulation
Pregnancy	Importance of family support for maternal and child well-being	
	Encouragement of family involvement	
	Iron during pregnancy	
	Diet and rest during pregnancy	
	Early and responsive breastfeeding with love and care	
	No pre-lacteal feeds	
Neonatal period	Exclusive and responsive breastfeeding with love and care	Talking or singing to the child while breastfeeding and doing daily activities, looking into the child's eyes during breastfeeding and allowing freedom of movement of limbs
	Avoiding insufficient milk through diet and frequent breastfeeding	
1–11 months	Continue exclusive breastfeeding until 6 months and then continued breastfeeding	Child and age specific activities such as: following objects, grabbing objects, copying sounds and actions, clapping, saying bye bye.
	In last visit before 6 months, introduce concept of weaning from 6 months	
	Complementary feeding age dependent messages on: - Responsive feeding - Consistency - Frequency, variety and quantity - Hygiene - Adding “super” foods (eg butter or oil) - Finger food - Enjoyable meal times - Avoiding “junk” foods (Pakistan only)	
	Importance of feeding for a sick child	
Second year	Eating with the family and balanced diet	Child and age specific activities such as: stacking; putting in and out; naming objects; following instructions; colour matching.
	Continued breastfeeding	

the content of the home visits up to the fifth month of age. The second phase focused on the content from 5 months to 2 years of age.

Supervision

In Pakistan the LHWs were supervised by integrating a SPRING supervision component into the LHW routine monthly group supervision meetings with the LHS, and through SPRING specific one-to-one supervision visits in the field. Once the LHS had completed their group supervision, the SPRING supervisor led a session that focused on sharing experiences, peer-learning, problem-solving, skills development through role play, motivation and peer support. They also identified issues faced by LHWs in the field, helped develop solutions and identified further training needs. The same SPRING supervisors provided individual feedback on LHW performance during monthly observation of a home visit. The supervision in India followed the same structure but the group supervision was arranged by the SPRING team and the size of the groups was slightly smaller ranging from 11 to 16 KW workers.

During the observed home visit the supervisors completed a checklist to record visit quality for monitoring purposes and provided supportive feedback after the completion of the visit. The tone of individual supervision followed the SPRING principles of empathetic listening, praise for the CW on things they had done well, suggestions and problem solving on areas that they could improve on, and

encouragement to adopt a more counselling-based approach if needed.

Process evaluation

Quantitative process data were collected on training (self-completed pre and post training test), supervision coverage (programme records), visit coverage (caregiver interviews) and visit quality (field supervision checklist and caregiver interviews). Qualitative data on acceptability and barriers and facilitators for change were collected through in-depth interviews with mothers (24); focus group discussions with mothers (8), grandmothers (12), and fathers (12) and in-depth interviews or focus group discussions with the community-based agents and their supervisors (13) provided. These data were not used to course correct in order to improve the quality of intervention delivery during the trial. The supportive supervision with its emphasis on problem solving was the only strategy used to do this.

Control interventions

Pregnant women and newborn babies living in both intervention and control zones continued to benefit from the routine maternal and child health care available. This consisted of home-visiting advice by LHWs in Pakistan, and home- and centre-based advice and care from ASHAs, Anganwadi Workers, and Auxillary Nurse Midwives in India,

plus access to routine maternal- and child-healthcare services in both countries.

Trial outcomes

Impact outcomes: child development and growth

Child development and growth were assessed by a team of outcome assessors (OAs) when trial children reached 18 months of age; this was changed from 24 months of age with agreement by the trial steering committee (TSC) at its meeting on 26 November 2013 due to political instability in Pakistan and a site-change in India. The time window for the assessments was -7 days to $+21$ days of the exact date the child reached 18 months of age. The assessments took a total of 2–3 h to carry out.

The OAs worked in pairs. They administered the gross motor, fine motor, cognitive, receptive language and expressive language subtests of the Bayley Scales of Infant and Toddler Development, Third Edition (BSID-III) (28). The subtests consist of a series of increasingly complex tests (items) covering ages 1–42 months. The assessment starting point depends on the child's age. This was section K (age 16 m 16 days – 19 m 15 days) for SPRING trial children who were aged 18 months. Items were administered until the child was not able to complete five consecutive items in a row, at which point the assessment for the subtest ended. Children received a point for every successfully completed item from their starting point plus points for all the items in the sections before their starting point. If a child was unable to complete the first three items of section K, the OA started the assessment from the beginning of section J (age 13 m 16 days – 16 m 15 days) instead, and if still not successful from the beginning of section I (age 11 m 0 days – 13 m 15 days). If this was still not successful, the assessment was aborted; the child received only the points for the items up to the end of section H.

Three child development outcomes, mean composite psychomotor, cognitive and language development scores, were calculated from the BSID-III subtest scores as specified in the BSID-III manual (28). First each subtest score was converted to a scaled score between 1 and 19 using age-specific conversion tables in the BSID-III manual – these scaled scores allow comparability between subtest results as the number of items (and therefore maximum possible score) in the subtests varies from 48 to 91. The scaled scores on the gross and fine motor tests were then added together as were the scores for receptive and expressive language to give overall psychomotor and language scaled scores. The three domain scaled scores were then converted to composite scores, which were designed to have a mean of 100 and standard deviation of 15 in the reference population; there are two different conversion tables in the manual, one for the psychomotor and language scaled scores which have a range of 2–38, and one for the cognitive scaled score with a range of 1–19.

The OAs also weighed and measured the children. Weight was measured to the nearest 0.01 kg using SECA-384 electronic scales which were calibrated weekly. When possible, the child was weighed without their clothes. If this was not possible, the child was weighed fully clothed and the mother then asked to change the clothes and give the original clothes to the OA to be weighed; this weight was then subtracted from the weight measured. Length was measured to the nearest 0.1 cm using the SECA-417 infantometer. The mother was asked to remove the child's shoes and lay them down on the board.

One of the OAs then cupped their hands over the child's ears and held their head against the end of the measurement board. The other then ensured that the child's body was straight on the board, placed one hand on the child's legs to stabilise them and brought the footpiece upwards toward the child's feet which were held perpendicular to the board. This OA then read aloud the length board reading and this was recorded by the first assessor. Height for age, weight for age and weight for height z-scores were calculated using the WHO Child Growth Standards for preschool children released in 2006 (29).

All three BSID composite scores (BSID-CS) plus the height for age z-score (HAZ) were designated as *primary impact outcomes*. Weight for age (WAZ) and weight for height (WHZ) z-scores were designated *secondary impact outcomes*.

Intermediate outcomes

The two main SPRING child development and growth intermediate outcomes reflect the quality of the home environment for child development assessed using the Home Observation for Measurement of the Environment Infant-Toddler version (HOME-IT) inventory (30, 31) and the quality of infant feeding practises assessed using a questionnaire based on the WHO infant and young child feeding (IYCF) indicators (32). These were assessed within -7 days to $+21$ days of the date the child reached 12 months of age by OAs working in pairs. These assessments took about 2 h to complete. The intermediate outcomes are mean HOME-IT score (*primary*) and % children receiving the WHO minimum acceptable diet (*secondary*), as described in the following paragraphs. Three other *secondary* outcomes, reflecting IYCF guidelines for the first 6 months of life and based on data collected through the surveillance system, were % babies: breastfed within an hour of birth, exclusively breastfed in period 4–5 m and received solids/semisolid food at 6 months of age.

The HOME-IT inventory includes 45 items which cover six subscales: Responsivity (11 items) of the primary caregiver captures communicative and affective interactions between caregiver and child; Acceptance (8 items) assesses how caregivers discipline the child and acceptance of less than desirable behaviour; Organisation (6 items) looks at how the child's time is organised outside the family house and what their personal space looks like; Provision of age appropriate play and Learning materials (9 items); Parental Involvement (6 items) captures how the caregivers interact physically with the child and Variety (5 items) explores how the child's routine is designed to include social interactions with people other than the primary caregiver. Each item is scored 1 (yes) or 0 (no) based on observation or elicited through questions. An example of the former is “Mother spontaneously vocalises to the child at least twice during the interview” and an example of the latter is “Children of your child's age can be difficult to manage. Sometimes they love to play in things that get them all messy and dirty—mud, water, their food, and so on. Is your child allowed to do this?” The number of positive responses is summed to yield a total HOME-IT score. The inventory takes about an hour to administer and to give adequate opportunity to observe mother–child interactions.

The IYCF questionnaire assesses the child's nutritional input during the previous 24-h period described as “the whole day yesterday or last night.” Questions covered breastfeeding, ORS, medication, liquids drunk, the specific foods the child had eaten elicited through a narrative approach from the time the child woke to the time they slept, the number of meals the child had, and the mother's estimate of

the total amount eaten. The food items were categorised into 15 types in the following 6 groups: starchy food, fruit and vegetables, oil & fat and condiments, sugary foods, milk products and non-vegetarian food (eggs, fish/seafood, meat, offal), with multiple entries possible for an item. The responses were checked against the WHO criteria for the minimum acceptable diet at age 12 months defined as:

- Breastfed (bf) or had 2+ milk feeds in the last 24h, AND
- Had food from 4 or more food groups (dairy included as food group for non-bf), AND
- Had 3 or more meals (if bf), 4 or more meals (if non-bf)

In India, the IYCF questionnaire was administered to all mothers who had a 12m assessment and not just those whose children were recruited for the 18m CDA.

Cultural adaptation

All evaluation data were collected using standardised protocols by surveillance fieldworkers (FWs) and by outcome assessors (OAs), who were independent to the CWs. It was not possible to achieve blinding of cluster allocation for surveillance FWs as they were resident in the clusters. However, every effort was made to ensure blinding of the OAs who carried out assessments at 12 and 18 months of age. A systematic process of cultural adaptation was used for all instruments (33). This comprised: (a) Translation of the psychometric instruments into the local languages spoken by residents in the trial clusters, and adaptation of the testing materials for the local context; (b) Ensuring technical equivalences; (c) Cognitive interviews with respondents and project staff (field research); (d) Modifications of translated versions, based on the field research; (e) Pretesting, including further modification; (f) training of assessors including establishing an inter-rater reliability of at least 70–80%; and (g) Pilot-testing, including testing of standard operating procedures.

Sample size

The SPRING trial aimed to recruit sufficient mother-newborn dyads to allow assessment at 18 months of age of at least 40 children in each of the 24 clusters in India and 50 in each of the 20 clusters in Pakistan, conservatively allowing for 20% loss of follow-up to 12 months of age and a further 20% follow-up loss to 18 months of age. These sample sizes were sufficient to give 90% power to detect effect sizes of 0.34SD in HAZ and 0.38SD in BSID-CSs plus 80% for gender-specific analyses. We used an estimated intra-cluster coefficient (ICC) of 0.035 for HAZ, based on the median value for rural areas reported in a review of ICCs of stunting based on height for age z-scores in DHS surveys (34). The ICC used for the BSID-CSs was 0.05; this was the ICC observed in the evaluation of the effectiveness of a parenting programme in Bangladesh to address early childhood health, growth and development, as calculated from the reported design effect (35).

Randomisation and masking

Equal numbers of clusters in each site were randomised to intervention and control groups using baseline information collected

at enrolment into the surveillance system from mothers with young children and a restricted randomisation procedure (36) to ensure balance in each site with respect to key factors related to the main trial impact outcomes. This used the following three criteria for the absolute maximum difference between intervention and control groups of: 0.5% for the percentage of children aged 18–30 months who were stunted ($HAZ < -2$); 2.5% for the percentage of mothers with children aged less than 5 years who had received no education; and 2.5% for the percentage of mothers with children aged less than 5 years who had delivered their youngest child in a health facility. All three measures are key determinants of child health. Stunting was chosen as the key restriction measure as it is a strong determinant of a child failing to achieve their developmental potential.

All possible allocation schemes were generated (total: 184,756 Pakistan; 2,704,156 India) and the subset meeting the criteria identified [Pakistan: 6,750 (3.7%); India: 527,776 (19.5%)]. These schemes were checked for anomalies in the frequency of co-allocations of pairs of clusters and one allocation scheme then selected at random by the trial statistician (LG) using a computer program. The allocation was shared with the SPRING implementation teams but not with the trial conduct teams.

It was not possible to achieve blinding of cluster allocation for the surveillance FWs as they were resident in the clusters. However, every effort was made to ensure blinding of the OAs who carried out assessments at 12 and 18 months of age. A strict triple blind approach was also put in place during the analysis and interpretation of the trial results. Blind analyses of trial outcomes were first discussed by the Trial Steering Committee (TSC) and Data Safety Monitoring Board (DSMB) with clusters randomly allocated to “meaningless” groups X and Y by the trial statistician using the `runiform()` random number generator in Stata v13. This was to agree the exact analyses to be used in reporting the trial findings and to ensure that all data procedures, methodological and statistical decisions were completed and agreed with the DSMB and TSC members before the true results were revealed, to minimise biases (37). Partially-blind analyses were then presented by groups P and Q, corresponding to intervention and control groups. The findings were then discussed, and the interpretation of any differences agreed, ignorant to the knowledge of which group was intervention and which control. A sealed envelope breaking the code was then handed to the Chair of the TSC identifying which of P and Q is the intervention group and which the control. Interpretation of findings could not be changed at this stage.

Statistical analysis

All analyses are intention to treat and include all data from trial mothers and infants, regardless of their exposure to intervention activities. Multi-level mixed effects regression models have been used to control for the clustered nature of the data. Specifically, the cluster indicator was included as a random intercept in regression models.

Binary outcomes (e.g., whether or not an infant was receiving the WHO minimum acceptable diet) were assessed by mixed effects logistic regression, with effect sizes presented as risk ratios. These were calculated post-estimation using marginals from the logistic regression model with 95% confidence intervals (Cis) determined using the delta method (38). Continuous outcomes (child development and HOME scores, HAZ, WAZ, and WHZ) were assessed by mixed

effects linear regression. The differences in mean outcomes between the two groups are also presented as effect sizes calculated as the differences divided by their pooled standard deviation; 95% CIs are given for both. Together with 95% CI.

Additional robustness check analyses were carried out to take account of factors that could have a strong relationship with the ECD and growth outcomes, and to check that no bias resulted from these. This included adjustment for month of birth, socio-economic status (SES) score (calculated using principle components analysis using data on mother, household demographics and animal and other asset ownership) and cluster level baseline factors used in the restricted randomisation (% stunting among children aged 18–30 months, % of mothers with no education among mothers with children aged less than 5 years and % of youngest children less than 5 years of age delivered in a facility). The robustness of the results from the cluster randomisation analysis strategy using random effects regression were then checked against results using randomisation inference (RI), which was run with 1,000 simulated re-randomisations of each outcome (39).

Economic evaluation

The financial and economic costs of the SPRING intervention were estimated from the provider perspective (40, 41), using a step-down approach (42). The provider costs were those incurred in the development and implementation of the intervention. The cost data were sourced from the financial accounts of the implementing institutions and entered annually into a costing tool created in Excel. Financial costs were converted to economic costs, i.e., any donated goods or volunteer time were added to the cost sheets and assigned a current market value (43, 44). Key informant interviews with intervention staff assisted in identifying donated or subsidised items, and in allocating joint costs between programme components. The costing spanned the start-up and implementation periods. Start-up costs were differentiated from implementation costs, and research costs were not included in the analysis.

The total and average annual provider costs of the SPRING intervention package implemented in Pakistan and India were estimated. Costs were calculated in current prices in Pakistani and Indian Rupees, and converted to International Dollars to facilitate comparison with similar studies. All costs were adjusted for inflation using the Consumer Price Index for Pakistan and India, discounted at 3% per year, and converted to 2017 International Dollars (INT\$) using the 2017 Purchasing Power Parity (PPP) conversion factor for both countries. The local conversion unit used to calculate 2017 INT \$ for Pakistan was 28.77 and for India was 17.45 (45).

Results

Trial flow and recruitment

Figure 2 shows the trial profiles for India and Pakistan. In India, 5,117 babies were identified by the surveillance system who were born alive on or after 18 June 2015, the date of full implementation of the SPRING Kilkari intervention, with the 1744 born up to April 2016 potentially eligible for the child development assessments (CDA) at 12

and 18 months. 1726 (99%) of these babies met the eligibility criteria and were recruited into the trial. Similar numbers for Pakistan were 5,048 born on or after 2 May 2014, the date of full implementation of SPRING Roshan Kal with 1,646 identified as potentially eligible for the CDAs and 1,631 (99%) recruited. Exclusion criteria were child not living with mother at time of assessment, major congenital defect, and mother not being able to complete the assessment.

The 12-month completed assessment rates were similar in India and Pakistan, with assessments completed for 1,303 (75.5%) of the recruited mother-baby dyads in India and 1,234 (75.7%) in Pakistan. There was a 6.6% loss to follow-up in India and 9.1% in Pakistan due to maternal or child deaths or having moved away. In addition, 17.6% were lost in India and 15.3% in Pakistan due to consent refusal for the assessment or the mother/child being temporarily unavailable or ill on the scheduled assessment day. Further loss to follow-up between the 12- and 18-month assessments was 2.6% in India and 4.4% in Pakistan with a total of 1,466 children scheduled for 18-month outcome assessment in India and 1,298 in Pakistan. Of these, assessments were done with 1,443 children in India, 83.6% of those recruited, and 1,016 (62.3%) in Pakistan. The follow-up rate for the 18-month assessment in India exceeded that expected based on the allowed for losses of 20% between birth and 12 months, and a further 20% between 12 and 18 months in the sample size calculations. The follow-up rate in Pakistan was similar to that planned. Assessment rates were comparable among participants in the control and the intervention groups as can be seen in Figure 2. In India, the percentage assessed at 18 months was 85.4% in the control and 81.8% in the intervention group, a difference of -3.6% (95% CI $-8.31, 1.08$; $p = 0.131$). In Pakistan, the percentage was 64.1% in the control and 61.9% in the intervention group, a difference of -2.2% ($-6.8, 2.5$; $p = 0.368$).

Comparability between intervention groups

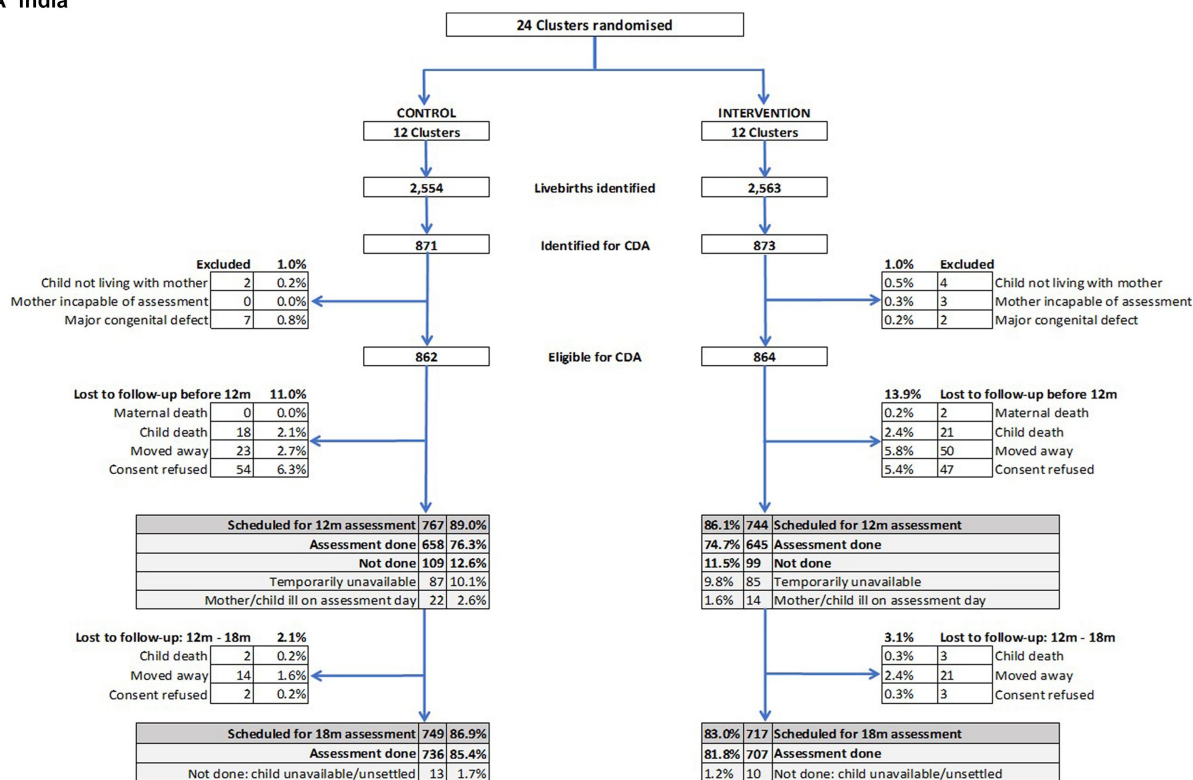
There was excellent comparability at recruitment between intervention and control groups arms with respect to key characteristics for babies who were assessed at 18 months for impact outcomes (Table 2). There was also good comparability between those who were assessed and those who were not in both sites with two exceptions. In India there was a lower rate of facility deliveries (94.3% versus 98.3%; $p = 0.006$) among babies who were not assessed at 18 months compared to those who were, and in Pakistan there was a percentage of mothers with no education (18.6% versus 13.4%, $p = 0.005$).

Impact of SPRING

The SPRING intervention failed to have an impact in either India or Pakistan on child development outcomes (Table 3) or growth (Table 4) at 18 months of age, or on the HOME-IT scores of the quality of the home environment for child development at 12 months of age (Table 5).

However, it did appear to have had some impact on reported feeding practices at 12 months of age (Table 6). The percentage of children in the SPRING intervention group who were receiving diets

A India



B Pakistan

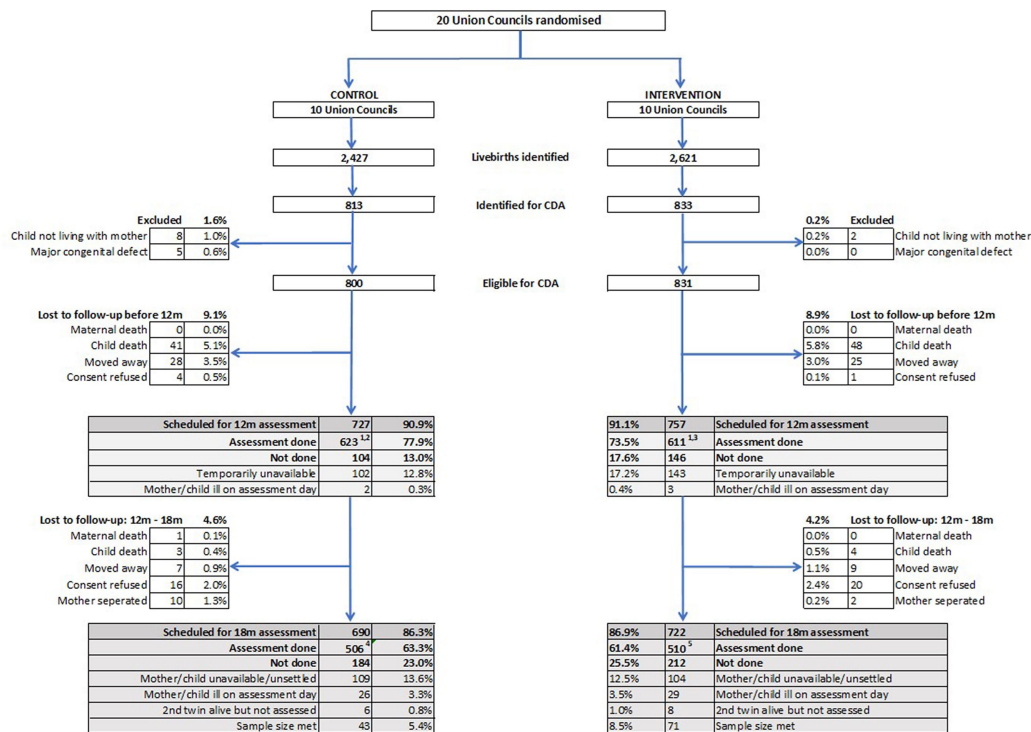
¹ HOME-IT not completed for 1 child² Feeding questionnaire not completed for 19 children³ Feeding questionnaire not completed for 18 children⁴ Height/Weight not completed for 1 child⁵ Height/Weight not completed for 3 children

FIGURE 2

Trial profiles for babies recruited for child development assessment (CDA) at 18 months of age. (A) India. The 12m feeding questionnaire was administered to all mothers who had a 12m assessment and not just those whose children were recruited for the 18m CDA, giving an additional 365 children in the control arm and 351 children in the intervention arm. (B) Pakistan.

TABLE 2 Comparability at recruitment between trial arms for participants with an 18month CDA.

Indicator	Control	Intervention	I-C Difference (95% CI)	<i>p</i>
(A) India				
Number with 18-month assessment	736	707		
% Mothers no education	6.3% (46)	5.9% (42)	−0.34% (−3.10, 2.42)	0.809
Maternal education level attained*: mean (sd)	2.91 (1.44)	2.99 (1.46)	0.06, (−0.26, 0.38)	0.717
% scheduled/backward caste/tribe (<i>n</i>)	58% (427)	62.4% (441)	6.67% (−16.23, 29.57)	0.568
% poorest (lowest 2 quintiles) (<i>n</i>)	42.7% (314)	41.3% (292)	−0.49% (−12.63, 11.65)	0.937
% Male (<i>n</i>)	54.6% (402)	52.3% (370)	−2.28% (−7.60, 3.04)	0.401
% Twins/Triplets (<i>n</i>)	1.4% (10)	1.4% (10)	0.00% (−1.08, 1.08)	0.994
% Delivered in facility (<i>n</i>)	98.1% (722)	98.4% (696)	0.35% (−1.00, 1.69)	0.614
Mean age of mother at delivery (sd)	22.1 (3.7)	22.5 (3.8)	0.360 (−0.232, 0.952)	0.233
Mean age of child at assessment (sd)	18.4 (0.28)	18.3 (0.32)	−0.03 (−0.17, 0.11)	0.676
Mean SES score (sd)	−0.07 (2.66)	−0.06 (2.69)	−0.019 (−0.710, 0.673)	0.957
(B) Pakistan				
Number with BSID-III assessment (18 m)	505 ¹	510		
% Mothers no education	12.3% (62)	14.1% (72)	1.66% (−4.10, 7.43)	0.572
Maternal education – number of years: mean (sd)	7.9 (4.18)	7.8 (4.38)	−0.15 (−0.90, 0.60)	0.702
% poorest (lowest 2 quintiles) (<i>n</i>)	39.6% (200)	42.2% (215)	2.2% (−11.16, 15.62)	0.744
% Male (<i>n</i>)	53.9% (272)	50.6% (258)	−3.28% (−9.94, 3.39)	0.336
% Twins/Triplets (<i>n</i>)*	1.2% (6)	1.2% (10)	0.77% (−0.76, 2.30)	0.328
% Delivered in facility (<i>n</i>)	91.7% (463)	89.2% (455)	−2.41% (−6.45, 1.63)	0.242
Mean age of mother at delivery (sd)	27.0 (4.50)	26.6 (4.52)	0.42 (−1.31, 0.98)	0.134
Mean age of child at assessment (sd)	18.7 (0.30)	18.7 (0.30)	0.01 (−0.08, 0.11)	0.791
Mean SES score (sd)	0.004 (2.326)	−0.093 (2.492)	−0.092 (−0.74, 0.56)	0.781

¹Excludes 1 child with missing information. *Only one twin/triplet assessed at 18m.

at 12 months of age that met the WHO minimum acceptable criteria compared to the percentage of those in the control group was 35% higher in India (95% CI: 4–75%, $p = 0.023$) and 45% higher in Pakistan (95% CI: 15–83%, $p = 0.002$). In both countries this appears to be largely due to an increase in the percentage of babies receiving 4 or more food groups. In Pakistan but not India, there was also a modest increase increase ($p = 0.016$) in the percentage receiving the recommended number of meals. However, the majority of children in the intervention group were still not receiving adequate diets; this was 68.5% in India and 57.7% in Pakistan.

There were also major gaps in recommended feeding practises in the first 6 months of life (Table 7). Only 50.4% of babies in India were breastfed within the recommended hour of birth and only 12% in Pakistan; the rates were comparable in intervention and control groups. The exclusive breastfeeding rates in the fifth and sixth months of life (age 4–5 m) were higher in the intervention groups in both countries but these were still below 50%; the majority the majority of babies had stopped exclusive breastfeeding before the fifth month. In India, the intervention successfully tackled the problem of late weaning, highlighted as a major problem during the formative research – the percentage of infants receiving solids/semisolid food at the recommended age of 6 months was

considerably higher in the intervention group than the control group, 51.9% compared to 28.8%, an estimated increase of 79% (95% CI 37–134%, $p < 0.001$), although almost half the children were still not receiving food at this age. There was no similar improvement in Pakistan where the rates were much higher in both groups with the majority (70.7%) of infants receiving solids/semisolid food at 6 months.

Intra-cluster coefficient for outcome measures are presented in Table 8. They are considerably lower than the assumed values for the primary outcomes of 0.05 for the BSID scores and 0.35 for HAZ used in the sample size calculations, with the exception of the composite language score in India which had an ICC of 0.78.

Robustness checks

Additional analyses adjusted for month of birth, socio-economic status (SES) score and cluster level baseline factors (% stunting among children aged 18–30 months, % of mothers with no education among mothers with children aged less than 5 years and % of youngest children less than 5 years of age delivered in a facility) did not materially change the results for any outcome. Similarly, using randomisation inference rather than random effects regression provided estimated results which were almost identical.

TABLE 3 Effect of the SPRING intervention on early child development: assessed at 18months of age using BSID-III.

Outcomes	Mean scores (SD)			Intervention – Control (I-C) difference (95% CI)	Effect size (95% CI)	p value
	Overall	Control	Intervention			
India						
No. of children	1,443	736	707			
BSID-III: composite psychomotor score	94.5 (9.79)	94.4 (9.87)	94.5 (9.70)	0.06 (−1.79, 1.92)	0.00 (−0.10, 0.11)	0.946
BSID-III: composite cognitive score	92.6 (10.69)	92.9 (10.48)	92.3 (10.90)	−0.62 (−2.66, 1.43)	−0.03 (−0.13, 0.07)	0.554
BSID-III: composite language score	90.5 (14.31)	91.0 (14.52)	90.0 (14.07)	−0.96 (−4.54, 2.62)	−0.03 (−0.13, 0.08)	0.601
Pakistan						
No. of children	1,016	506	510			
BSID-III: composite psychomotor score	98.1 (12.05)	98.7 (11.65)	97.5 (12.41)	−1.18 (−2.66, 0.30)	−0.10 (−0.22, 0.02)	0.118
BSID-III: composite cognitive score	90.2 (9.65)	90.3 (9.75)	90.1 (9.56)	−0.16 (−1.86, 1.54)	−0.01 (−0.13, 0.11)	0.852
BSID-III: composite language score	93.5 (12.45)	93.9 (12.73)	93.0 (12.17)	−0.90 (−2.72, 0.93)	−0.06 (−0.18, 0.06)	0.336

TABLE 4 Effect of the SPRING intervention on child growth, measured at 18months of age.

	Mean Z-Scores (SD)			I-C difference (95% CI)	Effect size (95% CI)	p-value
	Overall	Control	Intervention			
India						
No. of children	1,443	736	707			
Height for age z-score	−1.79 (1.08)	−1.80 (1.12)	−1.77 (1.04)	0.03 (−0.14, 0.21)	0.02 (−0.08, 0.12)	0.710
Weight for age z-score	−1.36 (1.01)	−1.37 (1.05)	−1.36 (0.97)	0.00 (−0.15, 0.15)	0.00 (−0.10, 0.10)	0.997
Weight for height z-score	−0.69 (0.93)	−0.68 (0.94)	−0.70 (0.92)	−0.02 (−0.13, 0.08)	−0.02 (−0.14, 0.08)	0.677
Pakistan						
No. of children	1012 ¹	505	507			
Height for age z-score	−1.16 (1.23)	−1.14 (1.24)	−1.19 (1.21)	−0.05 (−0.29, 0.18)	−0.03 (−0.15, 0.09)	0.648
Weight for age z-score	−1.08 (1.13)	−1.11 (1.13)	−1.05 (1.13)	0.06 (−0.12, 0.24)	0.04 (−0.08, 0.17)	0.511
Weight for height z-score	−0.72 (1.15)	−0.78 (1.15)	−0.66 (1.16)	0.12 (−0.08, 0.31)	0.08 (−0.05, 0.19)	0.244

¹Height and weight measurements not available for 4 children with BSID-III assessment; 1 in the control group and 3 in the intervention group.

Economic evaluation

In Pakistan, the total incremental cost from the provider perspective of SPRING home visits over the duration of the programme was INT\$ 654,164, and the average annual cost of delivery was INT\$ 167,021. In India, the total provider cost of SPRING home visits was INT\$ 727,717, of which INT\$ 283,994 was attributed to the salaries of the project-appointed KWs. The average annual cost of delivery in India was INT\$ 291,887.

Discussion

The SPRING programme has several strengths. It evaluated a culturally appropriate intervention which was based on existing global guidelines and designed using best practise in relation to formative research, counselling practises and supportive supervision (24–27, 46). SPRING was also designed from the outset to test the delivery using two different feasible delivery models for scale-up that could be taken up by governments. This contrasts with

most trials to date which have provided evidence that parent-focussed face to face interventions promoting nurturing care can be effective in improving child development outcomes (15–17). These have mostly tested interventions delivered to at-risk or small populations and/or with considerable levels of input to ensure quality of the intervention delivery. These high intensity interventions are neither affordable nor feasible at scale in most low- and middle-income countries, where the need is greatest. In Pakistan, SPRING worked in close partnership with the long standing LHW programme, to integrate the SPRING content and approach into the monthly home visits provided by the LHWS. In India, homes visits were implemented by a civil society organisation (NGO) that trained a new cadre of community agents to work alongside the existing services provided by ASHAs and Anganwadi workers.

SPRING was evaluated through rigorously designed cluster randomised controlled trials in both settings accompanied by detailed economic and process evaluations. The trials had high follow-up rates covering large whole-population samples and culturally adapted outcome measures. These trials show that the

TABLE 5 Effect of the SPRING intervention on intermediate outcomes assessed at 12 months of age: HOME-IT Mean Scores.

Total and sub-scale scores (no. of items involved)	Mean HOME-IT scores (SD)			I-C difference (95% CI)	Effect size (95% CI)	p-value
	Overall	Control	Intervention			
India						
No. of children	1,303	658	645			
Total (45)	31.6 (4.12)	31.2 (4.30)	32.1 (3.87)	0.85 (−0.35, 2.04)	0.08 (−0.03, 0.19)	0.164
Responsivity (11)	9.2 (1.62)	9.1 (1.72)	9.3 (1.50)	0.23 (−0.27, 0.74)	0.05 (−0.06, 0.16)	0.361
Acceptance of child's behaviour (8)	6.8 (0.86)	6.8 (0.88)	6.7 (0.84)	−0.05 (−0.22, 0.11)	−0.03 (−0.15, 0.08)	0.521
Organisation of the environment (6)	4.7 (1.02)	4.6 (1.04)	4.8 (0.99)	0.19 (−0.01, 0.39)	0.11 (−0.01, 0.22)	0.061
Learning materials (9)	4.9 (1.78)	4.7 (1.81)	5.2 (1.72)	0.43 (−0.05, 0.91)	0.10 (−0.01, 0.21)	0.078
Parental involvement (6)	4.0 (0.86)	3.9 (0.88)	4.0 (0.84)	0.11 (−0.10, 0.32)	0.06 (−0.05, 0.16)	0.304
Variety (5)	2.1 (0.88)	2.1 (0.87)	2.1 (0.88)	−0.06 (−0.18, 0.06)	−0.06 (−0.17, 0.06)	0.345
Pakistan						
No. of children	1232 ¹	622	610			
Total (45)	27.3 (5.06)	26.8 (4.91)	27.7 (5.19)	0.92 (−0.89,2.74)	0.06 (−0.05, 0.17)	0.320
Responsivity (11)	6.7 (1.94)	6.6 (1.93)	6.8 (1.94)	0.27 (−0.43,0.96)	0.04 (−0.07, 0.16)	0.448
Acceptance of child's behaviour (8)	6.5 (1.19)	6.5 (1.05)	6.5 (1.32)	−0.06 (−0.30,0.18)	−0.03 (−0.14, 0.09)	0.638
Organisation of the environment (6)	3.5 (1.26)	3.3 (1.24)	3.6 (1.27)	0.27 (0.08,0.46)	0.15 (0.05, 0.26)	0.005
Learning materials (9)	3.9 (2.27)	3.8 (2.26)	4.1 (2.28)	0.27 (−0.38,0.91)	0.05 (−0.07, 0.16)	0.420
Parental involvement (6)	4.0 (0.90)	3.9 (0.93)	4.0 (0.87)	0.12 (−0.20,0.44)	0.04 (−0.07, 0.16)	0.454
Variety (5)	2.7 (0.72)	2.7 (0.76)	2.7 (0.69)	0.05 (−0.06,0.17)	0.05 (−0.06, 0.16)	0.361

¹HOME-IT inventory not completed for 2 children with 12 m CDA; 1 in the control group & 1 in the intervention group.

TABLE 6 Effect of the SPRING intervention on intermediate outcomes assessed at 12 months of age: complementary feeding (CF) practices.

	% Infants (n/N)			RR (95% CI)	p-value
	Overall	Control	Intervention		
India					
No. of children	1,303 ¹	658	645		
Infants meeting WHO criteria for minimum acceptable diet at 12 months of age	27.5% (549)	23.7% (239)	31.5% (310)	1.35 (1.04, 1.75)	0.023
- Receiving recommended number of meals	75.8% (1513)	73.9% (746)	77.9% (767)	1.06 (0.97, 1.15)	0.194
- Receiving 4 or more food groups	34.4% (686)	30.4% (307)	38.5% (379)	1.27 (1.05, 1.55)	0.016
Pakistan					
No. of children	1,197 ²	604	593		
Infants meeting WHO criteria for minimum acceptable diet at 12 months of age	35.8% (429)	29.5% (178)	42.3% (251)	1.45 (1.15, 1.83)	0.002
- Receiving recommended number of meals	87.4% (1046)	85.1% (514)	89.7% (532)	1.05 (1.01, 1.10)	0.016
- Receiving 4 or more food groups	44.9% (537)	38.7% (234)	51.1% (303)	1.33 (1.08, 1.65)	0.008

¹In India, 12 m feeding questionnaire was administered to all mothers who had a 12 m assessment and not just those whose children were recruited for the 18 m CDA, giving an additional 716 children, 365 in the control group and 351 children in the intervention group. ²In Pakistan, feeding questionnaire was not completed for 37 children with 12 m assessment: 19 in the control group and 18 in the intervention group.

SPRING intervention failed to have any impact on child development or growth in either India or Pakistan. It did appear to have some impact on reported feeding practises (both breast- and complementary-feeding) in both countries, but this did not translate into change in growth outcomes. It is important to note

that the majority of children in the intervention arm continued to receive inadequate diets: 68.5% in India and 57.7% in Pakistan, and late weaning remained a major problem in India. It is also important to note that the criteria for the WHO minimum acceptable diet, which are based on the number of meals and the diversity of the

TABLE 7 Effect of the SPRING intervention on intermediate outcomes collected during surveillance visits: breastfeeding and start of weaning.

	% Infants (n/N)			RR (95% CI)	<i>p</i> -value
	Overall	Control	Intervention		
India ^{1,3}					
Babies breastfed within an hour of birth	50.4% (2,535/5031)	50.5% (1,269/2513)	50.3% (1,266/2518)	1.00 (0.88–1.14)	0.977
Exclusively breastfed in period 4–5 m ⁴	40.1% (1753/4373)	32.4% (722/2225)	48.0% (1,031/2148)	2.21 (0.90–5.44)	0.084
Infants receiving solids/semisolid food at 6 months of age ⁵	39.9% (849/2126)	28.8% (317/1100)	51.9% (532/1026)	1.79 (1.37–2.34)	<0.001
Pakistan ^{2,3}					
Babies breastfed within an hour of birth	12.0% (581/4831)	14.1% (326/2315)	10.1% (255/2516)	0.69 (0.36, 1.29)	0.243
Exclusively breastfed in period 4–5 m ³	34.8% (1,194/3436)	30.7% (509/1656)	38.5% (685/1780)	1.29 (1.05, 1.59)	0.015
Infants receiving solids/semisolid food at 6 months of age 5	70.7% (1,116/1579)	73.2% (567/773)	68.1% (549/806)	0.93 (0.84, 1.03)	0.143

¹India: 5117 babies were born on or after 18 June 2015 and enrolled in the surveillance system up to 01 July 2017. Breastfeeding data were collected for 5,032 babies; data on breastfeeding initiation was missing for one of these. This is less than the total number as breastfeeding data were not collected from children who had died by the time the birth was identified by the surveillance fieldworker. ²Pakistan: babies were born after 2 May 2014 and enrolled in the surveillance system up to 30 April 2016. Breastfeeding data were collected for 4,831 babies. ³The number of babies with breastfeeding data is less than the total number of babies as breastfeeding data were not collected from children who had died by the time the birth was identified by the surveillance fieldworker. ⁴Some babies contributed more than one entry to this age period, and some contributed none depending on when their surveillance visits occurred. All analyses have been adjusted for these repeated measures. ⁵Based on infants who had a surveillance visit when they were 6 months of age.

TABLE 8 SPRING outcomes: intraclass correlation coefficients (ICCs).

Outcome	India	Pakistan
BSID-III: composite psychomotor score	0.0377481	0.0000000
BSID-III: composite cognitive score	0.0392897	0.0190526
BSID-III: composite language score	0.0787696	0.0083743
Height for age z-score	0.0245728	0.0251728
Weight for age z-score	0.0159574	0.0123319
Weight for height z-score	0.0034404	0.0190417
HOME-IT Score	0.1198204	0.1523026
% Infants meeting WHO criteria for minimum acceptable diet	0.0492589	0.0535477

diet, do not guarantee that the baby is necessarily receiving an adequate amount of food.

This lack of impact on early child development in both settings in the SPRING trial is in contrast to the impact seen in the smaller scale effectiveness trials (17) that informed the WHO guideline on improving early child development (18). This evidence included 18 trials with combined caregiving and nutrition interventions (18), including the Pakistan Early Child Development Study (PEDS) (47). The PEDS study demonstrated, as a proof of principle, that ECD interventions can be effectively delivered through the LHW programme; significant impacts were found for a range of ECD outcomes but not for growth.

The detailed process evaluation reported in a companion paper (22) explores what could have caused this lack of impact in the SPRING trial, and draws lessons that can be learned for future scale-up. Implementation was sub-optimal in both settings. Problems due to political and logistical barriers, workforce constraints, low supervision and a lack of early child development skills development impacted the quality of home visits when using the existing LHWs in Pakistan. The intervention specific KWs in India conducted higher quality visits, but coverage was low in part due to employing new workers and an empowerment approach to visit scheduling. Coaching caregivers on skills, a key intervention element, was sub-optimal in

both sites, and is likely to have contributed to caregiver perceptions that the intervention content was not new and was focused on play activities rather than interaction and responsiveness. In both sites caregiver time pressures was a key reason for low uptake among families who received visits. The embedding periods of 2–3 months were also not long enough to ensure all operational aspects were fully functioning.

The absence of an observable effect of the SPRING intervention in either trial on the main outcomes although disappointing has important policy implications for achieving feasible and effective scale up as countries increase their efforts to improve early child development, nutrition and growth. The findings emphasise that impacts achieved in efficacy or proof of principle trials may not be achieved when interventions are delivered routinely at scale. The findings are consistent with the experience of scaling up Crianca Feliz in Brazil which found no impact on a range of ECD outcomes and reported that rapid scale up was a barrier to achieving quality and consistency (48); this is an important example that coverage should not be prioritised at the expense of quality (49). A programme review of 10 country experiences of scaling up CW postnatal home visits also demonstrates the difficulty of achieving high coverage at scale, with most countries achieving less than 10% coverage and none achieving more than 20% coverage (50); the magnitude of this challenge should not be overlooked.

Integrating additional tasks into the workload of already overloaded and stressed CWs can be challenging in low-capacity contexts or weak health systems (51–54). Simply adding a child development and nutrition component is unlikely to be successful without additional resources and re-organisation of the goals of the existing community-based intervention. The India ‘NGO delivery model’ with project specific CWs is likely to mirror the way expansions will occur in many low- or middle-income countries, at least in the short term, as few have the established infrastructure, systems and experience with community-based workers, such as LHWs, into which the promotion of early child development and nutrition can be integrated. This model does not guarantee adequate coverage, however.

Programmes will need strategies to maximise both coverage and quality of intervention delivery, including having a clear strategy for scheduling visits, monitoring coverage and other process indicators, identifying and managing poor performers, and developing feedback loops for course correction. Rapid scale will therefore require careful attention to the establishment of strong administrative and management systems to support its implementation.

Data availability statement

The datasets presented in this study can be found in online repositories. The names of the repository/repository and accession number(s) can be found at: World Bank International Household Survey Network (IHSN) microdata catalogue (<https://catalog.ihnsn.org/catalog/7952/study-description>). LSHTM Data Compass data repository (<https://doi.org/10.17037/DATA.00003124>).

Ethics statement

The studies involving human participants were reviewed and approved by London School of Hygiene & Tropical Medicine (LSHTM) Research Ethics Committee (UK), the Ethical Review Committee at the Human Development Research Foundation (Pakistan) and the Sangath Institutional Review board (India). Approval was also granted by the Indian Council of Medical Research's Health Ministry Screening Committee (HMSC). Written informed consent to participate in this study was provided by the participants' legal guardian/next of kin.

Author contributions

BRK, SiS, RR, RL, SB, BA, NB, BK, JS, ZH, and AR designed the cluster randomised trials and data collection instruments. ZH, SZ, GD, AH, SiS, RL, BRK, and AR designed the content of the SPRING home visits intervention. SiS, RR, SA, DK, DV, and KS were responsible for the surveillance system and outcome data collection. LG, SP, RR, SB, SiS and SA designed and managed the data management system and scheduling of the surveillance visits and 12 and 18 month assessments. LG was the independent trial statistician responsible for the restricted randomisation. SeS was the independent trial statistician responsible for all the analyses presented in this manuscript. BRK wrote the first draft of the manuscript which was then reviewed by all authors. All authors contributed to the article and approved the submitted version.

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Conflict of interest

The authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

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EDITED BY

Nita Bhandari,
Center for Health Research and Development,
Society for Applied Studies, India

REVIEWED BY

Beena Koshy,
Christian Medical College & Hospital, India
Ravi Prakash Upadhyay,
Center for Health Research and Development,
Society for Applied Studies, India

*CORRESPONDENCE

Zelee Hill
✉ z.hill@ucl.ac.uk

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Can home visits for early child development be implemented with sufficient coverage and quality at scale? Evidence from the SPRING program in India and Pakistan

Zelee Hill^{1*}, Shamsa Zafar², Seyi Soremekun³, Siham Sikander^{4,7}, Bilal Iqbal Avan³, Reetabrata Roy^{3,5}, Sarmad Aziz¹, Divya Kumar⁵, Nazia Parveen⁴, Shumaila Saleem⁴, Deepali Verma⁵, Kamal Kant Sharma⁵, Jolene Skordis¹, Assad Hafeez⁶, Atif Rahman⁷, Betty Kirkwood³ and Gauri Divan⁵

¹Institute for Global Health, University College London, London, United Kingdom, ²Fazaia Medical College, Air University, Islamabad, Pakistan, ³London School of Hygiene and Tropical Medicine, London, United Kingdom, ⁴Global Institute of Human Development, Shifa Tameer-e-Millat University, Islamabad, Pakistan, ⁵Sangath, Goa, India, ⁶Health Services Academy, Islamabad, Pakistan, ⁷Institute of Population Health, University of Liverpool, Liverpool, United Kingdom

Introduction: There is limited evidence from low and middle-income settings on the effectiveness of early child development interventions at scale. To bridge this knowledge-gap we implemented the SPRING home visiting program where we tested integrating home visits into an existing government program (Pakistan) and employing a new cadre of intervention workers (India). We report the findings of the process evaluation which aimed to understand implementation.

Methods and materials: We collected qualitative data on acceptability and barriers and facilitators for change through 24 in-depth interviews with mothers; eight focus group discussions with mothers, 12 with grandmothers, and 12 with fathers; and 12 focus group discussions and five in-depth interviews with the community-based agents and their supervisors.

Results: Implementation was sub-optimal in both settings. In Pakistan issues were low field-supervision coverage and poor visit quality related to issues scheduling supervision, a lack of skill development, high workloads and competing priorities. In India, issues were low visit coverage - in part due to employing new workers and an empowerment approach to visit scheduling. Coaching caregivers to improve their skills was sub-optimal in both sites, and is likely to have contributed to caregiver perceptions that the intervention content was not new and was focused on play activities rather than interaction and responsivity - which was a focus of the coaching. In both sites caregiver time pressures was a key reason for low uptake among families who received visits.

Discussion: Programs need feasible strategies to maximize quality, coverage and supervision including identifying and managing problems through monitoring and feedback loops. Where existing community-based agents are overstretched

and system strengthening is unlikely, alternative implementation strategies should be considered such as group delivery. Core intervention ingredients such as coaching should be prioritized and supported during training and implementation. Given that time and resource constraints were a key barrier for families a greater focus on communication, responsiveness and interaction during daily activities could have improved feasibility.

KEYWORDS

early child development, home visits, implementation, process evaluation, community health workers, community based agents, India, Pakistan

Introduction

The importance of early child development (ECD) interventions to improve short and long term outcomes and disrupt the intergenerational cycle of poverty is well recognized (1–5). ECD holds a central place in the Sustainable Development Goals, with multilateral support for implementation and scale up (6–9). Global guidelines recommend that all infants and children should receive responsive care and have early learning activities with their caregivers in the first 3 years of life (7). Interventions to achieve this include providing support for caregivers through individualized home visits and/or holding group sessions at home or in community spaces or through contacts at health facilities (5). In low and middle income settings interventions are most commonly community based and delivered by peer educators or community based agents (CBAs) who have some high school education and 1 to 2 weeks of ECD training (10).

We know from efficacy trials that community ECD interventions can improve child development outcomes in diverse settings, and can offset developmental risks such as poverty and malnutrition (5, 11, 12). However, evidence is lacking on effectiveness at scale, with a major gap in research on the ‘how to’ of ECD interventions (13–17). This lack of implementation evidence has been cited as a reason for the slow roll out of ECD programs in low and middle income countries (18). To support scale up we need to share implementation successes and failures and understand what processes and factors contribute to positive impacts, or lack of impact, in relation to the workforce, infrastructure needs, quality, coverage and demand (13, 16, 17, 19, 20).

To bridge the scalability knowledge-gap we implemented the SPRING program, which was designed from the outset to be feasible, affordable and appropriate for delivery at scale. SPRING designed and tested the impact of monthly home visits by CBAs to promote and support caregivers with responsive care, early learning and nutrition practices in India and Pakistan using a cluster randomized controlled trial design (21, 22). SPRING adapted WHO and UNICEF ECD and nutrition content (23, 24), and tested two delivery models for scale-up using CBAs: In Pakistan the intervention was called Roshan Kal (brighter tomorrow) and was integrated within the government Lady Health Workers program (25). In India the intervention was called Kilkaari (gurgling of a young child) and was delivered by a non-governmental organization (SANGATH) who employed a new cadre of intervention specific CBAs called Kilkaari workers (KWs). We refer to the Roshan Kal and Kilkaari programs collectively as the SPRING Program.

As reported in our companion paper, the SPRING Program did not achieve significant impacts on ECD or growth outcomes at 18 months of age (22). It is important to understand why this occurred, so that others can learn lessons for delivering community based ECD and nutrition interventions at scale. Embedded in the SPRING program was a process evaluation that aimed to understand implementation in relation to training, supervision, coverage, quality, acceptability and barriers and facilitators to behavior change among CBAs and families. In this paper we focus on the process evaluation findings that relate to ECD as this is where evidence is most lacking.

Materials and methods

The intervention

In Pakistan, SPRING was embedded in the government Lady Health Worker (LHW) program. The LHW program was established in 1994 and LHWs are well known and credible health workers in their communities. The LHW role comprises over 20 maternal and child health services including health education on breastfeeding and complimentary feeding, child growth monitoring, immunizations, family planning and basic curative care. Within the government program LHWs receive 15 months training, are aged 18–45 years, resident in the community they serve, have a minimum 8 years of education, are preferably married and are acceptable to the community. Each Union Council has 15–20 LHWs, each serving 150–200 households, they are supervised and monitored by a Lady Health Supervisor (25). LHWs conduct approximately 7 home visits per day and the SPRING content was integrated into these home visits.

In India the KWs were lay workers specifically identified, recruited, trained and supervised to only deliver the SPRING intervention. KWs were recruited by SANGATH with remuneration and characteristics similar to government frontline workers. They were resident in the community, had a minimum of 8th grade education, were married and had good communication skills. Each served a maximum of 100 eligible households. As new workers they had to identify eligible families so were asked to engage with local frontline workers and attend local community events such as Village Health Days to identify new pregnancies and mothers with young children.

In Pakistan SPRING was implemented in 10 predominantly rural Union Councils in Rawalpindi District by 150 LHWs; 70 of these

TABLE 1 Key SPRING content.

Age at visit	Nutrition related	Interaction and play (being responsive, follow child's lead, focusing on child, scaffolding, praise)
Pregnancy	Importance of/encouraging family support and involvement	Importance of play and interaction
	Iron, diet and rest during pregnancy	
	Early and responsive breastfeeding with love and care	
	No pre-lacteal feeds	
Neonatal period	Exclusive and responsive breastfeeding with love and care	Talking/singing and looking into the child eyes while breastfeeding or doing daily activities, caressing and cuddling, allowing freedom of movement of limbs
	Avoiding insufficient milk	
1-5 months	Exclusive breastfeeding until 6 months and then continued breastfeeding	Interacting through activities such as: following objects, grabbing and exploring objects, making sounds with rattles and by banging objects, singing, copying sounds and movements
	In the last visit before 6 months, introduce concept of weaning from 6 months	
6-11 months	Continued breastfeeding	Interacting through activities such as: peek a boo, rolling a ball, physical play such as bouncing, naming body parts and objects, finding objects, imitating actions
	Age dependent complementary feeding messages on:	
	- Responsive feeding - Frequency, variety, consistency, quantity - Hygiene - Adding “super” foods (e.g. butter or oil) - Finger food/self feeding - Enjoyable meal times - Avoiding “junk” foods (Pakistan only)	
	Importance of feeding for a sick child	
Second year	Continued breastfeeding	Interacting through activities such as: putting in and out, stacking, singing, following instructions, color matching, mark making, pulling, sorting, counting
	Eating with the family and balanced diet	

LHWs and the children in their catchment areas were included in the SPRING outcome evaluation. In India, SPRING was implemented in three blocks of the predominantly rural Rewari district in Haryana State by 54 KWs. The intervention was delivered to all pregnant women and families with children 0–2 year of age. The content (Table 1) was adapted based on formative research into current behaviors, and barriers and facilitators for adopting the desired ECD and feeding practices (26). In pregnancy, home visits focused on maternal health and sensitization about breastfeeding. Postnatal visits focused on caregiver-child interaction and play activities, breastfeeding, complementary and responsive feeding, with new messages introduced each month dependent on the age of the child.

SPRING was delivered using a counseling approach based on Cognitive Behavior Therapy techniques (27) which includes: family support; guided discovery using pictures; behavioral activation; empathic listening; problem-solving; and praise. Structured pre-tested counseling cards provided pictures for families to look at and instructions and key messages for the CBAs. In each visit approximately 4 messages were given – e.g. in postnatal visits this was two on nutrition and two on play and interaction with the infant. In Pakistan routine program messages were integrated into these counseling cards and families were also provided with a reminder calendar. The visits targeted the primary caregiver, and included providing information, problem solving and family engagement. The primary caregiver practiced play activities and received coaching and demonstrations from the CBA to enhance skills, self-efficacy and recall in relation to play

activities and responsivity. Community and health systems sensitization was also conducted.

CBAs received 8 days of skills based training, delivered in two phases to groups of 14–29 CBAs by SPRING supervisors – female social science graduates trained by a child development expert. Training included classroom sessions, participatory exercises, role play, discussions of videos and practical sessions with caregivers and children.

Monthly group supportive supervisory meetings were held in groups of 11–25 CBAs who shared experiences and supported each other, problem-solved and developed their skills. In Pakistan this was integrated into the LHW's routine monthly supervision meetings. During monthly one-to-one supportive field supervision, supervisors observed home visits and used a supervisory checklist to feedback on performance, problem solve and make suggestions on areas for improvement. The CBA to supervisor ratio was around 1:10 in India and 1:15 in Pakistan.

Process evaluation data collection

Quantitative data

Details of the quantitative process data collection can be found in Table 2. In brief, training knowledge gain was determined using a pre- and post-training test, group supervision coverage from program attendance record and field supervision from completed supervisory checklists. Data on visit coverage data came from the

TABLE 2 Quantitative process data collection methods.

Process domain	Data source	Content	Sample (n) = number of respondents
Training knowledge	Self-administered pre- and post-training multiple choice test	Knowledge of counseling, nutrition, play and interaction	All KWs (40) and LHWs (149) who attended the 8 days SPRING training
Group supervision coverage	Program attendance records	Number of supervision groups held and percent CBAs that attended	All KWs active during the evaluation period (n = 62) and evaluation zone LHWs* (69)
Field supervision coverage	Supervisor checklists completed	Percentage CBAs with a completed checklist	All KWs active during the evaluation period (n = 62) and evaluation zone LHWs* (69)
Visit coverage	Surveillance data from all women who had a pregnancy or infant under 2 years of age during the evaluation period	India: Visit by a maternal and child health worker in the last month and who they were** Pakistan: Visit by an LHW in the last month	India: 3446 women and 29,860 questionnaires Pakistan: 3237 women and 24,772 interviews
CBA skills	Supervisory checklists used in monthly observed supervision visits during the evaluation period	Percentage CBAs with a completed checklist with skills in: Counseling, family support, problem-solving and child stimulation.	All KWs active during the evaluation period (62 KWs and 1,398 checklists) and evaluation zone LHWs with at least one checklist completed* (68 LHWs with 381 checklists)
Duration of visit and use of job aids	Endline survey with primary caregiver	Duration of last visit and use of job aids	India: All 661 women with children under 2 years of age Pakistan: 120 randomly sampled women with children 0–11 months of age.

*Supervision focused on the evaluation zones in the last year of the program.

** Asked this way as the KWs in India were new and less easily identified.

SPRING surveillance system (22), implemented as part of the outcome evaluation, under which resident surveillance workers visited households every 8–10 weeks to collect outcome data. Data on visit quality were obtained from a supervisory checklist of 33–37 items, dependent on site and whether a pregnancy or child visit was being observed. The checklist covered counseling, family support, problem-solving and child stimulation with between 3 and 15 items for each of these domains. The checklist questions were not identical in each site, and to aid comparison we present a selection of overlapping indicators for each domain. Information on visit duration and the use of job aids was collected in a cross-sectional survey with caregivers.

Qualitative data

Data on acceptability of the intervention for families and the CBAs, and barriers to and facilitators for change were collected toward the end of implementation from four intervention clusters in each country. Data were collected by trained bilingual interviewers, who were not part of the implementation team. The clusters were selected to ensure a range of home visit coverage, and to reflect the diversity of the study area. Data were collected through narrative in-depth interviews (IDIs) with mothers and focus group discussions (FGDs) with mothers, grandmothers, and fathers. Supervisors were interviewed through FGDs in Pakistan and IDIs in India. Sample size was approximated based on when saturation had been reached in our previous studies in the area, and additional interviews and FGDs were added if needed. The methods, sample size and content are shown in Table 3.

IDI mothers were selected from the surveillance database to ensure that the sample had a variety of socio-demographic characteristics (age, education, parity, gender of the child, and socioeconomic status). Community FGDs participants were selected through community informants to have a range of parities,

education levels and socio-economic status and stratified for homogeneity where mixed groups could inhibit participant interaction. Topic guides were developed in local languages and pilot tested before data collection. All Interviews and FGDs were audio recorded in addition to notes taken. Narratives and IDIs were turned into expanded notes using the audio recordings to add verbatim quotes (28). Debriefs were held regularly during data collection to provide feedback to interviewers and discuss themes and saturation. These discussions and the topic guides were used to develop a deductive coding template, with inductive codes and themes added during analysis. A framework analysis approach was used for the narrative IDIs, and thematic analysis using a phenomenological approach for the other IDIs and FGDs (29, 30). In the results when reporting on the individual countries we refer to LHWs and KWs and when reporting combined results we refer to CBAs.

Results

Training and supervision

Training increased overall ECD and nutrition knowledge scores among LHWs from 50 to 91%, and among KWs from 70 to 85%. Areas where knowledge was suboptimal post-training were targeted during individual and group supervision sessions. Group supervision coverage was high in both sites, with more than 75% of the monthly groups occurring and high attendance (see Table 4). In India mean monthly individual field supervision coverage was 91%, but only 23% in Pakistan, where each LHW had field supervision an average of 5.5 times (range 2–7 times) over the 24 months of implementation. Field supervision was made difficult in Pakistan as the number of days LHWs were available for supervision was

TABLE 3 Qualitative data collection methods, sample size and content.

Method	Sample size per site	Content covered
Mother narrative in-depth interviews	14 in India 20 in Pakistan Divided between infants 7–9 months and 16–20 months	– Description of behaviors and the contexts within which they occur – Contacts with CBAs, and attitudes to visits and visit content
Mothers FGDs	4 FGDs	– Acceptability and response to the intervention and to CBAs – Barriers and facilitators to behavior change
Father and grandmothers FGDs	2 with each group in India 4 with each group in Pakistan	– Acceptability and response to the intervention – Role in intervention visits – Role in play and feeding behaviors – Barriers and facilitators to behavior change
CBA FGD	4 FGDs 2 additional FGDs and 2 IDIs in India to explore coverage	– Issues affecting coverage and quality of visits – Successes and challenges of the intervention – Impact of intervention on their life and other work – Barriers and facilitators to behavior change
Supervisor IDIs/FGDs	3 IDIs in India 2 FGDs in Pakistan	– As for CBA
Stakeholder IDIs	5 in Pakistan	– Acceptability of the visits – Perceived impact of the intervention on LHWs work – Views on integration between SPRING and other activities

TABLE 4 Training, supervision and visit coverage.

	India	Pakistan
Pre and post training knowledge scores	70–85% (<i>n</i> = 46)	50–91% (<i>n</i> = 149)
% of monthly supervisory groups that occurred	100% (<i>n</i> = 24 months)	75% (<i>n</i> = 24 months)
Mean monthly supervisory group attendance (of groups held)	100% (<i>n</i> = 62)*	89% (<i>n</i> = 69)**
Mean monthly supervision coverage	91% (<i>n</i> = 62)	23% (<i>n</i> = 69)
% caregivers ever visited by a CBA	95% (<i>n</i> = 3,446)	100% (<i>n</i> = 3,237)
% of caregivers who received a CBA visit in the last month	30% (<i>n</i> = 3,446 women and 29,860 visits)	92% (<i>n</i> = 3,237 women and 24,772 visits)

**n* refers to all KWs ever trained including replacements.

***n* = LHWs in evaluation zones.

limited due to polio activities, official meetings, training, maternal and child health week activities, measles campaigns, strikes and public holidays; with a new supervision round initiated only when all LHWs had been seen.

In both sites the CBAs valued SPRING supervision because it focused on feedback rather than on “*checking*,” allowed for collective problem solving and enhanced relationships with each other and their status in the community:

“In Roshan Kal [SPRING] supervision, LHWs are like a family and there is no hesitation, where as in the Lady Health Supervisor meetings they feel fear from ways of checking” [LHW FGD Pakistan]

“[The] Supervisor’s way of giving feedback is good. It does not hurt us. In fact we like it.... in group meeting supervisor asks everyone...so we get the solution from each other” [KW FGD India]

“Actually feedback was appropriate...they [KW]s never defended.....they have taken the feedback in a positive way” [Supervisor IDI India]

Coverage of visits

Based on data from the caregiver surveillance system, most caregivers were visited by a CBA at least once (>95%) (see Table 4), indicating that CBAs were able to locate families. In Pakistan the mean monthly visit coverage was 92% (monthly range 78–98%), but this was for any LHW visits including, for example, polio visits. In India only 30% of caregivers reported a visit in the last month (monthly range 20–45%), with coverage similar by age of the child and by socio-economic status but varied by KW cluster (ranging from 12 to 50%).

Supervisors in India identified 43% of KWs as either generally poor performers in relation to coverage or of facing issues such as a high load of migrant population, being replacement workers, lack of family support, taking sick leave and long travel distances. The KWs themselves did not perceive coverage as an issue, but when asked about reasons for low coverage they reported isolated households, the lack of safety in certain neighborhoods and a large workload reducing their ability to make frequent visits. Some households refused visits either because a household elder did not want the visit to occur, the mother themselves did not want it or because visits were not seen as needed. It was harder to find mothers during harvest time:

“Respondent 8: Maybe her [KWs] family refuses her or she has less time

Respondent 6: She doesn't get family support or her mother in law is upset

Respondent 3: Maybe she is busy in other work

Respondent 8: Maybe she has young children.... She isn't able to manage the time” [KW FGD India]

“The mother does not allow outsiders [to] visit her house. She doesn't go anywhere- always stays at home” [KW FGD India]

“During harvesting, mother goes in field – some don't go but many of them had to go... fewer visits happen” [KW FGD India]

KWs reported that they enjoyed conducting visits, particularly because of the identity and status that the role gave them: *“We have got a good identity in the houses. Earlier we did not used to go out, no one knew us. Now everyone knows”* [KW FGD India]. For some, it was their first paid employment outside the home and they described the role as transformative in terms of increasing their knowledge of the outside world and their ability to navigate it: *“I never went to the village alone but after I joined here.... I do not hesitate to go anywhere in the village”* [KW FGD India]. The financial independence the role gave them was also key for some workers: *“My husband drinks a lot. With the salary I pay children's school fee and manage household expenses. ...Earlier I used to cry and stayed at home..... Now I am managing everything by my own”* [KW FGD India].

Quality of visits

In India, home visits were SPRING specific, so if a home visit occurred we can assume that SPRING content was covered. In Pakistan SPRING content was added to existing visits and the high visit coverage may not reflect high SPRING content coverage. In the Pakistan endline survey ($n = 120$) 36% of mothers reported that their last visit was under 10 min long and only 29% that counseling cards were used, suggesting that coverage of SPRING content was most likely suboptimal. The SPRING protocol was more closely followed in India with women reporting longer visit lengths and 78% reporting that counseling cards were used in every visit.

Table 5 shows data from the field supervision observation checklist. Observed counseling skills were high in both settings, with the exception in Pakistan of using positive words and gestures, which was only observed in 53% of the supervision visits. In Pakistan the LHWs reported in the qualitative interviews an improvement in their overall approach to counseling: *“In the past, we just asked about a behavior, like whether mother has breastfed or not, now we explain in detail and tell the advantages of it and discuss the difficulties as well”* [LHW FGD Pakistan]. For the KWs their new counseling skills were also valued with impacts on their self-confidence: *“We have learnt a way of talking, developed self-confidence among people. So, I really liked to work here”* [KW FGD India].

The use of counseling cards during observed supervision visits was high in both settings, but visit fluency was much lower in Pakistan than India (48% observed as fluent compared with 88% in India), and in Pakistan all relevant topics were covered in only 28% of observations. Family engagement and problem solving were also lower in Pakistan than India as were ECD and coaching skills, with guiding, prompting and modelling particularly low in Pakistan (31–52%). In India there were striking improvements in ECD related skills over time. For example, guiding the mother to be responsive increased over the course of the intervention from 24% in the first supervision round to 75% in the final round, guiding to follow the child's lead increased from 19 to 47% and modelling behaviors from 35 to 79%. In Pakistan only observing the caregiver trying the activity (increased from 85 to 91%), prompting the caregiver to encourage the child (40–66%) and modelling behaviors (20–49%) increased over time, while skills related to family involvement, showing counseling cards and problem solving decreased over time in Pakistan.

Mirroring the quantitative results, caregivers in the qualitative interviews reported better use of counseling cards and the provision of messages in India compared to Pakistan. For example, in India most caregivers reported that counseling cards were used in the visits, that they were asked to describe the pictures which were then explained by the KW and they recognized most of the counseling cards. Caregivers less frequently reported that they were asked to try play activities with the KW present. In Pakistan caregivers reported that counseling cards were rarely used and that the play component was often limited to general advice to play more or a verbal description of an activity to try:

“LHW didn't tell any proper play activity told them [family] to give time to child” [Mother FGD Pakistan]

“LHW told us to play with the child to make her intelligent.... LHW also advised us to give blocks to the children.” [Mother IDI Pakistan]

Both the LHWs and the supervisors corroborated the mothers' descriptions of visits, reporting that the use of counseling cards and coaching/demonstrations were rarely done. There were some exceptions where mothers described being told about new activities with counseling cards and/or being guided to try them:

“I gave cups and glasses to my son and taught him to recognize things. This was new for me and I didn't know about it when I had my older child. LHW explained these activities to me through pictures” [Mother narrative Pakistan]

Barriers to conducting high quality visits

In the qualitative interviews, CBAs in both settings recognized the importance of appropriate counseling, family engagement, praise, and coaching and could describe high quality visits, reflecting that they knew what they should be doing: *“LHW should pay greetings, introduction of Roshan Kal [SPRING], family involvement, health calendar follow up, follow up of the play activity, which benefits they got from these messages, show pictures, ask about the pictures, tell about the picture, asking about problems, keep involving family and to conduct the play activity”* [LHW FGD Pakistan].

TABLE 5 Skills observed during supervision.

	India (62 KWs and 1,398 checklists)	Pakistan (68 LHWs and 381 checklists)
<i>Counseling</i>		
Greets the mother/family	94%	99%
Seat herself appropriately	93%	94%
Makes eye contact and nods during discussions	91%	95%
Uses positive words and gestures when mother says something right	83%	53%
<i>Use of counseling cards</i>		
Shows at least two pictures and asks the mothers opinions on them	98%	87%
Uses probes allowing mother to describe the picture/asks mother about the pictures	75%	70%
<i>Visit fluency</i>		
Fluent with the content	88%	48%
Covers all relevant topics	-	28%
<i>Family engagement/support</i>		
Welcomes family members to sit in and be part of the session	84%	51%
Encourages key family members to support the mother and infant:	65%	54%
<i>Problem solving</i>		
Asks about problems from previous visits	85%	68%
Asks about potential problems for current messages	67%	24%
<i>ECD and coaching (for children >2 months old)</i>		
Asks mum to demonstrate/discuss last visit's activities/Asks about activities the child has been doing since the last visit	75%	75%
Selects appropriate new activity	96%	74%
Clarifies/discusses benefits of the activity	86%	38%
Observes caregiver trying the activity	-	82%
Guides mother in trying the activity	-	40%
To be responsive	52%	-
To be focused	58%	-
To follow the child's lead	44%	-
To praise the child	73%	-
Prompts caregiver to encourage child	63%	50%
Prompts caregiver to praise the child's efforts	73%	36%
Models a behavior (e.g. clapping when child does something well)	59%	31%

The CBAs felt that new skills, especially ECD skills, took time to develop: “*We like the child play activities, but we only came to know about these through Roshan Kal [SPRING] trainings, this is something new and we will take some time to do these perfectly*” [LHW FGD Pakistan]. The lower quality visits in Pakistan were mainly attributed to a lack of LHW time due to competing activities such as polio and dengue, delivery referrals, mother and child weeks and trainings and meetings: “*We want to, but we cannot deliver Roshan Kal [SPRING] visits as planned because of program activities*” [LHW FGD Pakistan]. SPRING content was less of a priority than activities that had a direct impact on their salaries or were monitored by the program: “*We have to bring delivery referrals to the health unit, which takes a lot of our time. If we do not do that our salaries are deducted*” [LHW FGD Pakistan]. There were also issues around the LHWs assuming they did

not need to focus on play in educated families or where families reported they already played with their children, caregivers being busy or uninterested, children being asleep, absent or not in the right mood and LHWs being embarrassed to coach:

“LHWs don’t conduct play activities because of workload and because they think verbal messages are enough” [LHS FGD Pakistan]

“If mother says that she is doing, they believe in her and end the visit” [LHW FGD Pakistan]

“*Respondent 1*: People make fun of her, mothers says that they are already doing all this

Respondent 2: People start laughing when LHW tell them about play....

Respondent 3: People say what is this new thing?" [LHW FGD Pakistan]

In India, the KWs were SPRING specific and so had no competing activities. The main quality issues were related to inconsistently demonstrating, modelling and promoting ECD behaviors, mainly attributed to caregivers not having time or the KW perceiving them as being busy and to the KWs being poorly received:

"We [KW]s give enough time to the mother, but mother is in hurry" [KW FGD India]

"If mother was doing some work ...and left it - then mother-in-law gets angry for not completing the chore first. Sometimes they get angry in front of us" [KW FGD India]

"Her husband saw us and went outside. Next time he came in... he started grumbling. The husband got angry that she [mother] hadn't cooked the chapatti yet." [KW FGD India]

When mothers describe the KW visits, they more frequently reported that the KW asked them to show them the activity they had been doing previously rather than trying and being coached on the new activity, this was seen as "checking" what they had done. This "checking" was not included in the KW counseling cards, which focuses on trying and coaching around the new activity, but it was on the supervisor checklist.

Acceptability of visits

Overall, the CBAs were accepted and trusted by most families they visited. In both sites they were described as "patient," "helpful," and "supportive" and gave 'good' and 'right' information 'nicely,' 'calmly' and 'jovially'. Most mothers described the visits as being pleasurable and valued that someone else was concerned about their child: "There was another person to care about upbringing the child. We look after the child but when she comes, I feel different - it feels good" [Mother FGD India].

In Pakistan the LHWs were long standing workers who were well know and trusted in their communities. In India the KWs were newly recruited and trust and recognition took time to develop: "Initially when we used to go for a visit, mother did not pay attention...they used to ignore [what we said]. But now... they listen to us carefully and also give respect saying sit for a while, have tea..." [KW FGD India]. By the end of the intervention acceptance was high, but both community respondents and the KWs reported that it was not universal with some families finding their KW too young and inexperienced and that visits imposed on their time.

Families liked the counseling cards and, in Pakistan, the calendar. Families found them salient and felt they enhanced understanding: "We had some knowledge and some we gained through pictures... It was easy to understand through pictures" [Mother FGD India].... "When I looked at it, I said well this is my situation" [Mother IDI Pakistan]. The benefit of using counseling cards was echoed by the KWs,

especially for illiterate women: "Without picture they will not have understood so much. They understood more through pictures" [KW FGD India].

Grandmothers often looked after the child and SPRING aimed to encourage fathers and other family members to support the mother and interact with the child, but as seen in the supervisor checklist data family engagement in the visits was low in both sites. Family members were not always at home, but the qualitative data also showed that some grandmothers and fathers were reluctant to be involved in the visits due to time constraints or because they did not feel the visits were important for them, and for fathers in India because it would mean the KW would have to wear a veil during the visit:

"Sometimes it is only the mother-in-law who plays with the child.... Mother says, tell mother-in-law, let mother-in-law try the activity mother-in-law says, tell her [mother] only. I am uneducated. I don't know" [KW FGD India]

"Has to veil her face from male members of the house ... that's why male members also don't join" [Mother narrative India]

In Pakistan LHWs said another reason they did not involve families was because this added time to their visits and because not all of the content of their routine visits was appropriate for other family members: "They could not involve other family members because of workload they just told messages to mothers mostly and do not involve family members" [LHW FGD Pakistan].

Barriers and facilitators to family uptake

In both sites most caregivers reported that the visits had increased the amount of attention they gave their child and their knowledge of the importance of play, but families rarely reported that they had done the play activities routinely and frequently. Most reported that they did each activity once or twice or for a few days.

Among those who did the activities regularly the main drivers were trusting the CBAs, knowledge of the benefits of play and positive experiences/outcomes such as enjoyment by child and mother and pride that a child could do the activity:

"We thought if KW is saying then we can try.... they are saying for some benefit" [Mother narrative India]

"The child will be more intelligent and will pick quickly when she will join school" [Mother narrative Pakistan]

"She plays 2-3 times a day with child and the child enjoys a lot and she can also feel the child's happiness from his face" [Mother IDI Pakistan]

"When I make her learn and she does, then I feel like doing more things with her. I feel very happy" [Mother narrative India]

Barriers to family uptake are shown in Table 6, with illustrative quotes. In both sites all respondent groups reported caregiver time pressures as a key reason ECD activities were not done. Caregivers

TABLE 6 Barrier to families conducting ECD activities.

<i>Lack of time:</i>
"Each day we have some or the other work and get little time for children" [Mother narrative India]
"Women have more work to do and no free time to follow advice about play activities..... and then children can start playing by themselves" [Mother FGD Pakistan]
<i>Perceived lack of difference or novelty:</i>
"There is no effect, we play the same way as with elder children we knew it earlier At that time we never cared much about doing them" [Mother narrative India]
"Mother says that 'don't we know that how to play with our children? We are doing this generation after generation'" [LHW FGD Pakistan]
<i>Limited salience of long-term impacts</i>
"[The benefit is] so that he identifies the things and understands that he can play with them" [Mother IDI India]
"When child will play she will not cry and if she does not cry she will be healthy... The child is too young to learn something from the play" [Mother narrative Pakistan].
<i>Child will learn in their own time:</i>
"The child learns everything without any guidance....will learn by looking at you" [Mother narrative India]
"Leave it! Later when child will grow, he will be able to understand the activities and do them by own" [Mother narrative India]
<i>Child is too young for the activity:</i>
"Tried this activity 2-3 times but the child was unable to put things inside" [Mother narrative India]
"LHW tells me to give my child blocks to play and tell her about colours through them, but I feel my child is too young for it" [Mother IDI Pakistan IDI-mother]
<i>Child learnt the activity:</i>
"Why to repeat same thing with the child [laughs]....If there is something new, we can do Child doesn't do same activity again [laughs]... she learnt" [Mother narrative India]

were often in charge of most domestic chores, including cooking, heating up water for baths, hand washing laundry, care of the domestic livestock and harvesting twice a year. Time pressures lead to other household members looking after the child who, as described above, were infrequently engaged in the visits: "After doing all chores, I think to make child sleep and take rest. Mother-in-law and father-in-law are there. They play a lot with the child" [Mother FGD India].

Few families reported the potential for play and interaction to have long term effects, instead focusing on the child learning a new ability and the activity keeping them happy or distracted. Few felt that the CBAs was suggesting a new behavior, with play something that was already done, and caregivers focused their descriptions of the visits on the play and play activities being promoted rather than the responsiveness and interaction that doing the activity was aiming to enhance. Other barriers were beliefs that the child would learn in their own time without interactive play, that families desired children to play independently so they can occupy themselves, and a perception among some caregivers that their child was too young for the suggested activity, or conversely that their child could do the activity easily.

The key barriers to coverage quality and family uptake are summarized in Figure 1.

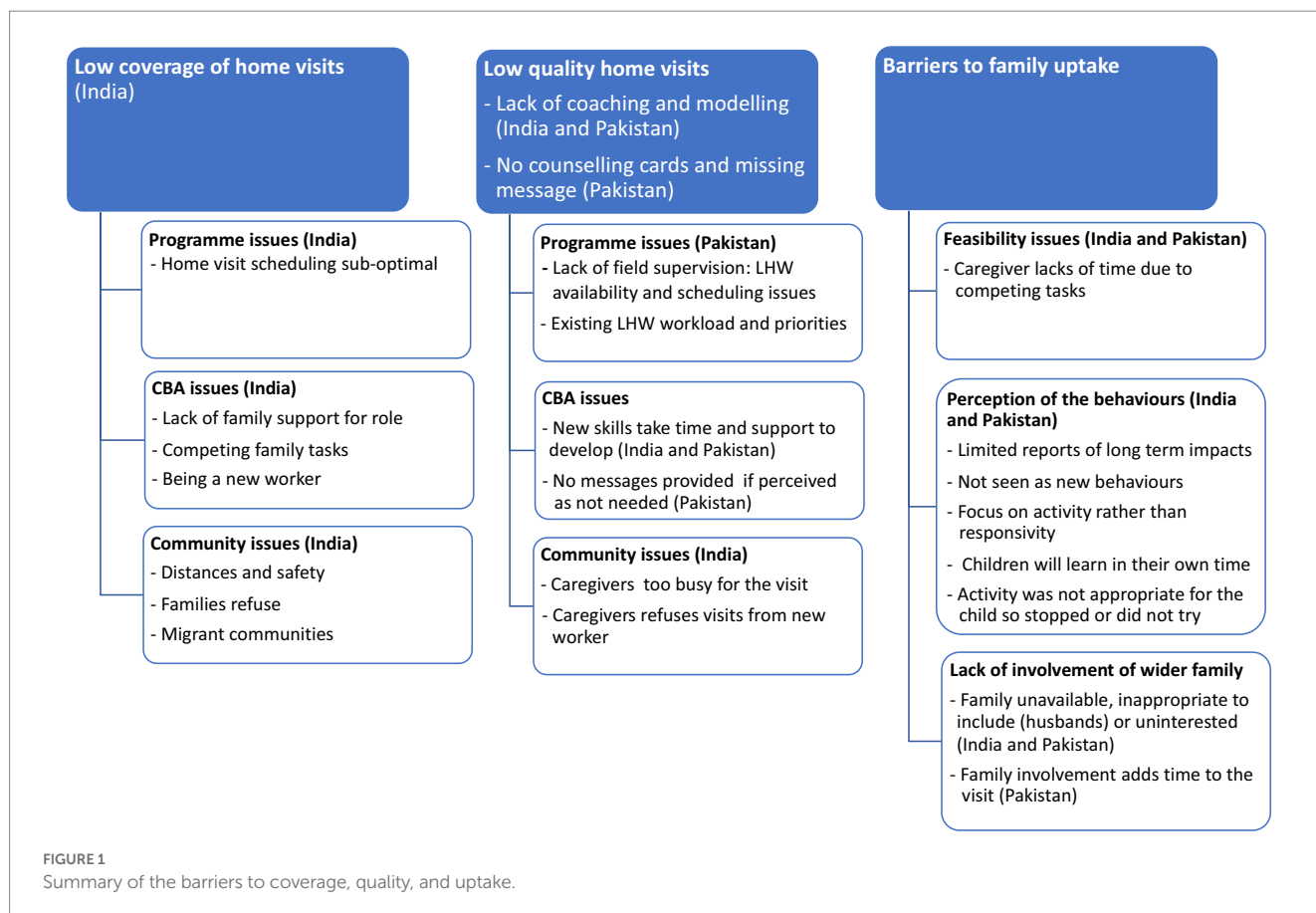
Discussion

The SPRING intervention was based on existing global guidelines, was designed using best practice in relation to formative research and counseling practices and included elements considered key to the success of ECD interventions such as a structured curriculum, actionable messages, opportunities for caregivers to practice activities and get feedback and coaching, demonstration, problem solving, skills based training and supportive supervision (10, 23, 24, 26, 27). SPRING was designed from the outset to be feasible, affordable and appropriate for delivery at scale, and thus to answer key questions about effectiveness at scale and implementation processes. Using a rigorous cluster RCT design we found no impact on ECD or growth outcomes neither when SPRING was integrated into the Lady Health Worker program in Pakistan nor when it was delivered by intervention specific NGO workers in India (22). It is essential to identify what could have caused this lack of impact given the consistent impact seen in efficacy trials (5) and the call for ECD interventions to be scaled up (7).

Key implementation issues were low supervision coverage and poor fidelity in Pakistan, and low visit coverage in India. In addition, the coaching element of the intervention was sub-optimal in both sites, which is likely to have contributed to caregivers feeling that the intervention was not promoting anything new and that visits focused on play and play activities rather than on the interaction and responsiveness - which was to be the focus of the coaching. This is important as interventions that promote responsiveness have a greater impact than those that focus only on play and learning materials (5).

Supervision of community health workers is often weak and under-supported with low and irregular coverage and an administrative focus (31). We were able to implement a supportive group supervision system in both settings which was well received by the CBAs. Individual field supervision focused on improving the quality of the visits through feedback and problem solving, but coverage was very low in Pakistan, which may in part explain the low content fidelity. In India individual supervision coverage was high and we saw ECD skills starting low and improving over time, this was seen to a lesser extent in Pakistan. Other studies have also found that skills take time to develop as workers need to become familiar with the new approach and be supported through supervision in order to complete all the objectives and cover key concepts in their visits (13, 32). The low supervision coverage in Pakistan was in part due to the realities of the LHW schedules and commitments, which needed to be taken into account more fully when designing the supervision system. Other home visit ECD interventions in Pakistan using LHWs have had good supervision coverage, so with the right system high coverage is achievable (13). SPRING field supervision in Pakistan required a better balance between ensuring that all LHWs were seen in a supervision round (leading to potentially long gaps between rounds), this could have been achieved through conducting monthly supervision for all available LHWs, but with a special focus on those missed the previous month.

In many settings it may be impossible for existing CBAs to cover the population in need (33–35) and new workers may need to be deployed. Utilizing an NGO model, with project specific CBAs who have no competing work tasks and carefully delineated catchment areas, does not guarantee adequate coverage with only 30% of eligible women in India reporting a home visit in the last month. The low KW visit coverage in India was in contrast to the 96% coverage achieved by the SPRING



Surveillance workers in the same sites. KW and Surveillance workers were similar in their education, pay, catchment area and access to transport. Their management structures differed with the Surveillance workers having independent checks on their coverage and performance and a more structured approach to scheduling their visits with mothers. The KWs, following an empowerment model, had more flexibility in scheduling their visits and fewer independent checks. A program review of 10 country experiences of scaling up CBA postnatal home visits demonstrate the difficulty of achieving high coverage at scale, with most countries achieving less than 10% coverage and none achieving more than 20% coverage (36); the magnitude of this challenge should not be overlooked. Programs need strategies to maximize coverage, including having a strategy for scheduling visits and identifying and managing poor performers through monitoring and feedback loops for course correction.

The experience of scaling up Crianca Feliz in Brazil, which found no impact on a range of ECD outcomes (37), was that rapid scale up was a barrier to achieving quality and consistency; this is an important example that coverage should not be prioritized at the expense of quality (38). In Pakistan LHW coverage was impressively high, but visit quality was low. As described above this was likely in part due to poor field supervision, but interacting with this were issues of integrating additional ECD tasks into the LHW workload. Resonating with our findings other studies have found that workforce constraints such as limited staff, high workloads, competing tasks seen to be of higher priority (e.g., immunizations), incentives for other work, large catchment areas and lack of supervision and remuneration structures inhibited coverage and quality visit by CBAs (32–35). There are clear

synergies of integration in relation to efficiencies, having a worker who can provide holistic care and understands the needs of the whole child and family (20), but where existing CBAs have low coverage, are overstretched and systems strengthening is unlikely then alternative implementation strategies included in the WHO global guidelines should be considered such as group delivery, primary health care contacts or a mixture of these (7).

The LHW program was going through a difficult period during SPRING implementation which was likely to have influenced LHW motivation and ability to take on new tasks. This included fallout from the abolition of the Federal Ministry of Health and the devolution of activities to provinces in 2011, and regularization of LHWs in 2012 (39–42). The SPRING study team recorded resulting changes in the program that affected implementation which included: an increase in the catchment population of LHWs from 1,500 to 2000 after regularization, 24-h delivery services at Basic Health Units leading to increased workload for LHW as they were to accompany women to the facility, difficulties for SPRING staff engaging with the provincial government, and delays in the disbursement of salaries to LHWs.

In both sites the qualitative data suggest that coaching and modelling of behaviors was low, and that caregivers saw the intervention to be related to play and play activities rather than to responsivity and interaction. Core intervention ingredients need to be made clear to programs for prioritization during training and implementation and steps put in place to fully support these, especially where they are time consuming and may be the first thing to be dropped by busy workers. For example, the practical coaching of

families in responsive care has been identified as a critical component of successful interventions, but this task takes time and skills and may be new to CBAs. We saw that in India, with frequent field supervision, KWs ECD skills increased over time and that acceptability also took time to develop—KW workers would have benefitted from a longer embedding period before the child outcomes were evaluated.

Mothers in the qualitative study reported a change in the attention they gave their children and as has been found in other studies most mothers liked the visits and enjoyed the play activities (13, 32, 34, 38). But, they rarely reported doing the play activities routinely and frequently. Time and resource constraints were a key barrier and although several activities were based around everyday activities a greater focus on communication, responsivity and interaction during daily activities could have improved feasibility. Few caregivers reported any perceived long-term benefit of play or saw the intervention as promoting anything new – perhaps related to the lack of coaching and modelling – and thus they had inadequate motivation to engage in the activities given their busy lives. Future programs need to ensure that interventions include a strong motivational element, ensure interaction and responsivity come across strongly and clearly communicate how the behaviors being promoted are different from existing behaviors. Utilizing approaches such as Trials of Improved practices (43), could provide tangible evidence of the impact of barriers such as time and resources and how these could be overcome.

Although the interventions were based on formative research, we adopted a relatively linear approach to implementation. Given the complexities of the contexts a pilot and having on-going adaptation, improvement and responsive feedback built into implementation would have given us the opportunity to refine the intervention and maximize impacts and should be built into future programs (44, 45).

The study had several strengths in that we could utilize coverage data from a rigorous surveillance system and use this to select a wide range of respondents for the qualitative component. The results of the supervision checklist show skills under observation which are likely to be CBAs' best rather than their routine way of working, but this data provides evidence of the CBAs' core competencies and highlights changes over time. The low supervision coverage in Pakistan meant we had fewer checklists than we had for India, and CBAs with more supervisory visits are over-represented in the data. There was good agreement around what typical home visits looked like both between data collection methods and between respondent groups which suggests our overall findings are valid. We were not able to accurately determine the content of the LHW home visits to identify the extent to which SPRING messages were delivered, but evidence from multiple sources suggest that fidelity was low. We utilized several qualitative methods and a variety of respondents enabling us to gain different points of views and experiences and to triangulate our findings. In the qualitative component transferability was enhanced by having multiple study sites, purposive sampling, sampling to saturation and reflexivity among those collecting and analyzing the data. Despite this the findings may not be transferrable to settings with very different contexts and there is likely to have been some social desirability bias (46, 47).

In conclusion, we identified several factors that could have improved implementation including: maximizing coverage and supervision by improving how visits and field supervision are scheduled and monitored through the use of feedback loops and course correction, using alternative delivery strategies such as group meetings when delivery by existing CBAs is unlikely to be feasible, identifying

and focusing on core intervention components such as coaching during training and supervision, acknowledging that ECD skills are new for CBAs and take time and support to develop and a focus on barriers to family uptake such as integrating ECD into daily activities and highlighting the long term impact of the behaviors and how they are different from existing interaction and play. This can be achieved by building in on-going adaptation, improvement and responsive feedback into implementation to refine the intervention and maximize impacts rather than taking a linear approach to implementation.

Data availability statement

The datasets presented in this article are not readily available, but data are available upon reasonable request. The qualitative data are confidential considering that participants could be identified if their interviews are read in full. Requests to access the datasets should be directed to z.hill@ucl.ac.uk.

Ethics statement

This study, involving human participants, was reviewed and approved by London School of Hygiene & Tropical Medicine Research Ethics Committee (UK), Ethical Review Committees at the Human Development Research Foundation (Pakistan) and the Sangath Institutional Review board (India). Approval was also granted by the Indian Council of Medical Research's Health Ministry Screening Committee (HMSC). The patients/participants provided their written informed consent to participate in this study.

Author contributions

ZH, S Sikander, BA, RR, JS, AH, AR, BK and GD designed the SPRING trial and evaluation and/or inputted into the design of the process evaluation. S Sikander, S Soremekun, RR and SA assisted with the quantitative data collection and analysis. ZH, GD, and SZ oversaw the qualitative data collection and analysis. DK, NP, S Saleem, DV, and KS conducted the interviews and inputted into their interpretation. ZH wrote the first draft of the manuscript which was then reviewed by all authors. All authors contributed to the article and approved the submitted version.

Conflict of interest

The authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

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EDITED BY

Dagrun Engeset,
University of Agder, Norway

REVIEWED BY

Seema Puri,
University of Delhi, India
Jennifer Cashin,
FHI 360, United States

*CORRESPONDENCE

Ranadip Chowdhury
✉ ranadip.chowdhury@sas.org.in

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Breastfeeding practices based on the gestational age and weight at birth in the first six months of life in a population-based cohort of infants from North India

Sitanshi Sharma¹, Ranadip Chowdhury^{1*}, Sunita Taneja¹, Sarmila Mazumder¹, Kiran Bhatia¹, Runa Ghosh¹, Sowmya C. Karantha¹, Neeta Dhabhai¹, Harish Chellani², Rajiv Bahl³ and Nita Bhandari¹

¹Centre for Health Research and Development, Society for Applied Studies, New Delhi, India, ²Department of Pediatrics, Vardhman Mahavir Medical College and Safdarjung Hospital, New Delhi, India, ³Department of Maternal, Newborn, Child and Adolescent Health, World Health Organization, Geneva, Switzerland

Background: Short and long term benefits of early Initiation of breastfeeding (EIBF) and exclusive breastfeeding (EBF) in the first six months of life are well established and recommended globally. However, reliable estimates of breastfeeding practices and impact of breastfeeding counselling interventions according to gestational age and weight at birth are not available in low and middle income countries.

Objective: To assess the impact of breastfeeding counselling on EIBF and EBF during the first 6 months of life according to gestational age and weight at birth.

Methods: We analysed the data collected from the Women and Infants Integrated Interventions for Growth Study (WINGS), an individually randomized factorial design trial. Mothers were counselled on EIBF during third trimester of pregnancy. They were supported throughout the first 6 months to continue EBF by early problem identification, frequent home visits and assistance in expressing breastmilk when direct breastfeeding was not possible. Breastfeeding practices were ascertained through 24 h recalls at infant ages 1, 3 and 5 months for both the intervention and control groups by an independent outcome ascertainment team. The World Health Organization (WHO) definitions were used for classification of infant breastfeeding practices. Generalized linear models of the Poisson family with a log-link function were used to estimate the effect of interventions on breastfeeding practices. The relative measures of effect on breastfeeding practices were estimated in term appropriate for gestational age (T-AGA), term small for gestational age (T-SGA), preterm AGA (PT-AGA), preterm SGA (PT-SGA) infants.

Results: Amongst all infants irrespective of gestational age and weight at birth, EIBF was (51.7%) higher amongst the intervention group (IRR 1.38, 95% CI 1.28–1.48) compared with the control group. The proportion of exclusively breastfed infants at ages 1 month (IRR 1.37, 95% CI 1.28–1.48), 3 months (IRR 2.13, 95% CI

Abbreviations

EBF, Exclusive Breastfeeding; LMIC, Low middle income countries; SGA, Small for gestational age; EIBF, Early initiation of breastfeeding; T-AGA, Term appropriate for gestational age; T-SGA, Term small for gestational age; PT-AGA, Preterm appropriate for gestational age; PT-SGA, Preterm small for gestational age; WINGS, Women and Infants Integrated Growth Study; USG, Ultrasonography; CRL, Crown rump length; LBW, Low Birth Weight; VLBW, Very Low Birth Weight; WHO, World Health Organization; PHQ-2, Patient Health Questionnaire-2; ORS, Oral Rehydration Therapy; ICDS, Integrated Child Development Services; IRR, Incidence Rate Ratio; OR, Odds ratio; CI, Confidence Interval; SD, Standard Deviation; NICU, Neonatal Intensive Care Unit.

1.30–1.44) and 5 months (IRR 2.78, 95% CI 2.58–3.00) were higher in intervention group than control group. We identified significant interaction (p value for interaction <0.05) between intervention and infant size and gestation at birth on exclusive breastfeeding at 3 and 5 months of age. Subgroup analysis showed that the impact of the intervention was greater on exclusive breastfeeding in PT- SGA infants at 3 months (IRR 3.30, 95% CI 2.20–4.96) and 5 months of age (IRR 5.26, 95% CI 2.98–9.28).

Conclusion: This is one of the first studies wherein impact of breastfeeding counselling interventions in the first 6 months of life was assessed according to infant size and gestation at birth wherein gestational age was reliably estimated. The impact of this intervention was higher in preterm and SGA babies compared to other infants. This finding is important as preterm and SGA infants have a higher burden of mortality and morbidity during early infancy. Intensive breastfeeding counselling to these vulnerable infants is likely to improve overall breastfeeding rates and reduce the adverse outcomes.

Clinical Trial Registration: [<http://ctri.nic.in/Clinicaltrials/pmaindet2.php?trialid=19339%26EncHid=%26userName=societyforappliedstudies>], identifier [#CTRI/2017/06/008908].

KEYWORDS

preterm, SGA, gestational age (GA), birth weight, breastfeeding, exclusive breast feeding (EBF)

Introduction

Exclusive breastfeeding (EBF) during the first 6 months of life is universally recommended as it reduces the risk of neonatal and childhood morbidity and mortality. EBF supports optimal growth, neurodevelopment and better school performance (1). Furthermore, evidence from literature supports maternal benefits for breastfeeding like reduced risk of type 2 diabetes mellitus, prolonging lactation amenorrhoea and protection from various cancers like ovarian and breast cancers (2).

Despite the evidence, EBF rates continue to be sub-optimal in the low-middle income countries (LMIC's) (3). Promotion of EBF for first 6 months of life is a part of all national and international guidelines. Breastfeeding practices of vulnerable babies like preterm and small for gestational age (SGA) babies are not reflected in demographic surveys (4).

Babies born preterm (born before completing 37 weeks of gestation) and small for gestational age (born with birth weight <10 th centile for gestational age at birth) are vulnerable to serious infections and feeding difficulties (5). This contributes to increased risk of growth failure, death in early and later life, and neurodevelopmental deficits (6, 7). Breastmilk provides protection for preterm and SGA infants by reducing severity of necrotizing enterocolitis, sepsis, and retinopathy of pre-maturity. Breastfeeding also improves neuropsychological performance, strengthens mother-child bond, reduces the length of hospital stay with lesser incidence of readmissions (8). In spite of the evidence on benefits of breastfeeding for preterm and small for gestational age (SGA) babies, the knowledge on their breastfeeding practices is scanty in LMICs when compared with term infants (9, 10). The data available on preterm births is robust in high income countries with higher birth registration coverage for preterm births in contrast to LMIC's, where birth registration coverage is low and data on preterm birth is scarce (11). Though, birthweight continues to be the primary measure for birth outcomes, it does not help in differentiating between

growth restricted or preterm infants. Gestational age is a better indicator but difficult to ascertain accurately, in low resource settings (12).

We conducted a secondary analysis from a population-based cohort in urban and peri-urban low-to-mid socio-economic neighbourhoods of South Delhi to estimate the impact of breastfeeding counselling on early initiation of breastfeeding (EIBF) and EBF during the first 6 months of life for infants according to both gestational age and weight at birth. We had reliable and early estimates of gestational age by dating ultrasounds and reliable measure of birth weights to be able to categorise infants in the groups: term appropriate for gestational age (T-AGA), term small for gestational age (T-SGA), preterm AGA (PT-AGA), preterm SGA (PT-SGA) infants.

Methods

Study design and setting

Data collected from a recently concluded randomized controlled study, Women and Infants Integrated Interventions for Growth Study (WINGS) was used (13). Total live births which occurred during the course of the study were included in this analysis. The infants who were born to mothers who received interventions during pregnancy continued to receive the interventions throughout early childhood, and those infants who were born to mothers who were in control group during pregnancy were part of the control group during early childhood. The women underwent randomisation twice during the study due to the factorial design of the trial. The first randomisation was done when eligible women were identified through a door-to-door survey and enrolled after getting a written consent. The second randomisation was done at the time when pregnancy was confirmed. Details on the main study design and randomisation have been previously published (14). The gestational age was

assessed between 9 and 13 weeks of gestation using Intergrowth-21st standards by calculating fetal crown-rump length (CRL), if CRL was >95 mm, femur length and head circumference was used to assess gestational age (14–16). Birth weight was taken at the place of birth or at home at age day 7 (± 6) days after birth by pair of trained and standardised study team workers using calibrated digital weighing scale (model 354; Seca, California, USA) to the nearest 10 gram.

Women in the intervention group received breastfeeding support which was initiated as soon as the woman reached the third trimester of pregnancy. Pregnant women were counselled on benefits of EIBF and EBF at each contact with the study team. Post birth, the study team supported mothers in EIBF within first hour of birth or as early as possible if birth occurred at the collaborating hospital. Home visits were made by study workers who were referred to as *Prernas* (inspiration) for the mothers in intervention group for all infants on days 3, 7, 10, 14, 28 after birth and thereafter monthly from 2 to 6 months of life to enquire about infant wellbeing, establish breastfeeding and promoting EBF for first 6 months (13, 14, 17). During these visits, mothers were counselled and supported for establishing and sustaining exclusive breastfeeding during the first 6 months of infant's life. Extra support through additional home visits was given by workers trained in breastfeeding support called lactation counsellors. The lactation counsellors supported those mothers who reported breastfeeding problems to *Prernas*. They addressed breastfeeding problems like inverted nipple and breast engorgement or helped mothers with preterm babies. In addition, breast pumps for expressing breastmilk were provided to the mothers of small babies (mostly preterm or SGA) who were unable to suckle effectively and for some mothers with breast problems. Repeat visit were made whenever required or requested by mothers. Monthly anthropometric measures for routine growth monitoring was taken by an independent team, to observe infant growth. When inadequate weight gain (<15th centile of weight/velocity per month from birth to 6 months) was reported, the infants were referred to physicians for evaluation (18). Nutritional supplementation included vitamin D (400 IU), to all infants and Iron supplementation was given from two weeks for the very low birth weight (VLBW) and from six weeks to low birth weight (LBW) infants until six months of age according to WHO guidelines (14, 19). Snacks, milk (600 kcal, 20 g protein), micronutrient supplements, iron folic acid, calcium, and vitamin D were given to mothers for six months to meet additional requirements during lactation. In addition, counselling on positive thinking, screening and management of depressive symptoms, and WaSH interventions were provided to all mothers in intervention group (14, 20–22).

In the control group, during pregnancy, women were encouraged to register for antenatal care at a government or private facility, have at least four antenatal care check-ups, consume iron folic acid, calcium, vitamin D daily throughout pregnancy, access supplementary foods through the Integrated Child Development Services (ICDS) scheme and deliver in health facilities. After child birth, mothers were advised to go for a postnatal health check-up, and to consume iron folic acid,

calcium, vitamin D, and supplementary foods daily through the ICDS scheme. They were also encouraged to allow home visits by the health workers from national health system like ASHA workers in the first 42 days of life. For early childhood, mothers were advised to breastfeed their babies exclusively for the first six months, and continue breastfeeding for at least two years and to collect supplementary food from ICDS (13).

Outcome assessment

Outcomes were assessed at birth and at infant ages 1, 3 and 5 months. These included rates of EIBF, EBF and breastfeeding practices. An independent outcome assessment team collected data on breastfeeding practices at birth (within 7 days of birth) and at 1,3, 5 months (150–170 days) of age through 24-hour recall from the mothers.

Definitions

Birth weight was defined as weight taken by the study team at day 7 (± 6 days) after birth.

T-AGA was defined as gestational age ≥ 37 weeks at birth and birth weight ≥ 10 th centile to ≤ 90 th centile; T-SGA: gestational age ≥ 37 weeks at birth and birth weight <10th centile; PT-AGA: gestational age <37 weeks at birth and birth weight ≥ 10 th centile to ≤ 90 th centile; PT-SGA: gestational age <37 weeks at birth and birth weight <10th centile, all in accordance to the Intergrowth-21st standards (15). Sub-group analysis included those infants whose gestational age and birth weight were available.

All breastfeeding practices were defined using WHO definitions (23, 24). Early Initiation of breastfeeding was defined as initiation of breastfeeding the infant within 1 h of birth. Exclusive breastfeeding was defined as feeding the infant only breast milk (including expressed breast milk) and no other food or drink, not even water, for first 6 months of life, other than ORS, vitamins, minerals and medicines.

Predominant breastfeeding was defined as feeding the infant breast milk (including expressed breastmilk). However, the infant may also have received other liquids like water and water-based drinks, fruit juice, ritual fluids or any other liquids.

Partial breastfeeding was defined as giving the infant some breastfeeds along with either packaged or powdered milk or cereal based feeds, or any food other than breastmilk.

No breastfeeding was defined as, any infant who did not receive either direct or expressed breastmilk (23, 24).

Statistical analysis

Data collection for the outcomes ended on 30th June 2021. For this analysis, we compared the mothers and infants received interventions during pregnancy and early childhood with the group who did not receive the interventions during that period. We assessed similarity of proportions of baseline characteristics

across groups to check for successful randomisations. Intention to treat analysis was used. We used generalised linear models of the Poisson family with a log link function to estimate the effect (Incidence rate ratio IRR, 95% CI) of intervention on EIBF and EBF at 1, 3 and 5 months of age. The final models were adjusted for place of birth, family possessing a below poverty line card, women's height, and women's body mass index which were potential confounders. We also adjusted the analysis for clustering due to twins. The relative measures of effect on EBF in T-AGA, T- SGA, PT-AGA and PT-SGA were estimated and presented as forest plots. Data analysis was conducted with Stata version 16.0. (Stata Corp., College Station, TX, USA).

Results

In the analyses all live births were included at the baseline (Table 1). For describing the breastfeeding practices at different time points, a cross sectional approach was followed. Out of the total live births at baseline, the number of infants who had the information on breastfeeding practices at age 1, 3 and 5 months were selected for the analysis. Reasons for exclusions included family moved away, refused for interview, child died or were not available at the time of interview (Figure 1).

Sociodemographic characteristics and infant details were represented as means (SD) or proportions as appropriate. The total number of live births were 2,382 in intervention group and 2,369 in control group. Baseline characteristics were comparable except for women's height, proportion of women underweight, families possessing a below poverty line card, and place of birth (Table 1).

Mothers of 51.7% of the infants in intervention group initiated breastfeeding within the first hour of birth, in contrast to only 35.6% mothers in the control group. Breastfeeding practices of infants at 1 and 5 months of age are graphically represented in Figures 2A,B respectively. At 1 month of age, the rates of EBF was higher (75%), in the intervention group as compared to the control group (54%). Predominant breastfeeding (11.1%) and partial breastfeeding (32.2%) were higher in control group which received no breastfeeding counselling and support through the study, when compared with intervention group (Figure 2A).

At 5 months of age, EBF rate in the intervention group was sustained at 73.8% (Figure 2B). The rates of predominant (23.7%) and partial (42%) breastfeeding further increased in control group from the first month. EIBF which was 51% (IRR 1.38, 95% CI 1.28–1.48) in the intervention group compared to control group (35.6%) (Table 2). The proportion of exclusively breastfed infants at ages 1 month (IRR 1.37, 95% CI 1.28–1.48), 3 months (IRR 2.13, 95%CI 1.30–1.44) and 5 months (IRR 2.78, 95%CI 2.58–3.00) were higher in intervention as compared to the control group.

The relative measures of effect on breastfeeding practice, estimated in term appropriate for gestation age (T-AGA), term small for gestation age (T-SGA), preterm AGA (PT-AGA), preterm SGA (PT-SGA) infants are shown in Figure 3. We identified significant interaction (p value for interaction <0.05)

TABLE 1 Baseline characteristics.

	Intervention	Control
Infant characteristics	N = 2382	N = 2369
Female	1,139 (47.8)	1,189 (50.2)
Twins	17 (0.7)	17 (0.7)
Infant size and gestation at birth ^a	N = 2172	N = 2127
T-AGA	1,404 (64.64)	1,240 (58.30)
T- SGA	517 (23.80)	607 (28.54)
PT-AGA	171 (7.87)	196 (9.21)
PT-SGA	80 (3.7)	84 (3.95)
Maternal characteristics	N = 2365	N = 2352
Age (years), mean (SD)	23.77 (3.1)	23.81 (3.0)
Height (cm), mean (SD)	152.38 (5.7)	152.11 (5.6)
Height <150 cm	807 (34.1)	808 (34.4)
Women schooling ≥ 12 year	1,204 (50.9)	1,163 (49.5)
Homemaker	2,254 (95.3)	2,248 (95.6)
Underweight (<18.5 kg/m ²)	356 (15.1)	347 (14.8)
Family had below poverty line card	82 (3.5)	98 (4.2)
Family covered by health insurance scheme	248 (10.5)	270 (11.5)
Joint or extended family ^b	1,579 (66.8)	1,511 (64.3)
Type of delivery	N = 2364	N = 2345
Caesarean	727 (30.8)	628 (26.8)
Normal Vaginal or Assisted vaginal (forceps or vacuum)	1,637 (69.2)	1,717 (73.2)
Place of delivery	N = 2382	N = 2369
Large Hospital	1,681 (70.6)	841 (35.50)
Other hospitals or birthing centres	621 (26.0)	1,321 (55.8)
Home	80 (3.4)	207 (8.7)

Figures are number (percentages) unless stated otherwise.

^aThere are 210 missing values for intervention group and 242 missing values for control group for infants whose gestational age or birth weight or both were not available; Term appropriate for gestational age (T-AGA): gestational age ≥ 37 weeks at birth and birth weight ≥ 10 th centile to ≤ 90 th centile as per Intergrowth standard; Term small for gestational age (T- SGA): gestational age ≥ 37 weeks at birth and birth weight <10th centile as per Intergrowth standard; Preterm appropriate for gestational age (PT-AGA): gestational age <37 weeks at birth and birth weight ≥ 10 th centile to ≤ 90 th centile as per Intergrowth standard; Preterm small for gestational age (PT-SGA): gestational age <37 weeks at birth and birth weight <10th centile as per Intergrowth standard.

SD, Standard deviation.

^bJoint or extended family: adult relatives other than enrolled woman's husband and children living together in household.

between intervention and birth weight and gestational age at birth on exclusive breastfeeding at 3 and 5 months of age. Subgroup analysis showed that the impact of the intervention was greater on exclusive breastfeeding in PT- SGA infants at 3 months (IRR 3.30, 95% CI 2.20–4.96) and 5 months of age (IRR 5.26, 95% CI 2.98–9.28).

Discussion

These analyses showed that provision of counselling and support to mothers for breastfeeding, improved practices on EIBF by 38% and lead to 2 times increase in practices of EBF in the first six months of life. The impact of this intervention was higher in preterm and SGA babies compared to other infants.

Similar findings have been observed from the evidence on breastfeeding counselling in LMIC's. Interventions delivered

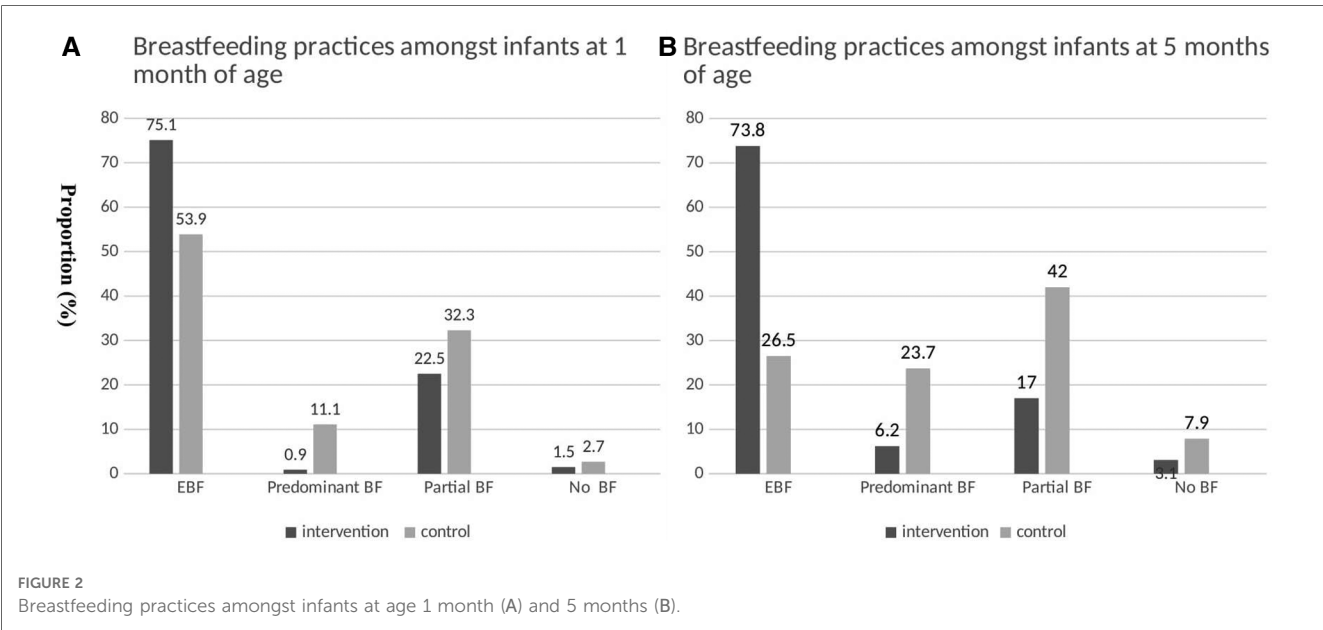
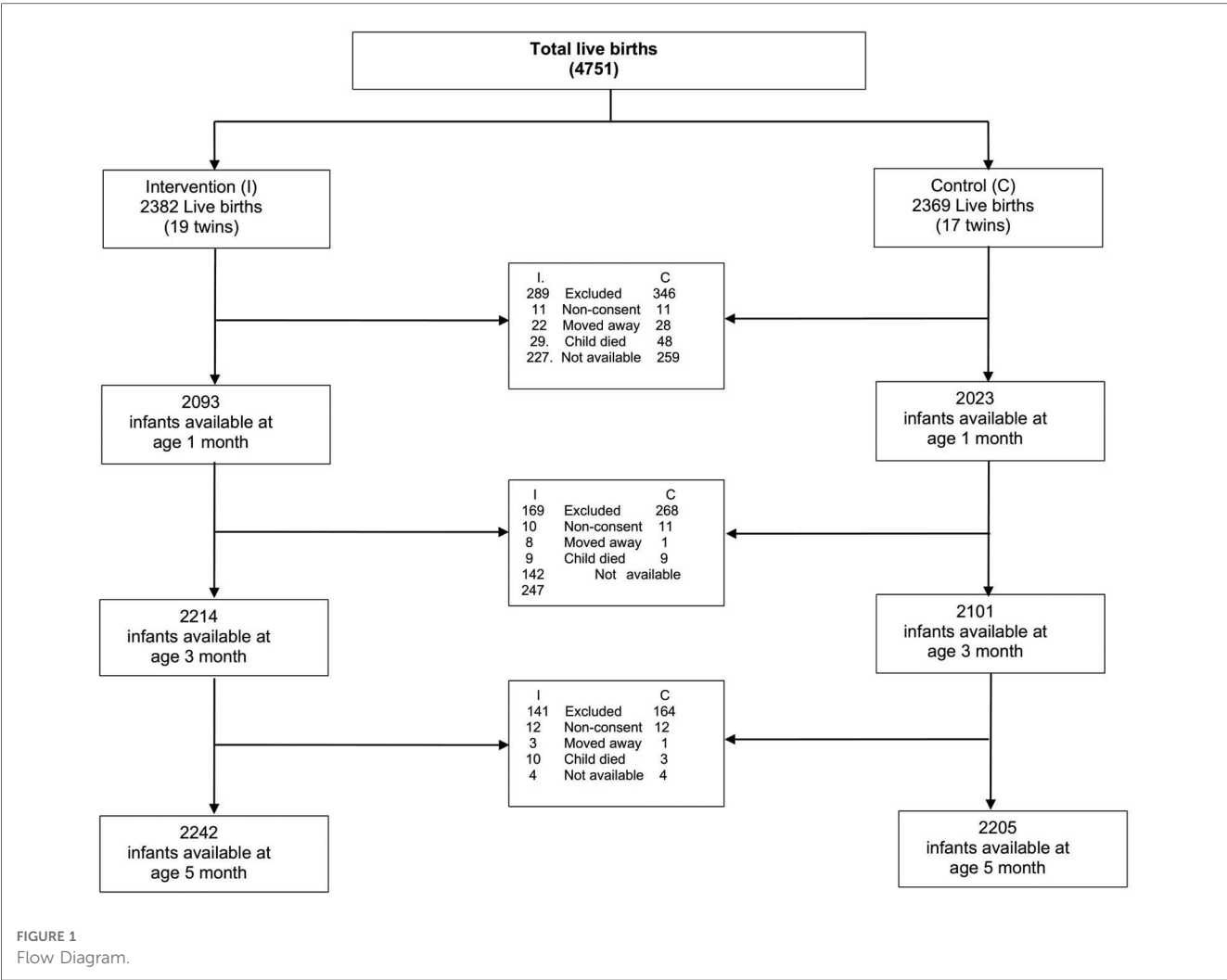


TABLE 2 Breastfeeding practices in all infants at infant age 1, 3 and 5 months.

Breastfeeding practices	Intervention	Control	Unadjusted IRR (95% CI)	Adjusted IRR ^a (95% CI)
Early Initiation	1213/2345 (51.7)	820/2303 (35.6)	1.45 (1.36,1.55)	1.38 (1.28, 1.48)
Exclusive breastfeeding				
1 month–n/total (%) ^a	1592/2093 (76.1)	1111/2023 (54.9)	1.39 (1.32,1.45)	1.37 (1.30, 1.44)
3 month– /total (%) ^a	1950/2214 (88.1)	863/2101 (41.1)	2.14 (2.03, 2.26)	2.13 (2.02, 2.26)
5 months–n/total (%) ^a	1655/2242 (73.8)	585/2205 (26.5)	2.79 (2.59, 3.00)	2.78 (2.58, 3.00)

^aAdjusted Incidence Rate Ratio (95% CI), adjusted for place of birth, family possesses below poverty line card, woman's height, woman's body mass index for potential confounder and twins for clustering within the household. Not corrected for multiple outcomes or comparisons.

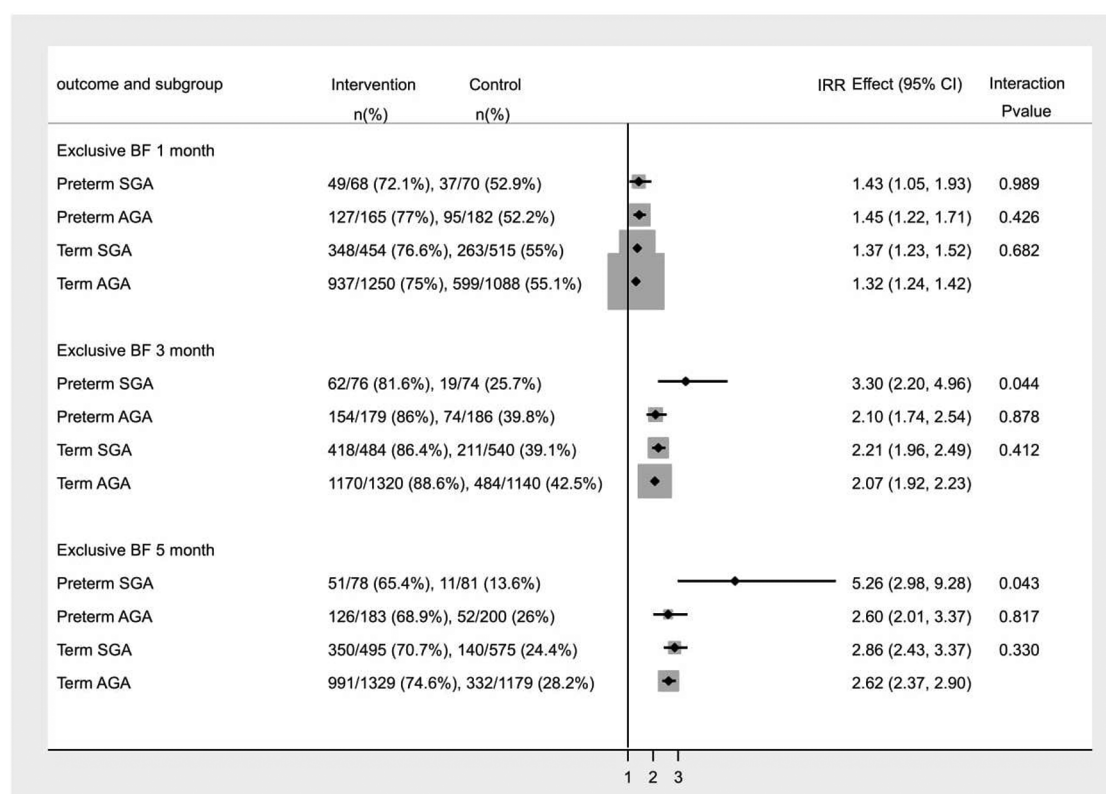


FIGURE 3

Subgroup analysis for Incidence of Exclusive breastfeeding in infants at 1, 3 and 5 months of age.

concurrently in health facility and home settings lead to improvement in rates of EIBF (OR: 4.96; 95% CI: 2.88, 8.54) compared with interventions delivered individually at home or at health facility. For effect on EBF, pooled estimates showed that the odds of EBF at 1–5 months increased 3-fold (OR: 3.08; 95% CI: 2.57, 3.68) with only breastfeeding promotion interventions. This impact was highest when interventions were delivered in combination settings which was both in health facility and home (OR: 6.80; 95% CI: 3.75, 12.33) (25). Best outcomes are thus achieved when several interventions are delivered simultaneously and through multiple channels (26).

However, there is no population based evidence documenting effects of counselling on breastfeeding practices amongst infants based on gestational age and weight at birth from LMIC's. It is widely known and accepted that small babies are at higher risk of non-exclusive breastfeeding due to factors like NICU admission,

feeding intolerance and susceptibility to infections which are influenced by the gestational age at birth. NICU practices also play an important role in establishing the EBF in these babies, however most evidence is limited to high-income settings (27–29). In our study, while the infant was in hospital after birth, the hospital guidelines were followed for feeding as per treating physicians judgment. The study team only provided extra support to babies in intervention group for early initiation of breastfeeding and establishing breastfeeding. All our interventions were based on counselling about initiating breastfeeding and maintaining exclusive breastfeeding. All infants across both groups received standard of care at the health facility immediately post birth and intervention babies had no additional benefits at the hospital.

Through our study we have shown that through breastfeeding counselling centred around the small, at risk babies, the rates of EIBF and EBF can be improved which in turn will reduce the

burden of morbidity and mortality in the first 6 months of life. This is the first study from India which has demonstrated the effects of breastfeeding counselling of mothers based on their infant's gestational age and weight at birth. In addition, it reinforces that by providing breastfeeding counselling in both health facility and home settings and by offering hands-on support to mothers to tackle breastfeeding problems there were significant improvements in the breastfeeding rates of preterm and SGA babies, and improved adherence to exclusive breastfeeding in the first 6 months of life.

The strengths of the study include standardised outcome assessments, early pregnancy ultrasound based gestational age assessment, and generalisability to low and middle income urban populations. It is the first population-based studies from India where breastfeeding practices were ascertained in a randomized control trial based on gestational age at birth and birth weight of the infant.

The lockdowns due to the covid-19 pandemic affected intervention delivery which was one challenge we faced which may have affected outcome assessments for some infants. Restrictions in mobility made it difficult to conduct home visits for observing breastfeeding and to provide support and hands-on help to mothers. However, we overcame this through virtual contacts by lactation counsellors with the mothers.

Policy implications

The key priority is support to small babies in breastfeeding right from birth and continued up to 6 months. This can only be achieved by early identification of these babies through Ultrasonography (USG) to ascertain accurate GA. The importance of EBF has been widely disseminated through various National programs, but the measures to be taken to improve the breastfeeding practices for vulnerable infants separately from the term and AGA infants needs to be defined. Special consideration should be given to understanding the barriers in implementation of breastfeeding interventions for these preterm and SGA babies. The availability of USG facility at different levels of the health systems to ascertain at risk infants (born preterm or SGA), though an expensive but one-time investment will improve lives of small babies by addressing the problems in breastfeeding in vulnerable infants right from birth.

Conclusion

This is the first study where impact of breastfeeding counselling interventions in the first 6 months of life was assessed according to infant's gestational age and weight at birth. The impact of this intervention was higher in preterm and SGA babies compared to other infants. In summary, the analyses show that breastfeeding counselling at both the health facility and at home can be translated to higher rates of EIBF and EBF, amongst the preterm and SGA babies thereby reducing adverse health outcomes during infancy and childhood. This is an important finding as preterm and SGA babies have a higher burden of mortality and morbidity during the first 6 months of life.

Data availability statement

The original contributions presented in the study are included in the article, further inquiries can be directed to the corresponding author.

Ethics statement

The studies involving human participants were reviewed and approved by the Ethics Review Committee of the Society for Applied Studies, New Delhi, India. Vardhman Medical College and Safdarjung Hospital, New Delhi, India. World Health Organization, Geneva. Written informed consent to participate in this study was provided by the participants' legal guardian/next of kin. Written informed consent was obtained from the individual (s), and minor(s)' legal guardian/next of kin for the publication of any potentially identifiable images or data included in this article.

Author contributions

SS and RC were involved in conceptualisation and literature search and drafting first draft of the manuscript. SS, RC, ST and KB were responsible for conducting data analysis. SS, RC, NB, ST, SM, RG, SC and ND were involved in developing interventions and implementation. RB, NB and HC provided technical guidance. All authors contributed to the article and approved the submitted version.

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Conflict of interest

The authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

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EDITED BY

Nita Bhandari,
Society for Applied Studies, India

REVIEWED BY

Savita Sapra,
Society for Applied Studies, India
Andi Faradilah,
Universitas Islam Negeri Alauddin Makassar,
Indonesia
Ravi Prakash Upadhyay,
Society for Applied Studies, India

*CORRESPONDENCE

Neha Batura
✉ n.batura@ucl.ac.uk

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Maternal time investment in caregiving activities to promote early childhood development: evidence from rural India

Neha Batura^{1*}, Reetabrata Roy^{2,3}, Sarmad Aziz⁴,
Kamalkant Sharma³, Divya Kumar³, Deepali Verma³, Ana Correa
Ossa¹, Paula Spinola¹, Seyi Soremekun⁵, Siham Sikander^{6,7},
Shamsa Zafar⁸, Gauri Divan³, Zelee Hill¹, Bilal Iqbal Avan²,
Atif Rahman⁶, Betty Kirkwood² and Jolene Skordis¹

¹Institute for Global Health, University College London, London, United Kingdom, ²Department of Population Health, London School of Hygiene and Tropical Medicine, London, United Kingdom, ³Child Development Group, Sangath, New Delhi, India, ⁴Department of Anthropology, University College London, United Kingdom, ⁵Department of Infection Biology, London School of Hygiene and Tropical Medicine, London, United Kingdom, ⁶Department of Primary Care and Mental Health, University of Liverpool, Liverpool, United Kingdom, ⁷Global Institute of Human Development, Shifa Tameer-e-Millat University, Islamabad, Pakistan, ⁸Fazaia Medical College, Air University, Islamabad, Pakistan

Introduction: Intervention strategies that seek to improve early childhood development outcomes are often targeted at the primary caregivers of children, usually mothers. The interventions require mothers to assimilate new information and then act upon it by allocating sufficient physical resources and time to adopt and perform development promoting behaviours. However, women face many competing demands on their resources and time, returning to familiar habits and behaviours. In this study, we explore mothers' allocation of time for caregiving activities for children under the age of 2, nested within a cluster randomised controlled trial of a nutrition and care for development intervention in rural Haryana, India.

Methods: We collected quantitative maternal time use data at two time points in rural Haryana, India, using a bespoke survey instrument. Data were collected from 704 mothers when their child was 12 months old, and 603 mothers when their child was 18 months old. We tested for significant differences in time spent by mothers on different activities when children are 12 months of age vs. 18 months of age between arms as well as over time, using linear regression. As these data were collected within a randomised controlled trial, we adjusted for clusters using random effects when testing for significant differences between the two time points.

Results: At both time points, no statistically significant difference in maternal time use was found between arms. On average, mothers spent most of their waking time on household chores (over 6 h and 30 min) at both time points. When children were aged 12 months, approximately three and a half hours were spent on childcare activities for children under the age of 2 years. When children were 18 months old, mothers spent more time on income generating activities (30 min) than when the children were 12 years old, and on leisure (approximately 4 h and 30 min). When children were 18 months old, less time was spent on feeding/breastfeeding children (30 min less) and playing with children (15 min). However, mothers spent more time talking or reading to children at 18 months than at 12 months.

Conclusion: We find that within a relatively short period of time in early childhood, maternal (or caregiver) time use can change, with time allocation being diverted away from childcare activities to others. This suggests that changing maternal time allocation in resource poor households may be quite challenging, and not allow the uptake of new and/or optimal behaviours.

KEYWORDS

time use, child health, early childhood development, India, time allocation

1. Introduction

The first five years of life lay the foundation for the development of human capital (1). This period is critical for the development of children's emotional, physical, and intellectual well-being (2, 3). Investments in children's health and development during this period can play a very important role in the accumulation of human capital in the short-term and throughout the life course (4). However, exposure to physical risks factors such as poor maternal nutrition, low-birthweight and infectious diseases; and psycho-social risks such as maternal depression, exposure to violence and lack of stimulation or nurturing care can prevent children reaching their full potential, especially in resource constrained settings (5–7).

In 2016 it was estimated that in low- and middle-income countries (LMICs), 250 million children under the age of five years were at risk of impaired cognitive and social-emotional development (8). Several strategies have attempted to improve early childhood development (ECD) outcomes (9–14). Typically, ECD programmes tend to be targeted at the primary caregiver(s) of children, and delivered through home visits, community groups, clinic or facility-based services or media campaigns. They promote optimum childcare practices, including infant and young child feeding, nurturing care through more engaged and responsive caregiver-child interactions, creating appropriate home environments and stimulation through play (3, 14–17). These programmes could lead to higher parental investment in their children's health and development in terms of physical resources and time (4). They could also directly impact ECD outcomes, either by enhancing the effectiveness of existing levels of parental inputs or acting as a new input for improved ECD (4).

For ECD programmes to improve outcomes, the primary caregiver, usually the mother, needs to assimilate new information and then allocate sufficient time and resources to adopt and perform development promoting behaviours (such as more engaged feeding, communication, play and stimulation activities) (4, 18). However, women face many competing demands on their psychological and physical resources and often return to familiar habits and behaviours in the short- or long-term, depending on the extent of the constraints they may face (19).

Using data collected within a cluster randomised controlled trial (cRCT) of a nutrition and care for development intervention in rural India, this study explores maternal time investment in caregiving activities for children under the age of 2. Specifically, this study will explore:

- (a) patterns of maternal time use to understand how time is allocated between childcare and other activities when children are aged 12 months and 18 months;
- (b) whether there is a difference in maternal time use between the intervention and control arms of the cRCT of a nutrition and care for development intervention; and
- (c) whether and how time allocation between childcare and other activities that mothers engage in could change as children grow older.

This may help unpack the black box of programme mechanisms that rely on behaviour change to achieve effect and reflect on intervention design to achieve maximum and sustainable impact.

2. Methods

2.1. Study setting

This study is nested within the Sustainable Programme Incorporating Nutrition and Games (SPRING) trial in India and Pakistan. Details about SPRING are presented elsewhere (20). In brief, SPRING aimed to develop and test an integrated, culturally appropriate, equitable and sustainable community-based intervention package that promotes child growth and development. SPRING involved the delivery of a home visit education and enablement package from the fifth month of pregnancy, through the first 24 months of life. The intervention design was based on formative research conducted in the study settings, where mothers reported that they felt stretched by multiple commitments and sometimes overwhelmed by their financial circumstances (21). Therefore, the intervention package was developed keeping these constraints in mind; for example, families were encouraged to support mothers so that they could engage with the intervention. SPRING was designed to be feasible, affordable and scalable through the national healthcare system.

During pregnancy, home visits made by a project-employed community-based agent (CBA) focused on maternal health, and sensitization about breastfeeding. Visits made during the post-natal period focused on breastfeeding, complementary and responsive feeding, communication, interaction and play activities. The CBAs used a counselling approach based on cognitive behaviour therapy (21), which comprised family support; guided discovery using pictures; behavioural activation; empathic listening; problem-solving; and praise. Within the child development component, CBAs explained child stimulation activities, and demonstrated these if required. CBAs also coached families on key elements such as praising children and

scaffolding new activities. CBAs were trained to use counselling cards that included the instructions and key messages the CBA was to deliver in each visit, as well as culturally appropriate illustrations for the family to look at (22).

In India, SPRING was implemented in Rewari, a predominantly rural district of Haryana in North India. Haryana has a population growth rate that exceeds the national rate by approximately 0.68% (23, 24). Female literacy in the state is approximately 66%, and the sex ratio is 879 females for every 1,000 males, far below the national average of 943 females per 1,000 males (25). Haryana has among the highest rates of child mortality and undernutrition in India (23, 25).

The intervention was evaluated using a cRCT design where 12 clusters were randomly allocated to receive the intervention and 12 clusters to a control arm. Each cluster was the catchment area of a health sub-centre with a functional Auxiliary Nurse Midwife that covers a population of at least 5,000. The target population were all pregnant women and mothers with babies aged less than two years of age living within the clusters. Estimates indicate that approximately 5,000 mothers and their babies received the home visits during the duration of the programme. The primary outcomes were height-for-age, and Bayley Scales of Infant Development III, and were collected from a sub-set of the target population with children aged 18 months. Intermediate outcomes were collected from when children were aged 12 months and 18 months.

SPRING offered mothers support to create stimulating and nurturing home environments for their young children to improve their children's nutrition and development outcomes by increasing the level of investment inputs for child health and development. Data on maternal time use as a potential investment input was collected to assess whether there were differences in the time that mothers spent interacting with their children between the intervention and control arms, and how this time investment may change as children grow older.

Ethical approval for this study was granted by the London School of Hygiene & Tropical Medicine (LSHTM) Research Ethics Committee (UK), and the Sangath Institutional Review board (India). Approval was also granted by the Indian Council of Medical Research's Health Ministry Screening Committee. Informed written consent was obtained from mothers at enrolment into the trial as well as at the time of the assessments carried out when the child was aged 12 and 18 months.

2.2. Tool development and in-field implementation

Quantitative data on maternal time-use were collected using a survey instrument designed by the study team. The instrument was based on narrative history, a tool adapted from clinical practice (26) but not often used to collect time-use data. The instrument began by identifying the most recent normal day, which served as a frame of reference for the respondent. The most recent normal day was defined as one where there was no festival, wedding, death or funeral and no long absences from the house, i.e., where the respondent's normal routine had not been disrupted.

Once the most recent normal day had been identified, the mother was asked for their time of waking on that day. They were asked about each successive activity undertaken, asked for a brief description of the activity together with how long they spent doing that activity (primary activity), and whether they did another activity at the same time to capture multi-tasking (secondary activities). They ended by reporting the time they went to bed. The narrative history style of interviewing did not ask specific questions about doing or not doing certain types of activities. As such, it allowed mothers to recount the activities that they engaged in chronologically, reducing the risk of social desirability bias (27). This also allowed them to formulate responses rooted in their own perspective and reflecting their priorities, using the language and phrases that they felt comfortable using (28).

Before the instrument was tested in field, a pilot version was shared with the principal investigators and field coordinators to discuss the content and acceptability of the questions. The instrument was then translated into Hindi and checked for consistency with the original English version. The instrument was tested in field using cognitive interviewing techniques to establish comprehensibility, acceptability, and local relevance. The instrument was pre-tested on nine women aged between 18 and 50 years who were either pregnant or had at least one child under the age of 2 years. The women were from heterogeneous socio-economic backgrounds that were representative of the site population. Cognitive interviewing was conducted by the study team in Hindi. The cognitive interviews took between 11 and 30 min to administer, with an average time of 20 min. This testing process confirmed that participants could follow all questions and that the flow of questions was acceptable.

The cognitive interviews were followed by a focus group discussion (FGD) that aimed to generate a near exhaustive list of activities that women with children under the age of 2 years might engage in on a normal day. The FGD was conducted with 12 women between 18 and 50 years of age, who were either pregnant or had at least one child under the age of 2 years and were from varied socio-economic backgrounds. We provided the discussants with the list of activities generated from the cognitive interviews as a starting point. We asked them to think about a normal day in their lives, think about what they did on that day, reflect on the activity list provided and add or remove activities. When suggesting activities, in addition to thinking about their own routine, discussants were also asked to think about what activities other women in their villages undertook. This generated 53 activities, listed by women, that we grouped into broader categories of activities that allowed for the ease of data collection and analysis, without inhibiting how respondents described the activities they engaged in. The tool and list of activities are included in [Supplementary Appendix S1](#).

2.3. Data collection

Data were collected from a sub-sample of mothers when their children were aged 12 months, and again when the children were

aged 18 months, to facilitate a comparison of maternal time use across different child ages, in addition to comparing time use between trial arms. Data were collected between 2016 and 2017.

We were unable to find data from the study setting or a comparable setting to inform assumptions about maternal time use for the control group. Thus, we adopted a pragmatic approach, and based the sample size of this study on the sample size calculations for an early life stress (ELS) sub-study that was nested within the SPRING trial (29). The aim of the ELS sub study was to explore the effect of adversity on growth. A minimum of 25 participants per cluster was needed to give 90% power at the 5% level of significance to detect effect sizes between 0.4SD and 0.5SD. We assumed an intra-cluster correlation of 0.05, and used an established formula (30). Our aim was to collect data from the same cohort at both data collection points. While every attempt was made to maintain the sample size at the second data collection point, the sample size was reduced to 20 per cluster due to practical considerations (Table 1).

2.4. Analytical strategy

As Less than 5% of mothers reported multi-tasking, we present time use data for the reported primary activities only. Activities were categorised as household chores, praying, income generating activities, caring for the elderly, leisure, travelling, other activities (such as personal grooming, eating a meal, studying), caring for children aged 0–2 years, and caring for children older than 2 years.

Mothers described each activity in which they engaged during the day, starting with the time they awoke and then giving start and end times for each subsequent activity. They ended by reporting the time they went to bed, giving an estimate of the time they spent asleep at night. These times were summed together to arrive at her total “reported day”. Given common reporting phenomena such as rounding e.g., reporting time in increments of rounded hours, half hours etc., heaping e.g., the tendency to report common increments of time such as “one hour,” and the risk of recall bias, many of these reported days did not sum to 24 h. As such, to allocate each woman only 24 h of time in a day, the time spent on each individual activity and the time spent sleeping at night, was calculated as a percentage of her reported day. This percentage was then multiplied by 24 to normalise all responses to a 24-hour day.

As these data are collected within a cRCT, we tested for statistically significant differences in maternal time use between the arms using linear regression. We adjusted for potential

correlation in outcomes in children within clusters by the inclusion of cluster ID as a random intercept in multilevel regression models (30). We also test for significant differences in the overall time spent on different activities when children are 12 months of age vs. 18 months of age, using linear regression with cluster as a random effect.

3. Results

The average age of the mothers in our sample was 23.37 years (SD 3.97, range 14–51). All mothers lived in rural areas. The average number of household members was 6.08 (SD 2.56, range 2–25). The majority of women had completed 10–12 years of schooling (36.36%), and were married and Hindu (Table 2). Similar proportions were from a general caste (34.52%) and other backward castes (36.65%). The majority of mothers lived in households with improved sources of drinking water such as household connections, public standpipes, protected dig wells and boreholes, and lived in household made from “pucca” materials such as cement, burnt bricks, concrete, timber or stone. However, the majority used unimproved cooking fuels (wood, charcoal, grass and shrubs), and had access to unimproved sources of sanitation such as a dry toilets, open spaces, and pit latrines without a flush.

We present maternal time use in the intervention and control arms for the subsample assessed when the child was 12 months of age (Table 3) and the subsample assessed when the child was 18 months of age (Table 4).

When the children were aged 12 months, mothers spent most of their day on household chores (over 6 h and 30 min) (Table 3). Mothers spent approximately 22 min engaging in activities that contributed to household income, and three hours on leisure activities. Approximately three and a half hours were spent on childcare activities for children under the age of 2 years. This included bathing children, feeding/breastfeeding, changing clothes/diapers, talking, or reading to children, playing with children. Of these activities, the longest duration was spent feeding/breastfeeding children (approximately 1 h and 50 min), while the shortest was on talking or reading to children. No significant differences between time-use were observed between the intervention and controls arms (Table 3).

When the children were 18 months old, continued to spend the majority of their day on household chores (Table 4). They spent approximately 31 min engaging in activities that contributed to household income, and four and a half hours on leisure activities. Approximately two and a half hours were spent on childcare activities for children under the age of 2 years. Of these activities, the longest duration was spent feeding/breastfeeding children (approximately 1 h and 20 min). No significant differences between time-use were observed between the intervention and controls arms (Table 4).

Table 5 compares the mean number of hours that mothers reported spending on different activities in the last normal day between the two time points. There were several differences between how mothers of 18-month-old children spent their time,

TABLE 1 Maternal time use, sample size and data collection time points.

Assessment timing	Overall sample size	Control arm	Intervention arm
12 months of child's age	704	347	357
18 months of child's age	603	300	303

TABLE 2 Sociodemographic characteristics of the study population ($n = 704$).

Socio-demographic characteristics	Frequency	Percentage
Mother's education level*		
Never been to school	34	4.83
Less than 5 years	26	3.69
5 to 9 years	180	25.57
10–12 years	256	36.36
More than 12 years	207	29.41
Marital status		
Widow	34	4.83
Divorced/separated	1	0.14
Married	669	95.03
Religion		
Hindu	701	99.57
Muslim	2	0.28
Christian	1	0.14
Caste		
General	243	34.52
Scheduled caste	188	26.7
Other backward caste	258	36.65
Scheduled tribe	15	2.13
Source of drinking water		
Improved sources of water	657	93.32
Unimproved sources of water	47	6.68
Type of sanitation facility		
Flush/pour flush toilet	159	22.59
Pit latrine without a flush	396	56.25
Dry toilet	3	0.43
Bush, field, open space	146	20.74
Type of cooking fuel used		
Improved/clean sources	266	37.78
Unimproved sources	438	62.22
Roof material		
Kutcha materials	2	0.28
Pucca materials	699	99.29
Others	3	0.43
Wall material		
Kutcha materials	9	1.28
Pucca materials	695	98.72
Floor material		
Kutcha materials	42	5.97
Pucca materials	662	94.03

*One missing observation.

compared with mothers of 12-month-old children. The biggest difference was seen in the time spent on leisure. Mothers with children aged 18 months spent an average of approximately 95 min more on leisure than mothers of children aged 12 months (p -value = 0.000). Other differences included time spent on:

- income generating activities, where mothers with older children spent approximately 10 min more on income generating activities per day (p -value = 0.013);
- travelling, where mothers with older children spent approximately 12 min more time travelling (p -value = 0.000); and

- other activities, where mothers with younger children spent approximately 16 min more time on other activities (p -value = 0.000)

There were also significant differences in time spent on childcare activities between mothers of younger and older children. Mothers spent almost 3.4 h of their day on childcare activities, when the child was 12 months of age. This reduced by 48 min when the child was 18 months of age (p -value = 0.000) (Table 5). Within this group of activities, the majority of time was spent on feeding/breastfeeding (approximately two hours). This sub-category remained the most time-consuming childcare activity when the child was 18 months of age but reduced by half an hour a day (p -value 0.000). The time spent playing with children also decreased between the two time points by approximately 10 min (p = 0.000). Mothers reported spending less time on changing babies' clothes/diaper (p -value = 0.000) between the two time points but while significant, these time differences are very small at 2 min. Mothers of children of 12 months of age spent almost 5 min more time calming and quietening a crying baby (p -value = 0.001). Mothers of children of 18 months of age spent approximately 1 min more time talking or reading to the child (p -value = 0.004). The time spent caring for children older than 2 years increased by 12 min when the SPRING trial child was 18 months old.

4. Discussion

In this study, we aimed to explore maternal time use as an investment in ECD in rural India. Within the framework of the SPRING trial, we explored whether there was a difference in maternal time allocated to childcare activities and other activities, between the intervention and control arms, and how this time investment might change as children grow older.

We found that when children were 12 and 18 months old, mothers tended to spend most of their waking day on household chores. When children were aged 12 months, mothers spent an average of three and a half hours a day caring for children under the age of 2 (bathing, feeding, breastfeeding, playing, etc). Within this category of activities, the highest allocation of time was to feeding or breastfeeding children, with a lower level of time investment in playing with children and talking or reading to children. When children were aged 18 months old, mothers spent an hour less on childcare activities, although the pattern of time use within this category of activities is similar to that seen when children were aged 12 months i.e., the highest allocation of time was to feeding or breastfeeding children, with a lower level of time investment in playing with children, and talking or reading to children. It may possibly be as that the mothers of 18-month-old children have other, younger children to whom caregiving time is allocated. These results provide us with a consistent pattern of maternal time investment in ECD.

We also found that when children were 18 months old, mothers spent more time on leisure activities and income generating activities than they did when children were 12 months

TABLE 3 Mean number of hours spent on different activities, last normal day, 12 months.

Activity	Overall	Control	Intervention	I-C difference	p-value
	Mean (SD)	Mean (SD)	Mean (SD)	(95% CI)	
Total respondents	704	347	357		
Household chores	6.556 (2.424)	6.460 (2.306)	6.649 (2.532)	0.188 (−0.466/0.843)	0.551
Praying	0.015 (0.071)	0.016 (0.075)	0.014 (0.066)	−0.002 (−0.012/0.008)	0.654
Income generating activities	0.364 (1.025)	0.336 (0.919)	0.391 (1.119)	0.055 (−0.145/0.257)	0.560
Caring for the elderly	0.002 (.0263)	0.000 (0.000)	0.003 (0.036)	0.003 (0.000/0.007)	0.054
Leisure	2.970 (1.652)	2.950 (1.601)	2.990 (1.701)	0.040 (−0.386/0.467)	0.771
Travelling	0.212 (0.846)	0.179 (0.813)	0.244 (0.877)	0.064 (−0.079/0.209)	0.358
Other activities	0.864 (1.312)	0.908 (1.216)	0.821 (1.399)	−0.086 (−0.304/0.131)	0.438
Child care activities (0–2 years)	3.399 (2.124)	3.392 (1.873)	3.406 (2.344)	0.013 (−0.591/0.618)	0.990
Caring for children (general)	0.540 (0.529)	0.575 (0.555)	0.506 (0.502)	−0.068 (−0.192/0.054)	0.396
Bathing children	0.229 (0.459)	0.248 (0.624)	0.211 (0.191)	−0.036 (−0.108/0.034)	0.287
Feeding/breastfeeding the baby	1.859 (1.368)	1.803 (1.155)	1.913 (1.547)	0.109 (−0.259/0.477)	0.611
Changing baby's clothes/diaper	0.142 (0.168)	0.159 (0.191)	0.126 (0.140)	−0.033 (−0.072/0.006)	0.104
To calm/quieten a crying baby	0.163 (0.459)	0.165 (0.429)	0.162 (0.487)	−0.003 (−0.115/0.109)	0.964
Playing with children	0.462 (0.876)	0.439 (0.782)	0.485 (0.958)	0.045 (−0.115/0.206)	0.596
Talking or reading to the child	0.001 (0.024)	0.001 (0.017)	0.001 (0.029)	0.001 (−0.003/0.004)	0.710
Caring for children older than 2 years	0.283 (0.544)	0.257 (0.505)	0.308 (0.579)	0.05 (−0.057/0.159)	0.340
In bed during the night	9.331	9.292	9.370	0.077	0.704

old. Less time was also spent on caregiving activities for children under the age of two years with decreases in time spent feeding/breastfeeding, playing changing babies' clothes/diaper but an increase in time spent talking or reading to the child, though some of these changes were very small. There was a small increase in the time spent on caring for children older than two years.

However, no statistically significant differences were found between the intervention and control arms at either time point, indicating that the intervention did not appear have a statistically significant effect on the level of time investment for ECD. The process evaluation component of SPRING indicates that there were implementation challenges in both sites, and could account for this (31). To be able to incorporate a new activity, women would either need to stop engaging with a current activity to replace it with the new one, or reallocate their current allocation to make time for a new activity (32). This may not be possible in settings where there are constraints on women's decision-making and bargaining powers. Estimates from the 2015–2016 Indian

National Family Health Survey (the year closest to the SPRING data collection) indicate that approximately 88% of currently married women (aged 15–49 years) participated in household decisions related to major purchases, their own health care and visits to family or relatives. In the state of Haryana, this was slightly lower (86%) (33). More recent estimates from the 2019–2020 Indian National Family Health Survey, indicate that women's participation in household decisions related to major purchases, their own health care and visits to family or relatives remains stable, with the proportion in Haryana being similar to that across the country (34). Both surveys found that that involvement in decision making was higher among older, wealthier and employed women, and women who lived in urban areas (33, 34). Thus, younger, and less wealthy women in rural areas are likely to have lower decision-making and bargaining power; a possible explanation for why women were not able to invest more time in ECD activities in our sample.

There also may be an opportunity cost to this time investment for households that face income constraints (32, 35). In such cases,

TABLE 4 Mean number of hours spent on different activities, last normal day, 18 months.

Activity	Overall	Control	Intervention	I-C difference (95% CI)	p-value
	Mean (SD)	Mean (SD)	Mean (SD)		
Total respondents	603	300	303		
Household chores	6.617 (2.479)	6.402 (2.327)	6.831 (2.607)	0.428 (−0.200/1.050)	0.169
Praying	0.017 (0.079)	0.012 (0.061)	0.023 (0.093)	0.01 (−0.004/0.026)	0.155
Income generating activities	0.524 (1.319)	0.535 (1.373)	0.514 (1.266)	−0.021 (−0.332/0.289)	0.898
Caring for the elderly	0.011 (0.149)	0.002 (0.030)	0.018 (0.208)	0.015 (−0.008/0.039)	0.207
Leisure	4.545 (2.560)	4.818 (2.988)	4.274 (2.019)	−0.544 (−1.22/0.138)	0.103
Travelling	0.418 (1.292)	0.393 (0.944)	0.442 (1.563)	0.049 (−0.298/0.396)	0.766
Other activities	0.599 (1.028)	0.652 (1.107)	0.547 (0.942)	−0.104 (−0.364/0.155)	0.410
Child care activities (0–2 years)	2.595 (2.507)	2.687 (2.904)	2.503 (2.041)	−0.184 (−0.817/0.448)	0.549
Caring for children (general)	0.508 (1.512)	0.607 (2.059)	0.410 (0.581)	−0.196 (−0.519/0.125)	0.215
Bathing children	0.240 (0.273)	0.236 (0.219)	0.244 (0.319)	0.008 (−0.046/0.062)	0.762
Feeding/breastfeeding the baby	1.347 (1.414)	1.370 (1.395)	1.324 (1.433)	−0.045 (−0.302/0.212)	0.719
Changing baby's clothes/diaper	0.103 (0.162)	0.096 (0.137)	0.110 (0.184)	0.014 (−0.033/0.061)	0.546
To calm/quieten a crying baby	0.085 (0.339)	0.063 (0.241)	0.107 (0.413)	0.044 (−0.075/0.164)	0.467
Playing with children	0.293 (0.692)	0.292 (0.650)	0.294 (0.732)	0.002 (−0.16/0.165)	0.978
Talking or reading to the child	0.016 (0.137)	0.022 (0.177)	0.011 (0.079)	−0.011 (−0.031/0.009)	0.324
Caring for children older than 2 years	0.485 (0.829)	0.476 (0.780)	0.493 (0.875)	0.017 (−0.202/0.237)	0.890
In bed during the night	8.187 (1.209)	8.226 (1.193)	8.148 (1.227)	−0.078 (−0.349/0.192)	0.558

there are likely competing priorities especially where women are expected to concurrently nurture children and their families as well as make important economic contributions (19, 32). As children grow older, it might seem that they are more independent or need less supervision, women reallocate their time to income generation activities or take time for themselves, for their own well-being (36).

Levels of parental investment have been shown to be positively correlated with parents' beliefs about the productivity of those inputs and/or the return on the level of investment (37). Thus, it is worthwhile to formally explore the role that beliefs and norms may play in ECD through the process evaluation of implemented programmes (31). This may help unpack the facilitators of or barriers to higher time investments that might arise from beliefs that mothers and other caregivers have about the effectiveness of time investments for ECD, relative to investment in more material resources such as buying toys (4, 35).

The strength of our study is that we adapted the narrative history methodology to collect time use data, which allowed

women to report on the activities that they engaged in chronologically, from their own perspectives, reducing the risk of social desirability bias. This provided us with rich and detailed data. By restricting the frame of reference to be the most recent normal day, we also reduced some of the noise attributed to recall bias. However, time use data are notoriously difficult to collect because of the relative nature of time, which does have an impact on recall, especially in resource constrained settings where individuals may not formally keep time.

5. Conclusion

ECD programmes can have a positive impact on children's outcomes either directly as a stand-alone investment in children's development or indirectly by increasing parental investment or improving the effectiveness of existing material and time investments. Both pathways require the incorporation of new behaviours by participants, usually the primary caregiver (who

TABLE 5 Difference in mean number of hours spent on different activities, last normal day, between 12 and 18 months.

Activity	Overall	Overall	Difference between 18 and 12 months	p-value
	(12 months)	(18 months)		
Total respondents	704	603		
Household chores	6.556 (2.424)	6.617 (2.479)	0.061 (−0.317/0.439)	0.666
Praying	0.015 (0.071)	0.017 (0.079)	0.002 (−0.004/0.008)	0.604
Income generating activities	0.364 (1.025)	0.524 (1.319)	0.16 (−0.010/0.331)	0.013
Caring for the elderly	0.001 (0.026)	0.010 (0.149)	0.008 (−0.004/0.0213)	0.135
Leisure	2.970 (1.652)	4.545 (2.560)	1.574 (1.264/1.883)	0.000
Travelling	0.212 (0.846)	0.418 (1.292)	0.206 (0.013/0.399)	0.000
Other activities	0.864 (1.312)	0.599 (1.028)	−0.264 (−0.445/−0.084)	0.000
Child care activities (0–2 years):	3.399 (2.124)	2.595 (2.507)	−0.804 (−1.232/−0.376)	0.000
Caring for children (general)	0.540 (0.529)	0.508 (1.512)	−0.032 (−0.193/0.129)	0.632
Bathing children	0.229 (0.459)	0.240 (0.273)	0.01 (−0.034/0.055)	0.618
Feeding/breastfeeding the baby	1.859 (1.368)	1.347 (1.414)	−0.511 (−0.737/−0.286)	0.000
Changing baby's clothes/diaper	0.142 (0.168)	0.103 (0.162)	−0.0389 (−0.074/−0.003)	0.000
To calm/quieten a crying baby	0.163 (0.459)	0.085 (0.339)	−0.077 (−0.166/0.010)	0.001
Playing with children	0.462 (0.876)	0.293 (0.692)	−0.169 (−0.289/−0.049)	0.000
Talking or reading to the child	0.001 (0.024)	0.016 (0.137)	0.015 (0.004/0.025)	0.004
Caring for children older than 2 years	0.283 (0.544)	0.485 (0.829)	0.202 (0.099/0.304)	0.000
In bed during the night	9.331 (1.360)	8.187 (1.209)	−1.144 (−1.424/−0.865)	0.000

tends to be the mother). We find that within a relatively short period of time in early childhood, maternal (or caregiver) time use can change, with time allocation being diverted away from childcare activities to others. This suggests that changing maternal time allocation in resource poor households may be quite challenging, and not allow the uptake of new and/or optimal behaviours. To promote effective and sustainable participation, and the uptake of ECD interventions, strategies should consider aspects related to bolstering women's decision-making and bargaining power, and support from family members such as fathers to allow women to increase their time investment, and manage available resources within their roles in households (19).

reasonable request. Requests to access the datasets should be directed to n.batura@ucl.ac.uk.

Ethics statement

This study involving human participants, was reviewed and approved by the London School of Hygiene & Tropical Medicine Research Ethics Committee (UK), and the Sangath Institutional Review board (India). Approval was also granted by the Indian Council of Medical Research's Health Ministry Screening Committee (HMSC). The participants provided their written informed consent to participate in this study.

Data availability statement

The datasets presented in this article are not readily available due to patient data protection, but data are available upon

Author contributions

JS and NB conceptualized the time use study within SPRING. NB, JS and RR designed the time use survey instrument. NB, RR,

SA, KS, DV, DK contributed to data collection and acquisition. NB led the formal analysis for this study. BK, AR, ZH, BA, SS, GD are members of the research team involved in conceptualisation, funding acquisition, methodology, data curation and/or formal analysis of the SPRING trial within which this study is nested. NB was responsible for the initial drafting of this manuscript. All authors contributed to the article and approved the submitted version.

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Supplementary material

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EDITED BY

Ranadip Chowdhury,
Society for Applied Studies, India

REVIEWED BY

James Orwa,
Aga Khan University, Kenya
Archisman Mohapatra,
GRID Council, India

*CORRESPONDENCE

Dagmawi Chilot
✉ dagimchilot21@gmail.com

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Effectiveness of eight or more antenatal contacts on health facility delivery and early postnatal care in low- and middle-income countries: a propensity score matching

Dagmawi Chilot^{1*}, Fantu Mamo Aragaw²,
Daniel Gashaneh Belay^{2,3}, Melaku Hunie Asratie⁴,
Mehari Woldemariam Merid², Anteneh Ayelign Kibret³,
Nahom Worku Teshager⁵ and Adugnaw Zeleke Alem²

¹Department of Human Physiology, College of Medicine and Health Science, School of Medicine, University of Gondar, Gondar, Ethiopia, ²Department of Epidemiology and Biostatistics, College of Medicine and Health Science, Institute of Public Health, University of Gondar, Gondar, Ethiopia, ³Department of Human Anatomy, College of Medicine and Health Science, School of Medicine, University of Gondar, Gondar, Ethiopia, ⁴Department of Women and Family Health, College of Medicine and Health Science, School of Midwifery, University of Gondar, Gondar, Ethiopia, ⁵Department of Pediatrics and Child Health, College of Medicine and Health Science, School of Medicine, University of Gondar, Gondar, Ethiopia

Background: Despite progress in reducing maternal and child mortality, many low- and middle-income countries (LMICs) still experience an unacceptably high level of the problem. The World Health Organization (WHO) recently recommended pregnant women should have at least eight antenatal care visits (ANC8+) with a trained healthcare provider as a key strategy to promote pregnant women's health. Antenatal care is an imperative factor for subsequent maternal healthcare utilization such as health facility delivery and early postnatal care (EPNC). This study aimed to examine the net impact of ANC8+ visits on health facility delivery and EPNC in LMICs using a propensity score matching analysis.

Methods: We used the recent Demographic and Health Survey (DHS) datasets from 19 LMICs. Women of reproductive age (15–49 years) who had given birth within 1 year preceding the survey were included. A propensity score matching analysis was employed to assess the net impact of eight or more antenatal care visits on health facility delivery and early postnatal care.

Result: After matching the covariates, women who attended ANC8+ visits had a 14% (ATT = 0.14) higher chance of having their delivery at health facilities compared with women who attended less than eight ANC visits. This study further revealed that women who had ANC8+ visits were associated with a 10% (ATT = 0.10) higher probability of early PNC compared with their counterparts.

Conclusion and recommendation: This study confirmed that ANC8+ visits significantly increased the likelihood of health facility-based delivery and early PNC utilization in LMICs. These findings call for public health programs to focus on pregnant women attending adequate ANC visits (according to revised WHO recommendation) as our study indicates that ANC8+ visits significantly improved the chances of subsequent care.

KEYWORDS

antenatal care, health facility delivery, early PNC, propensity score matching, low- and middle-income countries

Background

Despite progress in reducing maternal and child mortality, many low- and middle-income countries (LMICs) still experience an unacceptably high level of the problem (1, 2). In 2017, 295,000 women died due to complications in pregnancy and childbirth globally. The vast majority of these deaths (86%) occurred in Sub-Saharan Africa and Southern Asia (3). All countries with the United Nations have agreed and adopted 17 Sustainable Development Goals so that they can change the world for the better (4, 5). Sustainable development goal 3 (SDG-3) aims to reduce the global maternal mortality ratio to 70 deaths per 100,000 live births by 2030 (6). To achieve this goal, timely and frequent care for pregnant women by healthcare providers has paramount significance (7, 8).

The World Health Organization (WHO) recently recommended pregnant women should have at least eight antenatal care (ANC8+) visits with a trained healthcare provider as a key strategy to promote pregnant women's health (9, 10). Timely and frequent ANC endorses existing disease treatments, vaccination, malaria prophylaxis, iron supplementation, nutrition counseling, HIV counseling and testing, urinary tract infection treatment, and other related services (11–13). Antenatal care is also an imperative factor for subsequent maternal healthcare utilization such as health facility delivery and early postnatal care (EPNC) (14, 15). As advocated by the WHO, health facility delivery with trained birth attendants and EPNC have principal importance in reducing maternal mortality (16–18).

The first ANC visit should start in the first trimester while postnatal care should be given to a woman within 48 h after the delivery of the placenta and continue for 42 days (19, 20). In LMICs, numerous studies have revealed empirical evidence concerning the impact of individual, household, and community-level factors on this continuum of care utilization in different settings (21–24). However, the relationship between ANC and the subsequent continuum of care in a cross-sectional study might not be robust because of the presence of selection bias and confounding (25). Despite country-specific studies that have tried to link the ANC4+ visits with institutional delivery and early PNC (14, 25, 26), there is no evidence of the net impact of ANC8+ visits on subsequent institutional delivery and early PNC in LMICs. Many women in developing countries do not adhere to the WHO recommendation of at least eight ANC visits during pregnancy (27). Subsequent care aspects such as having delivery at a health facility and attending early postnatal care also remain a significant problem in those nations. Exploring the impact of ANC8+ on subsequent care can help to inform better policy and practice (28, 29). Therefore, our study aimed to examine the net impact of ANC8+ visits on health facility delivery and EPNC in LMICs using PSM and employing sensitivity analyses to assure the robustness of our findings.

Abbreviations: AOR, adjusted odds ratio; ANC, antenatal care; ANC8+, eight or more antenatal care; DHSs, Demographic and Health Surveys; EPNC, early postnatal care; LMICs, low- and middle-income countries; SDG-3, sustainable development goal 3; WHO, World Health Organization.

Materials and methods

Study design and setting

This study used secondary data from 19 LMICs that have a recent Demographic Health Survey (DHS) collected after the 2016 WHO ANC model (30). This model recommends a minimum of eight ANC contacts during pregnancy, with the first contact occurring in the first trimester of gestation followed by two and five contacts in the second and third trimesters, respectively (9).

The DHS is a nationally representative survey that uses a cross-sectional design to collect data on women, men, and children. The surveys use the same standardized data collection procedures, sampling, questionnaires, and coding, making the results comparable across countries. A total of 309,111 reproductive ages (15–49 years) were interviewed in 19 LMICs. However, this study was limited to women aged 15–49 years who had live births within the year prior to the surveys. Finally, 90,830 women aged 15–49 years were included in the analysis (Figure 1). The list of those countries and the respective year of surveys is provided in Table 1.

Definition of variables

Outcome variable

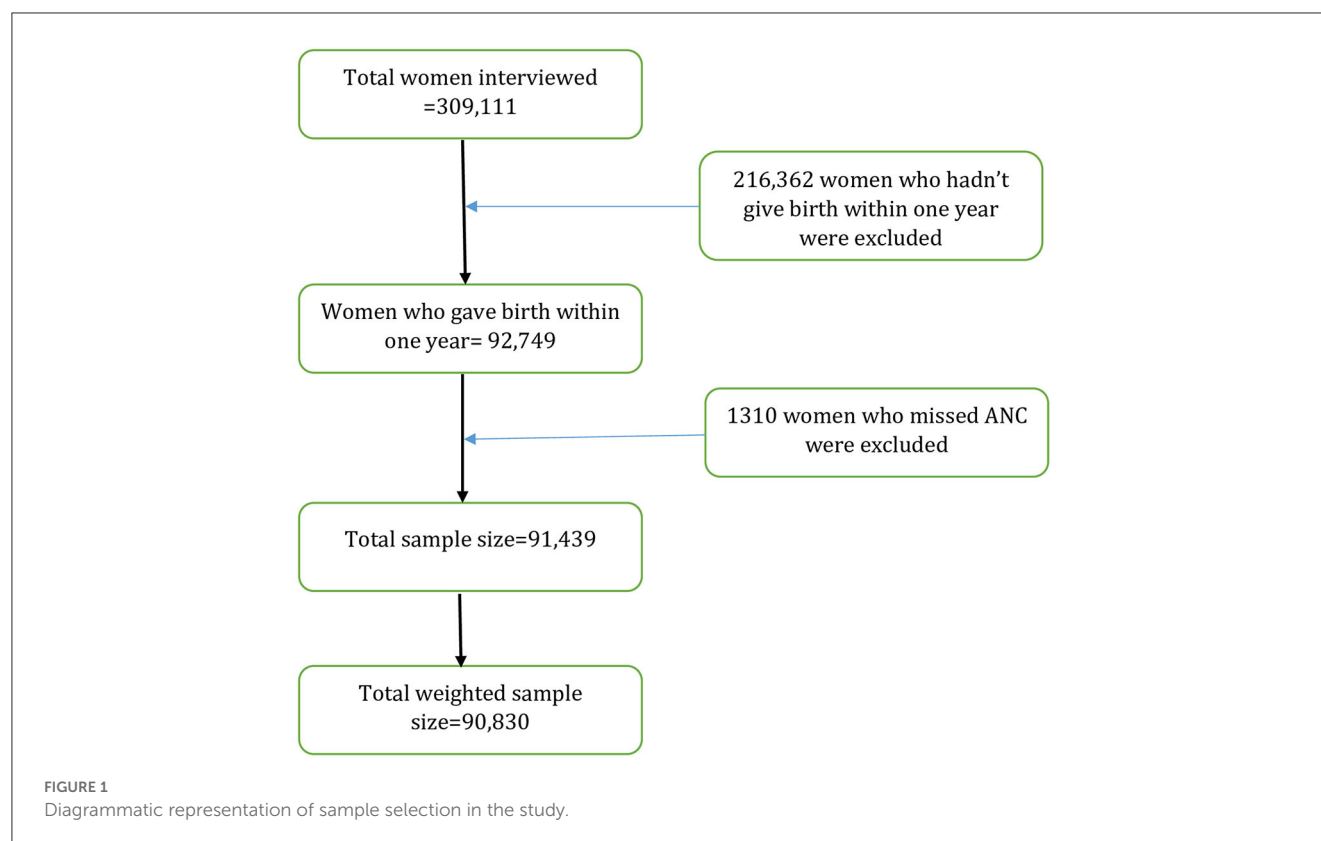
The outcome variables of this study were health facility delivery and EPNC. Health facility delivery was a dichotomous variable where respondents were coded as having an institutional delivery if they delivered within a public, private, or non-governmental organization facility. Early PNC is a postnatal checkup from a skilled health provider within 2 days after childbirth. It was coded into a binary variable where women who had a postnatal checkup by a skilled provider within 2 days of delivery were coded 1 and otherwise 0.

Treatment variable

The treatment variable was an ANC visit of their most recent pregnancy that ended with a live birth. The number of ANC contacts of pregnant women was categorized as those who had at least eight ANC contacts and those who had fewer than eight ANC contacts, according to the 2016 WHO recommendation.

Matching variables

This study considered covariates on the basis of available literature that was related to both the treatment (ANC visits) and the outcome variables (health facility delivery and early PNC) (14, 25, 26). The lists of included variables were as follows: age, education level, household wealth status, marital status, wanted pregnancy, media exposure, birth order, residence, sex of household head, and accessing healthcare.

**TABLE 1** Study setting and year of surveys.

Country	Year of survey	Region
Albania	2017/18	Southeastern Europe
Bangladesh	2017/18	South Asia
Benin	2017/18	West Africa
Cameroon	2018	Central Africa
Gambia	2019/20	West Africa
Guinea	2018	West Africa
India	2021	South Asia
Jordan	2017/18	Western Asia
Liberia	2019/20	West Africa
Madagascar	2021	East Africa
Mauritania	2020/21	Northwest Africa
Mali	2018	West Africa
Nigeria	2018	West Africa
Pakistan	2017/18	South Asia
Philippines	2017	Southeast Asia
Rwanda	2019/20	East Africa
Sierra Leone	2019	West Africa
Tajikistan	2017	Central Asia
Zambia	2018	Southern Africa

Statistical analyses

This study used PSM to draw causal inferences about the effect of eight or more ANC on health facility delivery, and early PNC. PSM is a statistical method that allows us to evaluate the treatment effects for observational data, in cases where randomized controlled trials are either infeasible, unethical, or when researchers need to evaluate treatment effects from survey data (31). It reduces bias due to observable individual characteristics by matching and helps create comparable balanced groups of respondents with respect to observed covariates (25).

STATA V.14.2 software was used to clean, recode, and analyze the data. Pscore Stata command was used to generate the propensity score including covariates associated with ANC visits (treatment variable) and both outcomes. The common support option was employed to limit testing of the balancing property to only treated mothers whose propensity scores for health facility delivery and EPNC were within the propensity score range. The average treatment effect on the treated (ATT) was estimated using the psmatch2 or teffects psmatch Stata command. To generate ATT, one-to-one nearest neighbor matching with replacement within a caliper range of ± 0.01 was performed. Balancing tests were performed using the pstest stata command. For each covariate included in the propensity score estimation model, percentage (%) bias and % reduction bias were reported. Finally, a sensitivity analysis was undertaken to assess the assumption of the unconfoundedness of PSM using a Mantel-Haenszel bounds procedure.

TABLE 2 Socio-demographic characteristics of study subjects in LMICs.

Variables	Categories	Antenatal care visits	
		<8 visits (%)	≥8 visits (%)
Maternal age	15–24	32,662 (85.78)	5,413 (14.22)
	25–34	35,033 (81.97)	7,705 (18.03)
	35–49	8,490 (84.76)	1,527 (15.24)
Women's education	Not educated	22,398 (93.15)	1,646 (6.85)
	Primary	14,332 (90.63)	1,481 (9.37)
	Secondary	31,741 (80.76)	7,560 (19.24)
	Higher	7,714 (83.88)	3,958 (16.12)
Wealth status	Poorest	21,528 (90.90)	2,155 (9.10)
	Poorer	18,245 (87.36)	2,639 (12.64)
	Middle	15,101 (82.80)	3,136 (17.20)
	Richer	12,289 (78.42)	3,381 (21.58)
	Richest	9,022 (73.02)	3,334 (26.98)
Marital status	Not in a union	3,722 (89.62)	431 (10.38)
	Married	72,463 (83.60)	14,214 (16.40)
Pregnancy wanted	No	11,214 (88.06)	1,520 (11.94)
	Yes	64,971 (83.19)	13,125 (16.81)
Frequency of watching television	No	34,451 (91.87)	3,047 (8.13)
	Yes	41,734 (78.25)	11,598 (21.75)
Frequency of listening to a radio	No	55,143 (84.58)	10,050 (15.42)
	Yes	21,042 (82.08)	4,595 (17.92)
Frequency of reading newspaper/magazine	No	61,619 (86.47)	9,645 (13.53)
	Yes	14,566 (74.45)	5,000 (25.55)
Birth order	1	23,599 (80.10)	5,864 (19.90)
	2–5	44,787 (84.64)	8,128 (15.36)
	>6	7,799 (92.27)	653 (7.73)
Sex of household head	Male	64,163 (83.64)	12,553 (16.36)
	Female	12,022 (85.18)	2,092 (14.82)
Residence	Urban	18,276 (74.74)	6,178 (25.26)
	Rural	57,909 (87.24)	8,467 (12.76)
Accessing healthcare	Big problem	35,239 (79.92)	8,853 (20.08)
	Not big problem	40,943 (87.61)	5,791 (12.39)

TABLE 3 Model significance and estimated propensity scores.

Model significance	Sample	Pseudo-R2	LR chi2	<i>p</i> > chi2
	Unmatched	0.089	7180.52	0.000
	Matched	<0.001	20.19	0.043
Mean propensity score		0.16		
Standard deviation		0.10		
Region of common support		0.015–0.565		

Results

Background characteristics of study participants

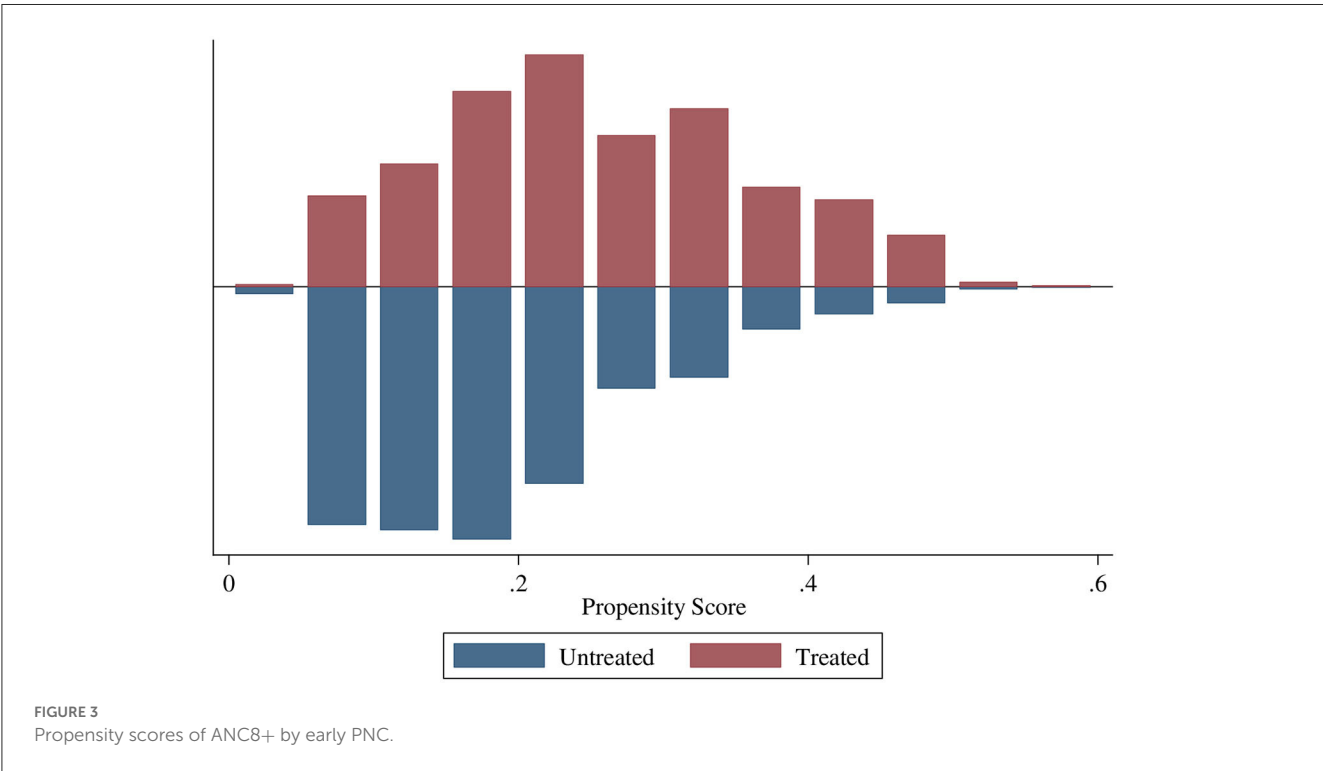
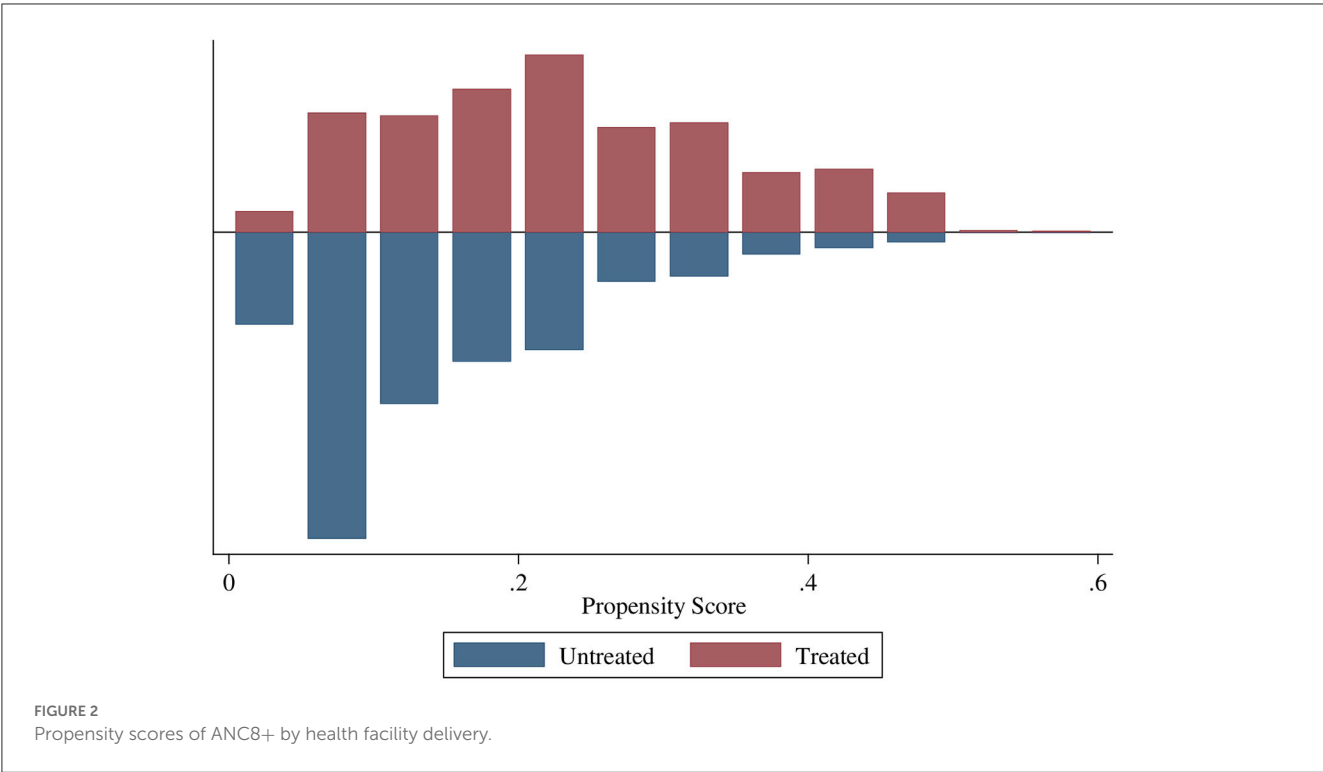
A total of 90,830 women were included in the analysis. Of the total, 47.05% were aged 25–34 years and 43.27% had attained secondary education. In total, 95.43% of women were married and only 15.54% of them were head of the household. Almost half (49.07%) of the participants were from low-wealth quintile households (poorest and poorer). In total, 85.98% of women had a wanted pregnancy. In total, 58.72% of respondents watch television. Almost a third-fourth (73.08%) of participants were rural residents, and healthcare access was a big problem for more than half (51.45%) of them (Table 2).

Estimated propensity scores and model significance

The mean propensity score was 0.16, with a standard deviation of 0.10 indicating the variability is little between the treatment and control groups. Regarding model significance, the pseudo-R2 before matching and after matching was 0.089 and <0.001, respectively. Very low pseudo-R2 (<0.001) indicates the distribution of covariates between both groups was similar (Table 3).

Common support

The region of common support ranges from 0.015 to 0.565. The common support improves the quality of matching by discarding individuals when there is no availability of a match. The treatment (ANC8 + visits) and control (<8 ANC visits) groups are matched and comparable as the quality of matching by health facility delivery and early PNC were balanced with no off support (Figures 2, 3).



Average treatment effect of ANC8+ on health facility delivery and EPNC

Our study showed that the average treatment effect on the treated (ATT) on facility delivery and early PNC was 0.14 and 0.10, respectively. This indicates that the probability of facility-based

delivery was 14% higher among treated women (who have ANC8+ visits) compared with the control group. Meanwhile, women who had ANC 8+ have an increased chance of having early PNC by 10% compared with those who had not. The net difference of ANC4 between treated and control was higher on institutional delivery; however, the ANC8+ had more impact on the EPNC. Generally,

TABLE 4 Estimation of average treatment effect on the treated, average treatment effect on the untreated, and average treatment effect of 8+ ANC visits on facility delivery and early PNC.

Variable	Sample	Treated	Control	Difference	SE
ANC8+ on institutional delivery	Unmatched	0.94	0.76	0.18	0.004
	ATT	0.94	0.80	0.14	0.013
	ATU	0.76	0.88	0.11	
	ATE			0.12	
ANC8+ on early PNC	Unmatched	0.76	0.65	0.11	0.004
	ATT	0.72	0.62	0.10	0.016
	ATU	0.73	0.65	0.08	
	ATE			0.08	
ANC4+ on institutional delivery	Unmatched	0.86	0.68	0.18	0.002
	ATT	0.86	0.62	0.24	0.017
	ATU	0.68	0.82	0.14	
	ATE			0.19	
ANC4+ on early PNC	Unmatched	0.71	0.65	0.06	0.004
	ATT	0.71	0.64	0.07	0.016
	ATU	0.77	0.66	0.05	
	ATE			0.06	

the ATT of ANC8+ has more impact in the treated (94%), while in ANC4+ it is 86% (Table 4).

Balancing test

This study depicted before and after matching mean values and bias of each covariate in both groups. There is a percentage bias reduction for all matching covariates presented along with the *t*-test. The significance level of the *t*-test was also calculated, and it showed that the majority of covariates were balanced (Table 5).

Sensitivity analysis for hidden bias

The sensitivity analysis was performed using the Mantel-Haenszel statistic to estimate the extent of unobservable covariates biases on our inferences about the effects of 8+ ANC visits. The *Q_{mh}*+ statistic adjusts the MH statistic downward for positive unobserved selection bias, and as the estimated ANC visits effect is positively related to outcome variables, we focused on the positive bias. Based on this, a critical value >1.4 indicates that the result will be insensitive and the conclusion could be uncertain (Supplementary Table).

Discussion

Maternal and child mortality remain a substantial public health concern worldwide, especially in LMICs (2, 32, 33). Complications during pregnancy and childbirth are the leading causes of maternal and child deaths (34, 35). The WHO recommended ANC8+ visits

as a key strategy to endorse pregnant women's health (9). In addition to ANC visits, health facility delivery and early PNC have been reported as major contributors to preserving women's and child's health (28, 36, 37). Previous studies showed that prenatal care is an imperative factor for subsequent healthcare utilization (38–40). This study revealed that ANC8+ visits have a significant and positive influence on health facility delivery as well as EPNC.

We used an innovative statistical method called the propensity score matching (PSM) to understand the net impact of ANC8+ visits on health facility delivery and EPNC. This method is useful to ensure that study participants in the control and treatment groups are similar based on measured characteristics. PSM reduces selection bias and offers an alternative for measuring treatment effects in cross-sectional/observational/non-experimental data when randomized clinical trials are not possible or unethical. Therefore, the groups are the same except for the treatment variable ensuring a less-biased estimate of treatment effects.

This study found that women who attended ANC8+ visits had a 14% higher chance of having their delivery at health facilities. Our finding was supported by previous studies conducted in the developing world (41–43). For example, a study from Uganda assessed the impact of ANC visits based on previous WHO recommendations (ANC4+ visits), and the result showed that the treated women were almost 12 and 10% higher to give birth at health facilities and have EPNC, respectively (26). This is likely due to the fact that women who attend adequate ANC receive maternal education and are often referred to health facilities for delivery. However, this result showed that ANC4+ contact has more impact (24%) on health facility delivery. Generally, we can conclude that adequate ANC contacts are critical for institutional delivery.

TABLE 5 Comparison of the standardized differences of baseline characteristics before and after matching.

Variable	Sample	Treated	Control	Bias	% reduction bias	<i>t</i>	<i>p</i> > <i>t</i>
Age	Unmatched	1.7357	1.6827	8.0		8.74	0.000
	Matched	1.7347	1.7296	0.8	90.3	0.68	0.495
Education status	Unmatched	1.9443	1.3252	64.8		69.36	0.000
	Matched	1.9443	1.9375	0.7	98.9	0.65	0.514
Wealth status	Unmatched	3.2117	2.5935	45.4		50.46	0.000
	Matched	3.2117	3.2432	−2.3	94.9	−1.98	0.048
Marital status	Unmatched	0.97057	0.95114	10.0		10.31	0.000
	Matched	0.97057	0.97521	−2.4	76.1	−2.45	0.014
Pregnancy wanted	Unmatched	0.89621	0.8528	13.1		13.87	0.000
	Matched	0.89621	0.90345	−2.2	83.3	−2.06	0.039
Frequency of watching television	Unmatched	1.3908	0.91195	55.8		59.62	0.000
	Matched	1.3908	1.396	−0.6	98.9	−0.55	0.585
Frequency of listening to radio	Unmatched	0.45401	0.41214	5.8		6.41	0.000
	Matched	0.45401	0.45005	0.5	90.5	0.46	0.642
Frequency of reading newspaper/magazine	Unmatched	0.47054	0.25184	34.2		41.43	0.000
	Matched	0.47054	0.46064	1.5	95.5	1.19	0.232
Birth order	Unmatched	1.6442	1.7926	−25.3		−27.39	0.000
	Matched	1.6442	1.6422	0.3	98.7	0.30	0.763
Sex of household head	Unmatched	1.1428	1.1578	−4.2		−4.58	0.000
	Matched	1.1428	1.1393	1.0	76.3	0.87	0.383
Residence	Unmatched	1.5781	1.7601	−39.4		−46.00	0.000
	Matched	1.5781	1.5802	−0.4	98.9	−0.36	0.723
Accessing healthcare	Unmatched	0.55401	0.51214	5.8		6.41	0.000
	Matched	0.55401	0.55005	0.5	90.5	0.46	0.642

Therefore, this health facility delivery in turn could advantageous for pregnant women to attend early PNC.

This study further showed that women who had ANC8+ visits were associated with a 10% higher probability of early PNC compared with their counterparts. ANC8+ contact showed a strong impact (10%) compared with ANC4+ contacts (7%) on EPNC. In LMICs, PNC is one of the most underutilized and weakest of all maternal and child health services. The result aligns with previous studies, which highlighted a positive association between ANC8+ visits and early PNC utilization (26, 44). This is probably because frequent contact with healthcare providers throughout the ANC period would create an understanding of the importance of attending early PNC.

Our study has strengths and weaknesses. Among the strengths, we used a large sample and conducted a propensity score matching to reduce selection bias between groups based on observable confounders. This gives better and unbiased estimates of the treatment effects of ANC8+ visits. Even though including women who had given birth within the year prior to the surveys is the

strength of this study to reduce recall bias compared with previous studies that included women who had given birth within 5 years prior to the surveys, still recall bias could happen (ANC8+). Among the weaknesses, although PSM removes bias based on observable variables, bias due to unobservable confounders (hidden bias) is not accounted for and could lead to overestimated effects of the treatment on outcome variables. Moreover, important covariates which may directly affect the net impact such as women with a high risk of pregnancy were not included.

Conclusion and recommendation

Our study confirmed that ANC8+ visits significantly increased the likelihood of health facility-based delivery and early PNC utilization in LMICs. Health policymakers and healthcare providers should focus on and target pregnant women to attend adequate ANC visits (according to revised WHO recommendation) as our study indicates that ANC8+ visits significantly improved the

chances of subsequent care, particularly the early PNC compared with the ANC4 visits.

Data availability statement

Publicly available datasets were analyzed in this study. This data can be found here: https://dhsprogram.com/data/dataset_admin/index.cfm.

Author contributions

DC: conceptualization. DC, FA, DB, MA, MM, AK, NT, and AA: study design, execution, acquisition of the data, analysis and interpretation, writing, and review and editing. All authors contributed to the article and approved the submitted version.

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Conflict of interest

The authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

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Supplementary material

The Supplementary Material for this article can be found online at: <https://www.frontiersin.org/articles/10.3389/fmed.2023.1107008/full#supplementary-material>

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EDITED BY

Nita Bhandari,
Center for Health Research and Development,
Society for Applied Studies, India

REVIEWED BY

Karleen Gribble,
Western Sydney University, Australia
Jing Zhu,
Beijing Academy of Science and
Technology, China
Jennifer Cashin,
FHI 360, United States

*CORRESPONDENCE

Archisman Mohapatra
✉ archisman.m@thegridcouncil.org
Arti Maria
✉ artimaria@gmail.com

[†]These authors have contributed equally to this work

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Implementing recommended breastfeeding practices in healthcare facilities in India during the COVID-19 pandemic: a scoping review of health system bottlenecks and potential solutions

Nonita Dudeja^{1†}, Divita Sharma^{1†}, Arti Maria^{2*}, Priyanka Pawar¹,
Ritika Mukherjee¹, Shikha Nargotra¹ and Archisman Mohapatra^{1*}

¹Generating Research Insights for Development (GRID) Council, Executive Office, Noida, Uttar Pradesh, India, ²Department of Neonatology, Atal Bihari Vajpayee Institute of Medical Sciences and Dr. Ram Manohar Lohia Hospital, New Delhi, India

Background: Breastfeeding practices in institutional settings got disrupted during the COVID-19 pandemic. We reviewed the challenges faced and the “work-around” solutions identified for implementing recommended breastfeeding practices in institutionalized mother-newborn dyads in resource constrained settings during the pandemic with the aim to identify learnings that could be potentially adapted to the Indian and relatable contexts, for building resilient health systems.

Methods: We conducted a scoping review of literature using the PRISMA ScR Extension guidelines. We searched the Medline via PubMed and Web of Science databases for literature published between 1st December 2019 and 15th April 2022. We included original research, reviews, and policy recommendations published in English language and on India while others were excluded. Further, we searched for relevant gray literature on Google (free word search), websites of government and major professional bodies in India. Three reviewers independently conducted screening and data extraction and the results were displayed in tabular form. Challenges and potential solutions for breastfeeding were identified and were categorized under one or more suitable headings based on the WHO building blocks for health systems.

Results: We extracted data from 28 papers that were deemed eligible. Challenges were identified across all the six building blocks. Lack of standard guidelines for crisis management, separation of the newborn from the mother immediately after birth, inadequate logistics and resources for infection prevention and control, limited health workforce, extensive use of formula and alternative foods, inconsistent quality of care and breastfeeding support, poor awareness among beneficiaries about breastfeeding practices (and especially, about its safety during the pandemic) were some of the challenges identified. The solutions primarily focused on the development of standard guidelines and operating procedures, restricted use of formula, use of telemedicine services for counseling and awareness and improving resource availability for risk mitigation through strategic mobilization.

Conclusion: The COVID-19 pandemic has provided rich learning opportunities for health system strengthening in India. Countries must strengthen learning mechanisms to identify and adapt best practices from within their health systems and from other relatable settings.

KEYWORDS

breastfeeding, COVID-19, maternal health, newborn care, hospital

1. Introduction

Breastfeeding is one of the best known interventions to reduce neonatal and infant mortality (1). However, despite investment in efforts, the 2019 Global Breastfeeding Score Card by World Health Organization (WHO) and United Nations Children's Emergency Fund (UNICEF) reported that breastfeeding practices were universally in poor alignment with the recommendations, especially in resource constrained settings (2–5). The COVID-19 pandemic that hit in 2020 caused further disruption to routine institutional breastfeeding practices in India and other low and middle income countries, and the rates are likely to have suffered further (6, 7).

India has the largest annual birth cohort in the world; about 23 million babies are born in India every year which is almost equal to the annual birth cohort of the next three countries i.e., China, Nigeria and Pakistan taken together. There is strong commitment to improve breastfeeding practices in healthcare facilities in India. However, inconsistencies persist. As per the latest National Family Health Survey [NFHS-5 (2019–21); India's Demographic Health Survey], while 88.6% of the deliveries in India happen in institutional settings, only about 42% of mothers manage to breastfeed their newborn within an hour of delivery (early initiation of breastfeeding) (8). This suggests that there is much need for strengthening breastfeeding practices in institutionalized mother-newborn dyads (9–13). It must be acknowledged that the aforementioned statistics could be an oversimplification. While on one hand there are health facilities both in the government and in the private sector that have world-class practices and capacity, there are the ones that are compromised in terms of skill, capacity and motivation. Thus, India provides a rich context for health system learning that need not be limited to within-country consumption but of immense value for global debate and adaptation (14–16). In the past, learnings from India have influenced global health action for maternal and child health. For example, India was the first country to launch a family planning program. India's Anganwadi Program is the largest community-based program in the world for early childhood education and nutrition (17). Even for polio eradication and for strengthening newborn programs, insights from India have been leveraged by other countries (18, 19). As the largest member in the South East Asia Region, India has major influence in the region's health performance and policy decisions. Nevertheless, the Indian context continues to be heterogeneous, resource inconsistent and complex with ample opportunity for improvement, standardization and cross-learning (20, 21).

The COVID-19 pandemic challenged the well-established practices of newborn care (22–24). At the beginning of the pandemic, the possibility of vertical or horizontal transmission was unknown, and it was not fully understood how neonates could be affected. Further, the pandemic posed challenges to the quality of care at health care institutions on various fronts including provisions for breastfeeding support to the mother and her newborn, kangaroo mother care (KMC), family participatory care, and human milk bank operations (6, 25, 26). Fears around the spread of COVID-19 infection, lack of resources, technical and infrastructural limitations and lack of coherent guidelines coincided with the simultaneous efforts toward protecting institutional practices for breastfeeding. Concerns revolved around practicing skin-to-skin contact (SSC), rooming-in and breastfeeding by COVID-19 suspected, probable or confirmed mothers.

In early 2020, WHO conducted a living systematic review, to identify studies including mothers with suspected or confirmed COVID-19 and their infants or young children, in order to assess the outcomes of COVID-19 infected mothers who were breastfeeding (27). It was found that the risk of COVID-19 infection was low and the infection was typically mild or asymptomatic in newborns, while the results of not breastfeeding and separation of mother and the newborn were significantly negative (27). Consequently, WHO recommended that mothers who were suspected, probable, or confirmed cases of COVID-19 should follow standard infant feeding practices along with necessary precautions for IPC. These recommendations included that for continuous and prolonged skin-to-skin contact immediately after birth, initiation of breastfeeding within 1 h of birth, rooming-in and exclusive breastfeeding. Mothers were advised to mandatorily take IPC precautions, including hand washing, using medical masks and cleaning of frequently touched surfaces (28). However, a survey of 33 countries conducted around that time showed that the guidelines in these countries were not in alignment with the recommendations from WHO (29). As knowledge accrued over the year 2020, many studies started reporting on neonatal outcomes and recommended approaches to handling of the mother-infant dyad during the COVID-19 pandemic. Gradually, countries' guidelines including those released by the Indian scientific bodies got in line with those from WHO (30, 31). Nevertheless, the chaos that prevailed in the meanwhile led to several work around solutions, some as innovations for resource optimization while many as temporary make-shift arrangements. These called for a careful compilation and gave an opportunity for critical learning.

This review was planned with a view to understand the breastfeeding related challenges in institutional settings during the COVID-19 pandemic and the approaches identified as measures to combat these challenges in resource constrained settings with India as a candidate example. The purpose was to collate scientific evidence on key interventions that may be useful in implementing recommended breastfeeding practices with resilience within institutional settings for mother-newborn dyads in India and relatable contexts in the event of a future pandemic/public health crisis.

2. Methods

The review followed the scoping review extension of Preferred Reporting Items for Systematic Review and Meta-Analysis (PRISMA-ScR) guidelines.

2.1. Data sources and search strategy

We searched Medline via PubMed and Web of Science databases for the combinations of four sets of keywords. The first set consisted of the words: “mother”, “female”, “woman”, “neonate”, “newborn”, “infant”, “nursing mother”. The second set included: “pandemic”, “COVID-19”, “Coronavirus”, “SARS CoV-2”, “severe acute respiratory syndrome coronavirus 2”. The third set included: “breastfeeding”, “breast feed”, “lactation”. The fourth set included: “institutionalized”, “hospitalized”, “maternity ward”, “nursery”. The words in each set were separated by an OR Boolean. We used all word variations and the searches were done in the title and abstract as well as MeSH word search. The fourth set of words were searched in all fields. In the final search, we used combination of words from the four sets by placing AND between the search sets (detailed search strategy is presented in [Supplementary Table 1](#)). The search was conducted for the time frame of 1 December 2019 to 15 April 2022. All study designs were included. We restricted the search to articles from India with an aim to collate information for the Indian context. Further, we searched for relevant gray literature using similar keywords (for e.g., mother, breastfeeding, lactation, COVID-19, hospital, etc.) as that of the search strategy on Google (free word search), Government of India website (www.nhm.gov.in) and on websites of major professional bodies in India i.e., IAP, NNF, FOGSI, BPNI, IAPSM, IPHA, WHO, and UNICEF; we looked for policy documents, guidelines and advisories.

2.2. Article selection and data extraction

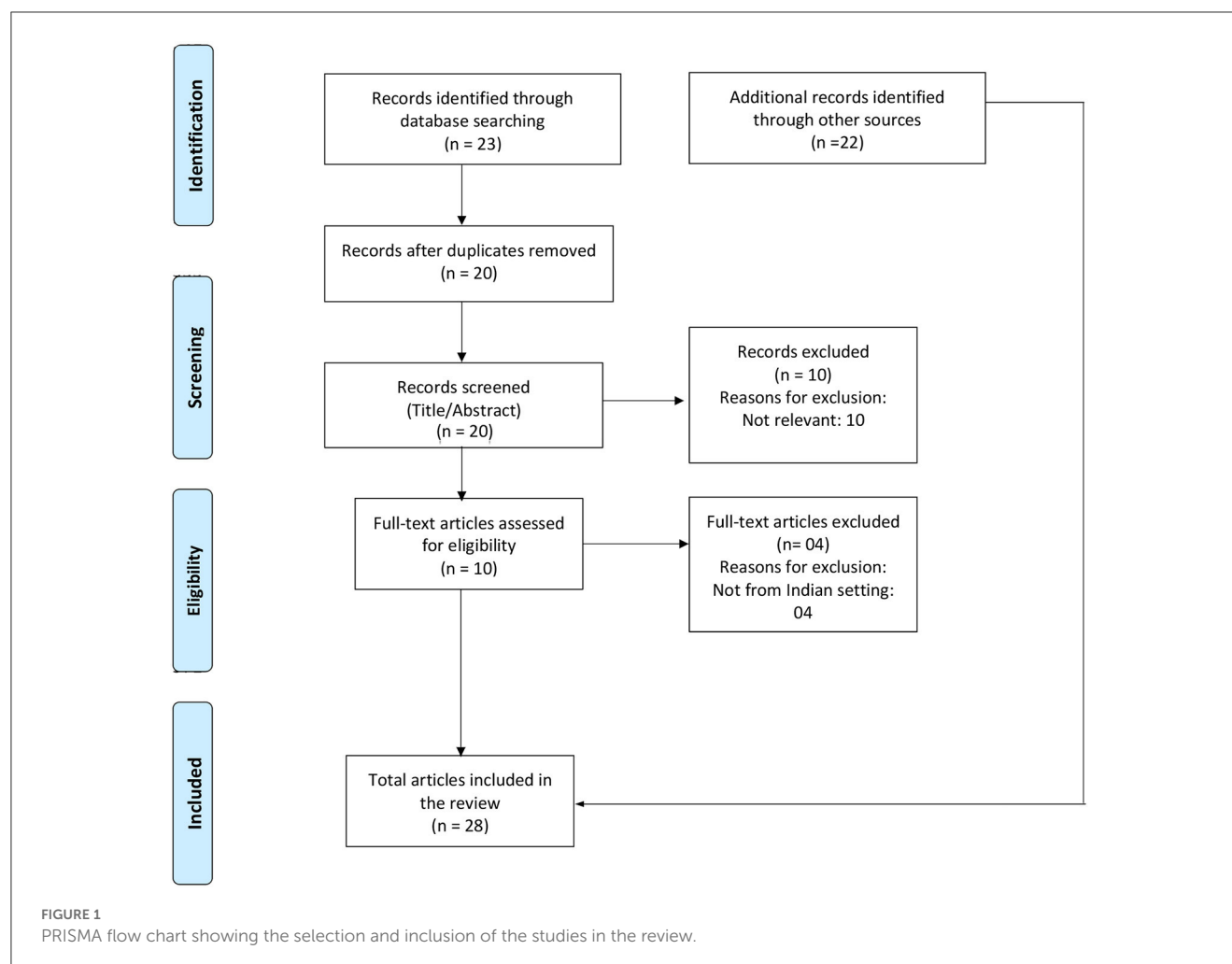
Three researchers (ND, DS, SN) independently screened the title and abstracts of the documents identified through the search, followed by screening those short-listed by reviewing the full text. The conflicts were resolved after discussion and fourth reviewer's comments, if necessary. Thereafter, information relevant to the study objectives was extracted onto a pre-defined data extraction tool. Extracted

information included details about the study characteristics (authors, country, publication dates, study design, location), objectives, inclusion/exclusion criteria, major findings related to breastfeeding practices and potential solutions suggested by authors of the evidence gathered. The analysis and summary of gray literature were recorded in the same way as it was done for primary studies. Data extraction form is given in [Supplementary File](#).

2.3. Data analysis

Challenges and potential solutions were identified from each study and from the gray literature were listed and categorized under one or more suitable headings based on the WHO building blocks for health systems (32). This framework describes health systems in terms of six core components or “building blocks” viz (i) leadership/governance, (ii) healthcare financing, (iii) health workforce, (iv) access to essential medicines, (v) service delivery, and (vi) health information systems, and has been a popular framework used for health systems research over the years. Studies conducted for assessing if the framework served the purpose for strengthening public health facilities in resource constrained settings have reported in its favor (33). We identified bottlenecks for each building block and they were tabulated as challenges with their potential solutions. Following working definitions were used:

- **Bottleneck:** any factor that hinders or limits the ability of a health system to deliver the care as per recommended guidelines and therefore poses a barrier to delivering high quality maternal and newborn care to improve health outcomes.
- **Leadership/governance:** refers to the management and governance of the health system, including policy development, regulation, and accountability, effectiveness of regulatory frameworks, new organizational practices and policies, capacity to assemble and manage resources.
- **Healthcare financing:** refers to the availability and use of financial resources to support the health system; efficient and effective healthcare financing system, effective budget consumption, ensuring financial sustainability, and cost-effective interventions.
- **Health workforce:** refers to the availability, distribution, and quality of health workers; number of health workers, their training and qualifications, motivation, appropriate and timely feedback.
- **Access to essential medicines:** refers to the availability and affordability of essential medicines, vaccines, and technologies; availability and affordability of essential medicines, the quality of medicines and technologies, effectiveness of procurement and supply chain management, networking with the external environment.
- **Service Delivery:** refers to the provision of essential health services to individuals and populations; on-time services, mode of communication suitable to patients, and coverage of essential health services.



- Health information systems: refers to the availability and use of reliable health information to support decision-making, planning, and management; availability of health information technology, up-to-date and appropriate guidelines and protocols.

($n = 3$), guidance documents ($n = 3$), professional bodies' recommendations ($n = 3$), narrative/expert reviews ($n = 2$), commentaries ($n = 2$), updates and advisories ($n = 2$), position papers and alerts ($n = 2$), case report ($n = 1$), and clinical practice guidelines ($n = 1$). The included articles and their main findings are given in [Supplementary Table 2](#).

3. Results

3.1. Study selection

The database search generated 23 articles. After removing duplicates ($n = 3$) and irrelevant articles ($n = 14$), 6 articles were shortlisted. After adding the resources from gray literature ($n = 22$), a total of 28 documents were included in the review. The PRISMA flow diagram shows the details of the selection of the documents ([Figure 1](#)).

3.2. Study characteristics

The 28 documents selected included open letters ($n = 5$), original research articles ($n = 4$), press releases and news briefs

3.3. Challenges to implementing recommended breastfeeding practices in institutionalized recently delivered mothers, and reported solutions

The primary challenge that surfaced from the study findings was the lack of accurate information on best practices for breastfeeding during a pandemic. This included the absence of standard guidelines, confusion among healthcare workers, and inadequate materials for educating and promoting breastfeeding during COVID-19. Most of the challenges identified were categorized under health service delivery, health workforce, and health management information systems. Specifically, 39.3% of the documents addressed challenges related to leadership

TABLE 1 Distribution of challenges under the WHO building blocks.

Health system building block	Number of challenges identified	Number of studies/documents* (N = 28)
Leadership and governance	2	11 (39.3)
Health financing	2	2 (7.1)
Health workforce	5	9 (32.1)
Essential medical products and technologies	2	5 (17.9)
Health service delivery	8	10 (35.7)
Health information system	5	6 (21.4)

*The percentage will not be equal to 100% as the challenges are addressed in more than one document.

and governance, while 35.7% addressed challenges related to health service delivery. In addition, challenges pertaining to the health workforce domain were found in approximately 32.1% of the documents, while 21.4% of the identified challenges fell under the health information system domain. Finally, around 17.9% and 7.1% of the documents included challenges related to the essential medicines and health financing domains, respectively (Table 1).

3.3.1. Leadership and governance

In the initial days, guidelines for breastfeeding during COVID-19 were not in place which led to poor decision-making and planning, and a lot of confusion and misinformation among the healthcare delivery staff as well as the mother and her family (34–38). For example, some guidelines recommended that mothers with COVID-19 should be separated from their infants (38–40). This could have contributed to restriction of skin-to-skin contact and rooming-in in recently delivered mother-newborn dyads. Timely issuance of guidelines/notifications to healthcare providers in all the institutions and case-to-case based decision making on separating mothers and infants were some of the solutions in the literature to overcome this challenge (34, 40–45).

3.3.2. Healthcare financing

Documents reported about the inadequacy of funds for scaling up breastfeeding initiation both in terms of deploying dedicated human resource and logistics (42, 44). For example, availability of donor milk or expressing milk were some of the measures mentioned in the guidelines when direct breastfeeding was not possible. However, maintenance and transportation of donor milk and equipment like breast pumps required additional funding support which was not adequately available. Provision of separate funds for breastfeeding initiation and scale up in hospitals was a probable solution suggested (42, 44).

3.3.3. Health workforce

Health workforce challenges primarily included shortage of health workers, lack of training in breastfeeding support and supervision in the hospitals (36, 37). Many healthcare workers were diverted to COVID-19 management tasks including contact tracing, laboratory testing, triaging and emergency care, leading to disruption of routine healthcare services (42). Additionally, there was a lot of confusion regarding breastfeeding practices during the pandemic. In such situation, health workers were unable to impart the usual counseling and support to mothers regarding breastfeeding (46). The documents recommended that responsive management practices be adopted for improving the workforce situation both in terms of quantity and quality by expeditiously recruiting and training human resources for health and strengthening their knowledge through webinars, online training, etc (36, 39, 42, 46–48).

3.3.4. Access to essential medicines, medical products, and technology

Lack of essential medicines and equipment was another set of challenges observed during the pandemic. Supply and logistics chain was disrupted; there was constant shortage of personal protective equipment (PPEs) and other essential medicines and equipment. Challenges were identified at two levels i.e., the facilities being historically under-resourced and procurement being relatively slow (36, 39). These being systemic challenges that may not be amenable to immediate correction, the reports suggested to focus on improving patient awareness and hospital staff for strengthened IPC for optimizing the need for resource reinforcement (36, 40, 42, 48, 49).

3.3.5. Health service delivery

Service delivery was affected mainly due to disruption in the availability and quality of breastfeeding support. Physical and logistical constraints like lack of space to monitor mothers during breastfeeding and lack of lactation counseling, poor quality of care issues and poor implementation of skin-to-skin contact and possibility of iatrogenic transmission of COVID-19 infection were some of the challenges under this domain (36, 38, 39, 43, 50). The guidelines mandated delivery of basic psychosocial and lactating support to mothers, training to providers and family members regarding breastfeeding support and continued SSC to streamline breastfeeding practices (36, 42–45, 51).

3.3.6. Health information system

A major challenge was the lack of information on breastfeeding initiation and practices in the health management information system (36). Community ownership and partnership related challenges included poor awareness among public regarding exclusive breastfeeding and correct breastfeeding techniques, fear of contracting infection and sociocultural barriers (36, 38, 50, 52). Subsequently, there was a lot of misinformation which led to stress and anxiety among mothers and other family

members (36, 43). Awareness campaigns and workshops through videos, infographics, live chats and helplines by professionals and health workers was one potential solution to deal with this challenge (35, 36, 47). It was also suggested that systems should be put in place to ensure that data related to breastfeeding practices was adequately recorded in the hospital's health information database for informing subsequent action (50).

The details of the challenges and suggested solutions for these challenges have been listed in Table 2.

4. Discussion

This review highlights the issues surrounding breastfeeding practices in institutionalized recently delivered mother-newborn dyads in India during the COVID-19 pandemic. Separation of mother and the newborn immediately after birth, inadequate human resources and resources for infection control practices, besides unavailability of supportive guidelines and protocols made implementation of recommended breastfeeding practices difficult. Infrastructural gaps e.g., donor milk storage and milk transport support, resulted in use of alternative feeding methods like formula milk. Solutions suggested by the evidence primarily focused on timely issuance of standard guidelines and protocols, awareness generation, lactation support and training of health care professionals regarding methods and importance of optimal breastfeeding practices. Use of telemedicine technology and group sessions were suggested by few articles as alternative strategies. We observed that institutions could identify work around solutions for every challenge they faced though many of these could be temporary. Thus, we are encouraged to infer that there is hope to work toward improved health system preparedness for resilience during health emergencies.

In hospital settings, it has been reported that separation of the mother and the baby at birth and delay in initiating breastfeeding during the COVID-19 pandemic had lasting adverse effect on breast milk feeding outcomes even in well-resourced contexts (54). In their review, Spatz et al. go on further to report that lack of skin-to-skin contact, inadequate lactation support, and insufficient care and education for mothers served as additional challenges to breastfeeding during the pandemic (55). Kotlar et al. also revealed that weak healthcare infrastructure and resources negatively impacted maternal outcomes and breastfeeding practices (48). These were the major challenges identified in our review as well. In our review, bottlenecks were noted for all the six building blocks of health systems with the maximum number of challenges being identified in the blocks of health service delivery ($n = 8$), health workforce ($n = 5$) and health management information system ($n = 5$). Of the six building blocks, challenges in the leadership and governance block appeared in the maximum number of documents that we reviewed (in 11 of 28; 39.3%). Two challenges were noted in the leadership and governance block i.e., unavailability of guidelines and separation of the mother and the newborn at birth. Similarly, even if just two articles mentioned about challenges with health financing, these

were quite serious ones—lack of resources for institutional infrastructure and inadequate cover for out-of-pocket expenditure. Thus, these two blocks could have offered significant operational and structural challenges to surge planning during the pandemic. In 2015, Dickson et al. in follow-through to the Every Newborn Action Plan and the Strategy for Ending Preventable Maternal Mortality (EPMM), did an in-depth analysis of health systems bottlenecks for scaling up quality interventions for newborn care in 12 low-and-middle-income countries in the Indian sub-continent and in Africa (56). They found that the major health system bottlenecks for breastfeeding were of health financing, health service delivery, health workforce, and essential medical products and technologies. Our findings concur with this. We, hence, observe that the pandemic uncovered inherent gaps in health systems for breastfeeding and if these gaps were plugged with contextual interventions, then the system could become more resilient.

We believe that the absence of clear, evidence-based guidelines in the local or regional context (block: leadership and governance) had a central role to play in the disruptions that the pandemic caused to institutional breastfeeding practices. Countries across the globe followed different approaches and protocols at the beginning of the pandemic. There were several modifications to international recommendations for breastfeeding at the hospital during the first year of the COVID-19 pandemic (57–59). Early in the pandemic, researchers through a collaborative effort conducted a review of 33 countries to assess the alignment of their national guidelines for maternal and child health practices during the pandemic with WHO recommendations. They found that none of these recommended all the aspects of the WHO guidance (29). India, like several other countries, had missed on many WHO recommended practices in the initial course of the pandemic (29, 30). Practices that had been overlooked initially were that of rooming-in, early initiation of breastfeeding and direct breastfeeding with infection control measures. However, in due course of time, India improved its alignment score by six points, as reported in a study by Gible et al., where 101 countries' guidelines were scored based on their alignment with WHO recommendations (30). We, thus, appreciate the leadership that WHO recommendations could play in motivating member states in sustaining breastfeeding practices during public health emergencies despite resource constraints, and the intentionality of countries to make efforts for safeguarding recommended breastfeeding practices.

A system with a strong resource base is likely to be more resilient to disruptions. India's health system is impeded by years of under-investment.

India allocates 1.3% of the GDP to health which is much less than other countries where the average share is 3.6–7% (60). Furthermore, the country does not have a dedicated workforce for supporting breastfeeding practices, even in its most apex healthcare institutions. Consequently, the inherent fragility of the institutional practices for breastfeeding was obvious in the initial days of the pandemic. Nevertheless, it was also evident that the country's health system has the potential to learn and adapt. Putting the needful systems in place and consistently updating the existing capacity is needed to make the breastfeeding

TABLE 2 Challenges to optimal breastfeeding practices and the potential solutions.

Health system building block	Sub-category	Significant challenges	Suggested solutions
Leadership and Governance	Policy and guidelines	Absence of national policies/strategies and/or service guidelines for breastfeeding during the COVID-19 pandemic (34–38)	Issuance of guidelines/notifications to healthcare providers in both government and private hospitals for breastfeeding practices in institutionalized mothers (34, 41)
		Mother infant separation into different wards or within the same room based on suspected/confirmed COVID-19 (38–40)	Decision on separation to be made on a case-to-case basis and clinical condition of mother. Rooming-in should be preferred even if the mother and her infant have suspected, probable or confirmed SARS-Co-V2 infection (40, 42–45, 53)
Health financing	Funding	Funding limited or not available for implementation and scale-up. Expression of breast milk and transport requires additional equipment (e.g., breast pumps) which may require funding support (31, 34).	Provision on separate funds for breastfeeding initiation and scale up in hospitals (31, 34).
	Out of pocket costs	Burden of out-of-pocket expenditures by caregivers (34)	
Health Workforce	Number, competence, distribution of health worker	Shortage of competent health workers and poor distribution of properly trained personnel authorized to provide breastfeeding support (36, 37) Diversion of existing health personnel to COVID wards and emergency care disrupting routine health care services (31) Limited staff for carrying out ICPs (36, 38, 39)	Improving workforce in terms of numbers and by training of existing personnel in breastfeeding support (31). Streamlining and ensuring infection control practices in the mother and newborn wards through appointment of new staff and training of existing staff (36, 37).
	Training	Lack of training of health workers on breastfeeding support to mothers during a pandemic (47)	Sensitization of Covid-19 disease managers and training of the health care workers looking after COVID-19 positive mothers in initiation of breastfeeding and supporting mother and family to breastfeed should be included as a part of management strategy of the pandemic. Training can be carried out by subject experts in batches and on a periodic basis to ensure all rotating staff are also covered (29, 45). Strengthening of knowledge regarding common neonatal issues, especially breastfeeding, among all pediatricians and obstetricians (36) Sensitisation of officials and frontline functionaries [such as community health workers] on COVID-19 and infant feeding may be conducted through webinars (29, 45). Online training for safe breastfeeding to Anganwadi supervisors in rural parts of the country can be explored in the event of a pandemic (29, 45).
	Mentorship and supervision	Lack of mentorship and supervision mechanisms for breastfeeding (46)	Periodic collection and audit of data on breastfeeding initiation and continuation needs to be put in place to improve supervision mechanisms (40, 46).
Essential medical products and technologies	Resources	Unavailability of resources and supplies needed for donor human milk	Expressed breast milk and donor milk needs to be provided where mother and baby are separated. For this, proper systems should be set in place (40) Greater vigilance of donor screening procedures needs to be followed. Symptomatic/at-risk donors should be avoided (36) Strict hygiene procedures need to be followed while supporting expression, transportation, and handling of milk (40) A social media group of lactating mothers can be developed to motivate them to donate milk and methods may be devised to pick donated milk from homes (45). Funding of research on donor breastmilk and COVID-19 is necessary for future planning (31).
	Procurement	Poor procurement and supply chain logistics for Infection control practices (ICPs) (36, 39)	Hospitals should have isolation zones which should include outpatient, ward, ICU, labor rooms and operation theaters demarcated for COVID-19 infected women. This needs to be achieved primarily by reorganization of exiting infrastructural setup (49) Mothers should have access to appropriate guidance and logistics like masks, water and soap etc. to practice respiratory hygiene in the health facility and at home (40, 42, 49, 53) Individual dedicated breast pumps should be used. After each pumping session, all parts that come into contact with breast milk should be thoroughly washed and the entire pump should be appropriately disinfected as per the manufacturer's instructions (42) All surfaces in the breastfeeding room should be routinely disinfected and cleaned with readily available products (40)

(Continued)

TABLE 2 (Continued)

Health system building block	Sub-category	Significant challenges	Suggested solutions
Health service delivery	Physical and logistical constraints	Lack of space and logistical constraints related to support and monitor mothers during breastfeeding (38)	Counseling for lactating mothers is critical for maintaining breastmilk supply from mother to the baby and should be ensured throughout (42, 53) Restriction of the word “COVID” in both verbal and written statements given to patients alleviates anxiety (43)
		Lack of lactation counseling support (38, 39)	Basic psychosocial support and practical feeding support needs to be provided to manage common breastfeeding difficulties during the post-natal period and should be available in all health facilities (43, 53) Introduction of music and religious book reading sessions can make mothers feel relaxed (31). Providers or family members (with personal protection equipment) should provide support in breastfeeding and caring for new-borns. This training should be reinforced once before discharge and such reinforcement can be continued in the community by health workers (36).
	Quality	Poor quality of care issues and poor implementation of skin-to-skin contact (Kangaroo mother care) (36, 38)	Continued skin to skin contact to be mandatorily practiced (40, 42, 44, 45, 51, 53)
		Possibility of iatrogenic transmission of COVID-19 infection (38)	
		Higher numbers of operative deliveries (50)	
	Follow up	Lack of follow-up of breastfeeding practices after discharge (43)	
	Availability and delivery	Shortage of staff to handle the collection and transfer of expressed mother's milk (36, 50) Poor access to services at the health facility (38)	
Health Information system	Availability of information	Lack of information, records and data on breastfeeding practices and initiation of breastfeeding (36)	Ensuring data related to breastfeeding practices is recorded in hospital health information systems (36)
	Knowledge and Awareness	Lack of awareness and knowledge of benefits of exclusive breastfeeding and correct breast feeding techniques (38) Fear of transmitting COVID-19 to the infant (36, 38) Use of breast milk substitutes (38, 50) Unpredictable, uncertain, serious nature of COVID19, along with misinformation and social isolation contributes to stress and mental morbidity (36, 43)	Information on optimal breastfeeding practices may be disseminated through platforms like calls, live chats, and dedicated helplines (36) Awareness on breastfeeding can be generated through videos and infographics (36) Obstetricians may be involved in awareness programs related to breastfeeding (47, 50) Lactation counselors can use microphone to conduct group counseling while maintaining adequate distance (50) A well -structured seminar/webinar by an expert would be a better way to share crucial information/guidelines where further doubts can be cleared (35) In-person workshop for lactating mother may be conducted (35, 50) One to one virtual consultation may be done to overcome difficulties of feeding during pandemic by volunteer lactation consultants (50) Launch of applications to provide access to skilled counseling support for breastfeeding mothers may be explored (50)
	Socio-cultural barriers	Socio-cultural barriers to the practice of KMC (36) Distribution and donation of breast milk substitutes (38, 52) Administration of alternative supplementary foods (38)	
	Access	Travel restrictions in the form of limited public transport and restriction on private vehicle use. Reduced outpatient clinics (36)	

services strong and resilient to collateral damage from a pandemic. It is important to highlight the fact that recommendations against breastfeeding should not be made without sufficient evidence that they are necessary. At the same time, mass

communication channels can be used to increase awareness regarding early initiation and continued exclusive breastfeeding among the general public to reduce myths and misinformation during pandemics.

4.1. Limitations

The major limitations of this review are that we did not take into account the breastfeeding practices after discharge, at home and thereafter. Understanding that the pandemic situation was exigent, we also acknowledge that available (published) literature may not be comprehensive. Further, we did not include articles from countries other than India. So, there is a likelihood of potentially relatable learnings that remain to be enumerated beyond that highlighted in this manuscript. While our analysis highlights that the challenges to breastfeeding existed across all the six pillars, these were complex and systemic. It is inadequately understood as to how populations and health systems respond to public health emergencies given their unique lived experiences, risk perceptions and preparedness (61). Nevertheless, breastfeeding practices continue to be amenable to socio-cultural influences, at least in resource constrained settings (62–64). The WHO building blocks for health systems does not allow for commentary on interdependencies between the blocks and with due consideration of the socio-cultural context; we accept this as a major limitation to our study since we have weaved our findings around these building blocks. The framework's inadequacies were obvious during the pandemic when global public health approaches demanded systems thinking with due attention to complexities. It is in the pandemic context that governance was identified as the major “under-pinning” of health system strengthening that cuts across all the building blocks (65).

5. Conclusion

The COVID-19 pandemic had a significant impact on the breastfeeding practices among institutionalized recently delivered mothers. Health service delivery, health workforce and health management information system were the most commonly affected areas. Nevertheless, the pandemic has provided rich learning opportunities for health system strengthening. A roadmap should be in place as a result from these learnings and experiences. Establishing learning loops at individual, team and at organizational levels can facilitate the adaptation of best practices from within and beyond institutional settings, and help optimize breastfeeding practices during future pandemics.

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Data availability statement

The original contributions presented in the study are included in the article/Supplementary material, further inquiries can be directed to the corresponding authors.

Author contributions

ND and DS: tool development, literature search, data acquisition, data analysis, manuscript preparation, and manuscript editing. PP, RM, and SN: data acquisition, manuscript editing, and manuscript review. AMa: concepts, design, definition of intellectual content, tool development, manuscript editing, manuscript review, and guarantor. AMo: concepts, design, definition of intellectual content, tool development, data acquisition, data analysis, manuscript editing, and guarantor. All authors contributed to drafting of the article and approved the submitted version.

Conflict of interest

The authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

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Supplementary material

The Supplementary Material for this article can be found online at: <https://www.frontiersin.org/articles/10.3389/fnut.2023.1142089/full#supplementary-material>

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EDITED BY

Ranadip Chowdhury,
Society for Applied Studies, India

REVIEWED BY

Rukman Manapurath,
Center for Health Research and Development,
Society for Applied Studies, India
Uttara Partap,
School of Public Health and Harvard University,
United States

*CORRESPONDENCE

Arti Bhanot

✉ arti.bhanot@gmail.com

Vani Sethi

✉ vsethi@unicef.org

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Right message, right medium, right time: powering counseling to improve maternal, infant, and young child nutrition in South Asia

Arti Bhanot^{1*}, Vani Sethi^{2*}, Zivai Murira²,
Konsan Dinachandra Singh³, Sebanti Ghosh¹ and
Thomas Forissier¹

¹Alive & Thrive, FHI360/FHI Solutions, New Delhi, India, ²UNICEF Regional Office for South Asia,
Kathmandu, Nepal, ³Independent Consultant, New Delhi, India

Introduction: Quality counseling can positively impact maternal, infant and young child nutrition (MIYCN) behaviors linked to poor nutrition outcomes. Global guidance includes 93 recommendations on MIYCN counseling.

Methods: A desk review and key informant interviews sought to assess compliance to the recommendations, reach and quality, systemic gaps and opportunities for MIYCN counseling in seven South Asian countries. Ninety-three (93) policies and guidelines, 180 counseling materials and over 50 documents were reviewed; 115 key informant interviews were conducted. Information synthesis captured eight domains. Data from national surveys were analyzed to determine MIYCN counseling reach, quality and association with nutrition behaviors.

Results: Results showed that national guidelines were inconsistent with global recommendations for seven thematic areas. Coverage of contacts points like antenatal and postnatal care (ANC, PNC) with potential to deliver MIYCN counseling was highly variable. Having at least four ANC contacts was significantly associated with consumption of 100+ iron folic acid tablets in all countries. Rates of early initiation of breastfeeding (18% Pakistan to 90% Sri Lanka) were lower than institutional delivery rates, except for Bangladesh and Sri Lanka. PNC contact within 48h of birth was positively correlated with exclusive breastfeeding in India, Pakistan and Sri Lanka (OR 1.4, 3.1, 3.2). Health worker contacts and wealth status equally influenced child's dietary diversity in India. MIYCN services were add-on roles for community-based workers, except in India. Supervision mechanisms exist but were not focused on quality of MIYCN services. Counseling resources were predominantly paper based (>70%), had rural-focused messaging on diets and mainly targeted women. Platforms to engage men were largely missing. Health management information systems included indicators on maternal contact points in all countries but not for children. Assessing funding for MIYCN counseling was challenging as costs were subsumed across several budget line-items.

Discussion: The research findings can be used to (1) align country guidance with global recommendations, (2) review workforce responsibilities and capacity building with supervision, (3) assess the need for new counseling materials based on coverage of content, service providers and audience, (4) integrate MIYCN counseling indicators in information systems and (5) include MIYCN counseling services with activities and budget in country plans.

KEYWORDS

counsel, maternal, child, nutrition, diet, breastfeeding, complementary feeding, South Asia

Introduction

Considerable progress has been made on improving child survival in South Asia. Six of eight countries are either on track to achieve or have already met the Sustainable Development Goal to reduce the under-five child mortality rate to 25 per 1,000 live births or lower by 2030 (1). Nutrition targets, however, will still fall short: Unless nutritional improvements are made, all South Asian countries will miss achieving the World Health Assembly (WHA) 2025 nutrition targets on lowering child wasting to <5% and reducing low birth weight by 30% (2). About 40% of the world's children affected by stunting and half of those affected by wasting are in South Asia (3). Over 54 million South Asian children are at risk of irreversible physical and cognitive impairment due to chronic undernutrition or stunting, and 27 million are thin or wasted (3). Further, almost 8 million children are dangerously thin or severely wasted (3). The regional prevalence of low birth weight, 27%, is the highest among all regions, indicating poor maternal nutrition (4). Hidden hunger is also the highest among all regions, with an estimated 44–50% of preschool children affected by Vitamin A deficiency (5). Prevalence of anemia continues to be a severe public health problem ($\geq 40\%$) in all South Asian countries among children of 6 to 59 months, except Sri Lanka.

Maternal undernutrition and poor diet and hygiene among young children are critical drivers of child undernutrition in South Asia (6). One in five women is underweight (body mass index $<18.5 \text{ kg/m}^2$) and one in 10 is short statured (height $<145 \text{ cm}$) (7). South Asian countries are off-track to achieve the WHA nutrition target on anemia reduction among all women. Anemia among women remains a moderate to severe public health problem in the region (2, 7). The situation is exacerbated by high rates of adolescent pregnancies in Bangladesh, Nepal, and India (8). While the current prevalence of overweight in children at 2.5% is the lowest in the world, the scenario will worsen due to increased exposure to obesogenic environments and increasing maternal overweight and obesity (2, 9). Prevalence of overweight among women is already exceeding thinness in six of the eight South Asian countries (10). The high prevalence and concurrence of different forms of malnutrition among women fuels an intergenerational cycle of malnutrition. The complex interaction of nutritional deficiencies in the first 1,000 days of life covering pregnancy until a child's second birthday, and later childhood obesity increases lifetime risk of non-communicable disease (11). Socio-economic disparities persist, with the most vulnerable women and children most deeply affected by undernutrition in both rural and urban settings (5, 12).

Owing to the strong linkages between maternal malnutrition, inadequate diets, and other feeding and hygiene behaviors with child malnutrition, counseling should start early in the first trimester of pregnancy or even before the first 1,000 days (6, 9, 10). Counseling is an interactive process between service providers, pregnant women, mothers, and other family members that can positively influence the practice of recommended behaviors by women and families (13). Governments rely heavily on individual agency to change nutrition behaviors through Social and Behavior Change Communication (SBCC) interventions including counseling (14). In most South Asian countries, women have limited agency with little to no influence in household decision making or access to financial resources. However, regional evidence indicates that even in these settings, quality counseling can positively impact maternal diets and child feeding practices. In India, the likelihood of pregnant women consuming a

more diverse diet was 1.5 to 3 times higher among those receiving health and nutrition services and counseling on diets than those not receiving these services (15). Similar findings were noted in Nepal where pregnant women with nutrition knowledge were up to three times more likely to consume a diverse diet (16). More equitable dissemination of nutrition counseling services in the first 1,000 days of life is possible through a strong primary health care (PHC) system. A PHC system aims to bring evidence-based preventive and promotive health care services closer to communities. In the context of the first 1,000 days of life, these include antenatal and postnatal care (ANC, PNC) contacts, care around birth, and all health contacts with infants and young children in the community or first tier public health facilities. However, recent evidence on quality of maternal infant and young child nutrition (MIYCN) counseling during ANC in South Asia revealed that obstacles exist to higher quality counseling. The counseling lasted under five minutes and was more likely to be available at higher tier health facilities than PHC facilities, among other barriers (17).

We identified 93 global recommendations by WHO and UNICEF on counseling for pregnant women, breastfeeding mothers, and children under-two years (18–26). These include 30 recommendations for pregnant women, 24 for breastfeeding mothers and 38 for mother or caregivers of children under-two years. Twelve of the 30 recommendations on pregnancy counseling, six of 25 for counseling breastfeeding mothers and four of 38 pertaining to counseling mothers/caregivers of children under-two are context specific, meaning these recommendations are only applicable when a country meets certain criteria based on population estimates for nutritional status and dietary practices. Other counseling recommendations are described as universally applicable (Tables 1, 2).

World leaders, including leaders from South Asia, have committed to strengthening PHC by increasing attention to human resources, knowledge and capacity building, technology advancements, and financing for better health outcomes (27). In 2018–19, governments and development partners from all South Asian countries committed to align national guidance to global recommendations on MIYCN and maximize the use of available platforms to integrate MIYCN services and evidence-informed SBCC, among other consensus action points (28). In keeping with their commitments, governments from South Asian countries are calling for action to strengthen PHC and nutrition services.

UNICEF Regional Office of South Asia (ROSA) and Alive & Thrive, a nutrition initiative managed by FHI Solutions, collaborated to landscape MIYCN counseling in South Asian countries to: (1) ascertain coverage of global counseling recommendations in MIYCN-related policies in South Asian countries, (2) analyze the latest national survey data sets to assess coverage, continuity, intensity, and quality of MIYCN counseling, (3) identify system bottlenecks to deliver quality MIYCN counseling and opportunities to overcome these and (4) curate lessons from country experiences in strengthening MIYCN counseling services.

Methods

A mixed-methods approach was used to achieve the four objectives listed above. The study duration was eight months from July 2022 to February 2023. Seven of eight South Asian

TABLE 1 Global recommendations on maternal nutrition counseling.

Recommendation	Counseling focused actions	Context specific	PW	BM
1. Counseling about healthy eating	1.1 Consumption of a variety of locally available foods, including green and orange vegetables, eggs, meat, fish, beans, nuts, whole grains and fruit	No	✓	✓
	1.2 Consume fortified foods (iodized salt and others)		✓	✓
2. Counseling about keeping physically active	2.1 Attain or maintain a healthy weight and/or prevent excessive weight gain	No	✓	✓
	2.2 Take adequate rest		✓	✓
	2.3 Avoid heavy workload		✓	✓
3. In undernourished populations (thinness $\geq 20\%$ among women), nutrition education on increasing daily energy and protein intake	3.1 Increasing number of meals using locally available foods	Yes	✓	✓
	3.2 Consuming food supplement provided through government program (balanced energy-protein supplement)		✓	✓
4. Daily oral iron and folic acid supplementation with 30 mg to 60 mg elemental iron and 400 μg folic acid	4.1 Importance of daily consumption	No	✓	✓
	4.2 Continued and consistent consumption		✓	✓
	4.3 How to take supplements		✓	✓
	4.4 How to manage side effects		✓	✓
5. Intermittent oral iron and folic acid supplementation with 120 mg of elemental iron and 2,800 μg (2.8 mg) of folic acid once weekly (If daily iron is unacceptable, anemia prevalence among pregnant women $< 20\%$)	5.1 Dosage and how to consume	Yes	✓	✓
	5.2 How to manage side effects		✓	✓
6. Antenatal multiple micronutrient supplement in context of rigorous research	6.1 Dosage and how to consume	Yes	✓	
	6.2 Continued and consistent consumption		✓	
7. In populations with low dietary calcium intake, daily calcium supplementation (1.5–2.0 g oral elemental calcium)	7.1 Importance of daily consumption	Yes	✓	
	7.2 Continued and consistent consumption		✓	
	7.3 How to take supplements		✓	
	7.4 How to manage side effects		✓	
8. Among pregnant women with high daily intake of caffeine (> 300 mg) reducing caffeine	8.1 Reduced frequency of caffeinated drinks	Yes	✓	✓
	8.2 Avoid tea/coffee with meals		✓	✓
9. Breastfeeding	9.1 Importance of breastfeeding	No	✓	✓
	9.2 Immediate and uninterrupted skin-to-skin contact after birth		✓	✓
	9.3 Early initiation of breastfeeding		✓	✓
	9.4 Correct positioning and attachment		✓	✓
	9.5 Exclusive breastfeeding till completion of 6 months of age		✓	✓
	9.6 Responsive breastfeeding		✓	✓
	9.7 Risks of giving formula, breast milk substitutes, using bottles, teats and pacifiers		✓	✓
10. Counseling on handwashing at critical times and food hygiene	10.1 Handwashing at critical times	No	✓	✓
	10.2 Safe handling, preparation, and storage of food		✓	✓
11. Dietary advice and information on factors associated with constipation for prevention of postpartum constipation	11.1 Consumption of high fiber foods and fluids	No		✓

[†]The International Federation of Gynecology and Obstetrics recommends planned 30 min exercise daily (Practice guideline. Available at <https://pubmed.ncbi.nlm.nih.gov/26433807/>). PW, Pregnant woman; BM, Breastfeeding mother.

countries—Bangladesh, Bhutan, India, Maldives, Nepal, Pakistan, and Sri Lanka—were included. Afghanistan was excluded as access to key respondents and documents was challenging in the time

frame. In both India and Pakistan, two sub-national geographies were closely examined to understand intra-country variations in MIYCN counseling. Sub-national geographies were the states of

TABLE 2 Global recommendations on IYCN and their counseling focused actions.

Recommendation	Counseling focused actions	Context specific
1. Immediate skin-to-skin contact at birth and initiation of breastfeeding within one hour	1.1 Importance of immediate and uninterrupted skin-to-skin contact	No
	1.2 Avoiding separation of mother and baby	
	1.3 Early initiation of breastfeeding within one hour of birth	
	1.4 Benefits of colostrum	
	1.5 Observe and assist infant self-attachment	
	1.6 Support correct attachment and position	
	1.7 Identifying feeding cues	
2. Exclusive breastfeeding from birth until infant reaches 6 months of age	2.1 Benefits of exclusive breastfeeding	No
	2.2 Correct position and attachment	
	2.3 Responsive breastfeeding	
	2.4 Avoidance of fluids or food other than breastmilk (unless medically indicated)	
	2.5 Management of breastfeeding difficulties	
	2.6 Harmful effects of formula feeding	
	2.7 Risks of using bottles, teats and pacifiers	
	2.8 Manual expression of breastmilk as needed	
	2.9 Breastfeeding small, preterm, sick baby with no medical complication	
3. Timely introduction of complementary feeding	3.1 Importance of timely introduction of complementary foods	No
	3.2 Feeding techniques	
	3.3 Quantity, consistency and frequency of introductory complementary feeding	
	3.4 Responsive feeding	
4. Age-appropriate complementary feeding	4.1 Importance of appropriate complementary feeding	No
	4.2 Age-appropriate quantity, consistency and frequency of feeding	
	4.3 Including locally available diverse foods	
	4.4 Responsive feeding	
	4.5 Handwashing at critical times	
	4.6 Safe preparation, handling and storage of complementary foods	
	4.7 Child feeding during illness	
5. Continued breastfeeding until child is 2 years and beyond	5.1 Importance of continued breastfeeding	No
6. Growth Promotion and Monitoring	6.1 Weight and height/length measurement for all children under 5	No
	6.2 Nutritional counseling for children based on assessment	
	6.3 Management plan for overweight, obese children at primary health care facilities	
7. Assessment and management of wasting	7.1 Screening for severe acute malnutrition (SAM) and counseling (in-patient)	No
	7.2 Screening for SAM and counseling (out-patient)	
	7.3 Screening for moderate acute malnutrition (MAM) and counseling	
8. IFA supplement to children >6 m: 10–12.5 mg elemental iron as syrup/drops daily for three consecutive months if anemia prevalence in infants and young children is $\geq 40\%$	8.1 Importance of daily consumption	Yes
	8.2 Continued and consistent consumption	
	8.3 How to take supplements	
	8.4 How to manage side effects	

Bihar and Telangana in India, and the provinces of Punjab and Balochistan in Pakistan. Target groups of interest were pregnant women, recently delivered women and their newborns, mothers or caregivers of children under-two years, and families. Technical scope covered all routine counseling as per global recommendations. At-risk counseling was considered for those affected by

undernutrition, including thin women, children with severe and moderate acute malnutrition (SAM/MAM), those affected by overweight, obesity and anemia, and women and children with adolescent pregnancies. Medical complications associated with nutritional risks were excluded. Individual and group counseling along with information dissemination services were included. Mass

media was only covered as an enabler. Special campaigns for nutrition verticals like Vitamin A were excluded.

Three sources of information were desk reviews, key informant interviews (KIIs) and the Demographic Health Survey (DHS) in all countries except Bhutan (29–35). In Nepal, DHS released a new report in 2022. As the 2022 data set was not released until the time this study was completed, the earlier version (2016–17) was used for analysis. However, for any published DHS data, the new 2022 report was used. In Bhutan, the National Nutrition Survey was more recent, and thus used for this study (36).

Documents for the desk review were sourced from Ministry websites, PubMed, snowballing, and key informants. The search for research papers was restricted to the last 10 years and published in English. Ninety-three (93) policies and guidelines, 180 counseling materials and over 50 program, research, and data documents were identified. A review of country policies and guidelines was done against the list of 93 global recommendations, disaggregated by recommendations for pregnant women, breastfeeding mothers, and infants and young children. Counseling materials were reviewed against messages extracted from the list of 93 global recommendations. Counseling materials which included pictures or illustrations of people were also reviewed against an eight-point gender and inclusion checklist. The eight points were: (1) equal number of men and women depicted, (2) equal number of boys and girls depicted, (3) images do not enforce stereotypes (e.g., girls/women doing household chores while boys playing, using gadgets), (4) professionals—doctors, nurses, counselors—are either women or both men and women depicted equally, (5) leaders—village head/elected officials—are either women or both men and women depicted equally, (6) use of gender neutral pronouns or he/she, (7) any images of adults/children with disability, and (8) images reflect national diversity.

A total of 115 KIIs were conducted with the support of national staff or consultants in the seven countries. These staff and consultants were selected based on in-depth understanding of country health and nutrition systems and their access to key respondents, especially from national government departments. In each country, the key informants included representatives from government departments engaged with health and nutrition services, development partners, and UNICEF. By country, the breakdown of key informants was as follows: four in Bangladesh, 10 in Bhutan and Sri Lanka, 32 in India and Maldives, 14 in Nepal, and 13 in Pakistan. In Bangladesh, information was also sourced from over 90 interviews undertaken in another UNICEF-supported project in 2020–21 (37). In Bhutan and Maldives, representatives from public health training institutes were also interviewed. Eight domains were identified for information synthesis from desk reviews and key informant interviews. Three domains related to workforce for MIYCN counseling: (1) types of counseling providers and platforms, (2) capacity and motivation of counseling providers, and (3) supervision. The other five were counseling content and materials, information systems, quality improvement, budgets and expenditures, and social-safety nets linked to MIYCN counseling.

A standard set of indicators was necessary to compare survey data from countries in the region. Thus, survey data analysis was structured after mapping indicators relevant for MIYCN counseling coverage and quality in country datasets. Data analysis was done at three levels. At level one, the reach of platforms to potentially deliver MIYCN counseling – ANC contacts for pregnancy, institutional delivery, and postnatal contacts for breastfeeding mothers, and any health worker contacts for children six to 23 months – was assessed. Reach was

assessed by location (rural vs. urban), wealth index-based quintile classification, access to mobile phones and mass media, and type of service providers (skilled vs. unskilled, public vs. private). At the second level, delivery of counseling services through these platforms was inferred by comparisons with nutrition behaviors. The five nutrition behaviors of interest were: (1) consumption of iron folic acid tablets for 100+ days among those receiving at least four ANC checkups (2) early initiation of breastfeeding among those receiving at least four ANC checkups and institutional delivery, (3) exclusive breastfeeding among those receiving postnatal care (PNC) within 48 h, (4) timely initiation of complementary feeding among those receiving any health worker contacts, and (5) minimum dietary diversity among children receiving any health worker contacts (or not). Finally, five regression models were constructed for each country to determine association of practice of recommended nutrition behaviors with background characteristics of respondents, reach of mass media, ownership of mobile phone, reach of MIYCN contacts, and type of providers. Adjusted effect of these variables, that is background characteristics of respondents and others, on the nutrition behaviors of interest were checked using binary logistic regression analysis. All analysis was done on STATA 15.

Results

Country policies on MIYCN counseling

In all seven countries, policies on 18 universally applicable counseling recommendations for pregnant women are available. These recommendations pertain to diet diversity, physical activity, iron folic acid (IFA) compliance, breastfeeding, and hygiene. However, not all are aligned with recent global updates (Table 3). Recommendations on gestational age-specific counseling on diet (and other care) are available in three of seven countries: Bangladesh, India and Maldives. Only one in seven countries, Maldives, has detailed guidance on physical activity in pregnancy and gestational weight gain counseling based on pre-pregnancy body mass index (BMI). The 12 context-specific counseling recommendations in pregnancy have variable policy coverage across countries. Universal food supplementation with counseling is available only in India, and remains needed in two more countries, Bangladesh and Bhutan, where the prevalence of thinness among women is >20%; Sri Lanka follows this recommendation, despite the country's 9% prevalence of thinness among women. Counseling for management of acute malnutrition among pregnant women is covered in guidance from Bangladesh, Nepal, Pakistan and Sri Lanka. Despite high multiple micronutrient deficiencies among women, none of the countries has policy for antenatal multiple micronutrient supplements (MMS) and counseling to promote its use. It is noted that MMS has only 30 mg iron, half of the recommend levels for antenatal supplementation in countries where anemia is a public health problem. Counseling on calcium supplementation in pregnancy is not included in pregnancy care in Bhutan and Nepal, despite evidence that it is effective in reducing the risk of pre-eclampsia. Policy for counseling on caffeine reduction in pregnancy is unavailable in all countries, except Bangladesh. In India, counseling on caffeine reduction is covered only for women with hypertensive disorder (Table 3).

In all countries, policies support 17 of the 19 universally applicable counseling recommendations for breastfeeding mothers (Table 4). The

TABLE 3 Coverage of key recommendations on pregnancy counseling in policy documents (Pol) and programs (Prg), South Asia.

Global nutrition recommendations	Counseling recommendations	Context specific	BGH		BHN		IND		MAL		NPL		PAK		SRL	
			Pol	Prg	Pol	Prg	Pol	Prg	Pol	Prg	Pol	Prg	Pol	Prg	Pol	Prg
Counseling about healthy eating	Consume variety of locally available foods	No														
	Consume fortified foods (iodized salt and others)															
Counseling about keeping physically active	Attain or maintain a healthy weight and /or prevent excessive weight gain	No														
	Take adequate rest															
	Avoid heavy workload															
In undernourished populations, nutrition education on increasing daily energy and protein intake	Increase number of meals using locally available foods	Yes. ≥20% women thin			NA	NA			NA	NA	NA	NA			NA	NA
	Consume food supplement provided through government programs				NA	NA			NA	NA	NA	NA	NA	NA	NA*	NA*
Daily oral iron and folic acid supplementation (30 mg to 60 mg elemental iron, 400 µg folic acid)	Importance of daily consumption	No														
	Continued and consistent consumption															
	How to take supplements															
	How to manage side effects															
Intermittent oral iron and folic acid supplementation with 120 mg of elemental iron and 2,800 µg (2.8 mg) of folic acid once weekly	Dosage and how to consume	Yes. <20% women anemic	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA
	How to manage side effects		NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA
Antenatal multiple micronutrient supplement (MMS)	Dosage and how to consume	Yes. Rigorous research		NA		NA		NA		NA		NA		NA		NA
	Continued and consistent consumption			NA		NA		NA		NA		NA		NA		NA
In populations with low dietary calcium intake, daily calcium supplementation (1.5–2.0 g oral elemental calcium)	Importance of daily consumption	Yes diet calcium deficient										NA				
	Continued and consistent consumption											NA				
	How to take supplements											NA				
	How to manage side effects											NA				

(Continued)

TABLE 3 (Continued)

Global nutrition recommendations	Counseling recommendations	Context specific	BGH		BHN		IND		MAL		NPL		PAK		SRL	
			Pol	Prg	Pol	Prg	Pol	Prg	Pol	Prg	Pol	Prg	Pol	Prg	Pol	Prg
Reducing caffeine among pregnant women	Reduce frequency of caffeinated drinks	Yes. Daily intake				NA		NA				NA		NA		NA
	Avoid tea/coffee with meals	>300 mg										NA				
Breastfeeding	Importance of breastfeeding	No														
	Immediate and uninterrupted skin-to-skin contact after birth															
	Early initiation of breastfeeding															
	Correct positioning and attachment															
	Exclusive breastfeeding till completion of 6 months of age															
	Responsive breastfeeding															
	Risks of giving formula, breast milk substitutes, using bottles, teats and pacifiers															
Counseling on handwashing at critical times and food hygiene	Handwashing at critical times	No														
	Safe handling, preparation, and storage of food															

Green: Fully aligned to recommendation. Yellow: Partially aligned to recommendation. Red: Not aligned to recommendation. NA, Not Applicable (In reference to policy, implies country context does not support recommendation. In reference to programs, implies lack of policy support). *Sri Lanka does not require universal food supplementation in pregnancy but has policy and program support.

TABLE 4 Coverage of key recommendations on counseling for breastfeeding mothers in policy documents (Pol) and programs (Prg), South Asia.

Global nutrition recommendations	Counseling recommendations	Context specific	BGH		BHN		IND		MAL		NPL		PAK		SRL	
			Pol	Prg	Pol	Prg	Pol	Prg	Pol	Prg	Pol	Prg	Pol	Prg	Pol	Prg
Counseling about healthy eating	Consume variety of locally available foods	No														
	Consume fortified foods (iodized salt and others)															
Counseling about keeping physically active	Limit time spent sedentary	No														
	Do at least 150 min of physical activity throughout the week															
	Incorporate a variety of physical and muscle-strengthening activities; add gentle stretches															
In undernourished populations, nutrition education on increasing daily energy and protein intake	Increase number of meals using locally available foods	Yes. $\geq 20\%$ women thin			NA	NA			NA	NA	NA	NA			NA	NA
	Consume food supplement provided through government programs								NA	NA						
Daily oral iron and folic acid supplementation (30 mg to 60 mg elemental iron, 400 μ g folic acid)	Importance of daily consumption	No														
	Continued and consistent consumption															
	How to take supplements															
	How to manage side effects															
Intermittent oral iron and folic acid supplementation with 120 mg of elemental iron and 2,800 μ g (2.8 mg) of folic acid once weekly	Dosage and how to consume	Yes. $<20\%$ women anemic	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA
	How to manage side effects		NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA
Reducing caffeine among breastfeeding mothers	Reduce frequency of caffeinated drinks	Yes. Daily intake >300 mg														
	Avoid tea/coffee with meals															

(Continued)

TABLE 4 (Continued)

Global nutrition recommendations	Counseling recommendations	Context specific	BGH		BHN		IND		MAL		NPL		PAK		SRL	
			Pol	Prg	Pol	Prg	Pol	Prg	Pol	Prg	Pol	Prg	Pol	Prg	Pol	Prg
Breastfeeding	Importance of breastfeeding	No														
	Immediate and uninterrupted skin-to-skin contact after birth															
	Early initiation of breastfeeding															
	Correct positioning and attachment															
	Exclusive breastfeeding until completion of 6 months of age															
	Responsive breastfeeding															
	Risks of giving formula, breast milk substitutes, using bottles, teats and pacifiers															
Counseling on handwashing at critical times and food hygiene	Handwashing at critical times	No														
	Safe handling, preparation and storage of food															
Dietary advice and information on factors associated with constipation	Consumption of high fiber foods and fluids	No														

Green: Fully aligned to recommendation. Yellow: Partially aligned to recommendation. Red: Not aligned to recommendation. NA: Not Applicable (In reference to policy, implies country context does not support recommendation. In reference to programs, implies lack of policy support). *Sri Lanka does not require universal food supplementation for breastfeeding mothers but has policy and program support.

two missed counseling recommendations pertain to type and duration of physical activity in all countries except Maldives. All countries, except Maldives, follow a daily IFA supplementation program, including counseling, to promote IFA supplementation compliance for breastfeeding mothers. The duration of IFA supplementation varies from 30 days post-partum in Pakistan to 180 days in India and Sri Lanka. The coverage of six context-specific counseling recommendations for breastfeeding mothers varies, similar to those for pregnant women (Table 4).

The 28 universal infant and young child feeding (IYCF) counseling recommendations are covered in policy documents across all seven countries (Table 5). Growth monitoring promotion (GMP) policies for counseling for children at normal and below-normal thresholds for growth are consistently recommended across all seven countries. Other than Maldives and Sri Lanka, none of the countries has policy support for screening and management of overweight and obesity in children under 5. In-facility treatment for SAM is well defined and mostly available; however, outpatient treatment for uncomplicated SAM as well as MAM is sparingly available – most countries offer only counseling to improve diets and hygiene behaviors to manage MAM. Of five countries that require counseling on IFA supplementation for children 6–59 months, namely Bhutan, India, Maldives, Nepal, and Pakistan, only India has a universal program (Table 5).

Coverage, continuity, intensity, and quality of MIYCN counseling

The proportion of women who report initiation of ANC within first trimester ranged from 37% (Bangladesh) to 96% (Maldives) (Figure 1) (29–32, 34–36). Five to six of every 10 pregnant women in Bangladesh, Bhutan, and Pakistan did not initiate ANC within the first trimester, a critical time to manage pregnancy symptoms, modify diets, and consume essential nutritional supplements like folic acid, with or without iron. In sub-national geographies of India, half the women in Bihar missed early pregnancy ANC contact. Telangana did much better, with only one in 10 pregnant women missing out on ANC in the first trimester (30). Published data on first trimester ANC contacts were unavailable for the Punjab and Balochistan provinces in Pakistan.

Coverage of at least four ANC contacts ranged from 47% (Bangladesh) to 98% (Sri Lanka) (29–32, 34–36). The proportion of women who reported the receipt of four ANC contacts was lower than those reporting ANC within first trimester for India, Maldives, and Pakistan. About half the pregnant women in Bangladesh, India, and Pakistan did not have at least four ANC contacts, which would be ideal to reinforce recommended antenatal nutrition behaviors. Further, coverage of WHO- and UNICEF-endorsed eight ANC contacts was low in all countries, except Sri Lanka. More than eight in 10 women had a consultation with a skilled health care provider in public or private sector at least once in pregnancy.

At least four ANC contacts was the most consistent and strongest influencer on consumption of 100+ IFA across all countries (Odds Ratios [OR] Bangladesh 3.4, Bhutan 25.2, India 2.3, Maldives 2.7, Nepal 4.8, Pakistan 4.6, Sri Lanka 7) (Table 6). However, in Bangladesh, India, Maldives, and Pakistan, at least 50% of the women who received

at least four ANC contacts did not consume 100+ IFA, which suggests opportunities to improve counseling and possibly supply chains.

Compared to 100+ IFA consumption, the reported practice of early initiation of breastfeeding was less influenced by receipt of at least four ANC contacts (Supplementary Table S1).

Positive correlation between early initiation of breastfeeding with number of ANC contacts was noted only in three countries: Bhutan, India, and Maldives (OR 4.9, 1.4, 1.6, respectively). Receiving ANC from private sector provider reduced odds of early initiation of breastfeeding in India (OR 0.9) and Pakistan (OR 0.7). Further, delivering at a private health facility had a negative influence on early initiation of breastfeeding compared with delivering at a public health facility in Bangladesh, India and Nepal (OR 0.7, 0.8 and 0.8, respectively). In addition to counseling in ANC contacts, promotion of early initiation of breastfeeding requires support and counseling immediately after birth.

The widest gap in early initiation of breastfeeding and institutional delivery was noted in Pakistan (48% points) followed closely by India (46% points). In contrast, Bangladesh and Balochistan province of Pakistan had higher proportions of early initiation of breastfeeding than institutional deliveries (Figure 2).

Rates of PNC within 4 hours of birth, which is crucial to establish breastfeeding, were lower than the institutional delivery rates in all countries for which data were available – India, Maldives, Pakistan, and Sri Lanka (29–31, 35) (Supplementary Table S2).

PNC contact within 48 h of birth was positively correlated with exclusive breastfeeding among children under 6 months in India (OR 1.4), Pakistan (OR 3.1) and Sri Lanka (OR 3.2) (Table 7).

Data on health worker contacts for infants and young children to promote appropriate feeding practices are available for only two of the seven countries: India and Nepal. In India the data reflect recall of contacts with any skilled or unskilled provider 3 months before the survey but not specifically for nutrition counseling. However, as India has home-based contacts for nutrition counseling and there are monthly GMP sessions, the data potentially represent nutrition counseling contacts. In Nepal, the data reflect recall of contacts specifically on IYCF counseling one year before the survey. The average number of contacts per child were 2.9 for both India and Nepal, but the reference periods were three and 12 months, respectively. In India, data were available on contacts for GMP, specifically weight measurement and counseling post weight measurement. About 62% of children under two were weighed in the 12 months preceding the survey, and 75% of their mothers/caregivers received counseling. Data on all basic vaccination covered by the time a child completes 2 years of age indicate these children were reached at least five times in that time period; most of these contacts occur in the first year of life. Coverage of all basic vaccination (Expanded Program for Immunization [EPI] contacts) is higher than 75% for all countries, except Pakistan where it is 66% (Figure 3). Due to its high and assured service reach, there is an opportunity to layer child nutrition services to EPI platforms in all countries.

Health worker contacts were positively correlated with children six–23 months receiving minimum diversity diet or foods from at least four different food groups in India (OR 1.3). However, the cost of food is a consideration with children belonging to richest wealth quintile faring better on minimum dietary diversity than others in both India and Nepal (Table 8).

TABLE 5 Coverage of key recommendations on IYCN counseling in policy documents (Pol) and programs (Prg), South Asia.

Global nutrition recommendations	Counseling recommendations	Context specific	BGH		BHN		IND		MAL		NPL		PAK		SRL	
			Pol	Prg	Pol	Prg	Pol	Prg	Pol	Prg	Pol	Prg	Pol	Prg	Pol	Prg
Immediate skin-to-skin contact at birth and initiation of breastfeeding within 1 h	Importance of immediate and uninterrupted skin-to-skin contact	No														
	Avoid separation of mother and baby															
	Early initiation of breastfeeding (within an hour of birth)															
	Benefits of colostrum															
	Observe and assist infant self-attachment															
	Support correct attachment and position															
	Identifying feeding cues															
Exclusive breastfeeding from birth till infant completes six months of age	Benefits of exclusive breastfeeding	No														
	Correct position and attachment															
	Responsive breastfeeding															
	Not given any other fluid or food other than breastmilk (unless medically indicated)															
	Management of breastfeeding difficulties															
	Harmful effects of formula feeding															
	Risk of using bottles, teats and pacifiers															
	Manual expression of breast milk as needed															
	Breastfeeding small, preterm, sick baby without medical complication															

(Continued)

TABLE 5 (Continued)

Global nutrition recommendations	Counseling recommendations	Context specific	BGH		BHN		IND		MAL		NPL		PAK		SRL	
			Pol	Prg	Pol	Prg	Pol	Prg	Pol	Prg	Pol	Prg	Pol	Prg	Pol	Prg
Timely introduction of complementary feeding	Importance of timely introduction of complementary feeding	No														
	Feeding techniques															
	Quantity, consistency and frequency of introductory complementary feeding															
Age appropriate complementary feeding	Responsive feeding															
	Importance of appropriate complementary feeding															
	Age-appropriate quantity, consistency and frequency of feeding	No														
	Including locally available diverse foods															
	Responsive feeding															
	Handwashing at critical times															
	Safe preparation, handling and storage of complementary foods															
	Child feeding during illness															
Continued breastfeeding till child is two years and beyond	Importance of continued breastfeeding	No														
Growth Monitoring Promotion	Weight and height/length measurement for all children under-5	No														
	Nutritional counseling for children under-5 based on assessment															
	Management plan for overweight and obese children under-5 at primary health care facilities															

(Continued)

TABLE 5 (Continued)

Global nutrition recommendations	Counseling recommendations	Context specific	BGH		BHN		IND		MAL		NPL		PAK		SRL	
			Pol	Prg	Pol	Prg	Pol	Prg	Pol	Prg	Pol	Prg	Pol	Prg	Pol	Prg
Assessment and management of wasting	Screening for SAM and counseling (in-patient)	No														
	Screening for SAM and counseling (out-patient)															
	Screening for MAM and counseling (community)															
IFA supplement to young children >6 m: 10–12.5 mg elemental iron as syrup/drops daily for 3 consecutive months	Importance of daily consumption	Yes (anemia $\geq 40\%$ in infants & young children)	NA	NA											NA	NA
	Continued and consistent consumption		NA	NA											NA	NA
	How to take supplements		NA	NA											NA	NA
	How to manage side effects		NA	NA											NA	NA

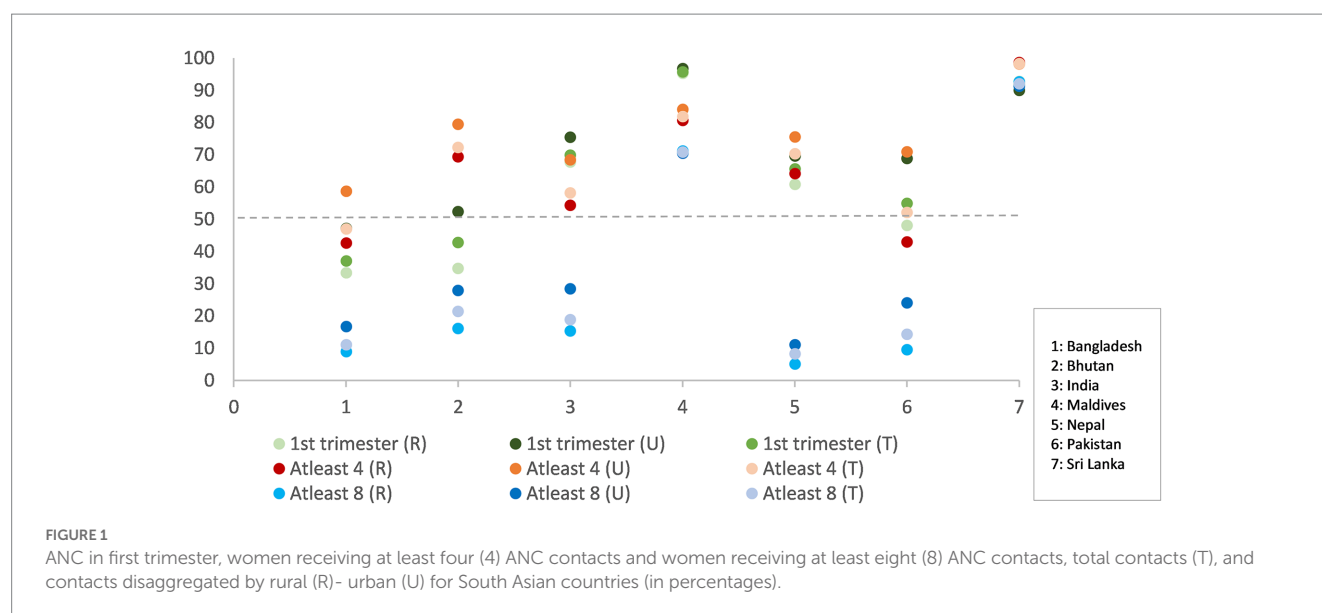
Green: Fully aligned to recommendation. Yellow: Partially aligned to recommendation. Red: Not aligned to recommendation. NA: Not Applicable (In reference to policy, implies country context does not support recommendation. In reference to programs, implies lack of policy support).

Workforce for MIYCN counseling

All South Asian countries except Maldives have a network of community-based health workers with MIYCN counseling roles. In all countries except Bhutan, the workers are either salaried or incentivized for service delivery. MIYCN counseling is an add-on role to traditional roles of family planning, ANC, newborn care, and immunization services for community-based health workers. India is the only country to also have dedicated early child development and nutrition workers. Most countries are affected by a shortage of government supported community-based health workers. The situation is most severe in Bangladesh, with a shortfall of over 20% for all cadres of community health workers (37). However, Bangladesh has over 100,000 non-government supported community workers active in both rural and urban areas. There is a wide range in entry-level capacity of community-based workers. In Bhutan, there is a training requirement of 7 days, while in Pakistan and India, there are certification courses lasting 15 to 18 months. Thus, pre- and in- service training and supervision support requirements need to be contextualized, and the complexity of tasks in job descriptions should be assessed against qualifications (Table 9).

Quality of trainings is a concern. In Balochistan, Pakistan, annual refresher trainings for Lady Health Workers are stalled due to lack of funds. Evidence from Bihar, India indicates that despite high coverage of incremental learning among *Anganwadi* Workers (~90% trained) and organization of community-based events (events hosted in ~80% community sites), coverage has not translated to expected changes in nutrition behaviors at the household level (38). The qualifying trainings for community-based health workers, including skilled workers, include some nutrition components but are universally weak on maternal nutrition counseling. Also, trainings across the region have limited content on gender sensitization and negotiation skills. Key informants in Bangladesh and India stated that female community health workers face the same socio-cultural and gender barriers as other women in the community. They need training on negotiating nutrition behavior changes with family members of pregnant women and children. Key informants also stated that even when SBCC resources were available, their use by both skilled and unskilled workers is not guaranteed. Reasons for this include a lack of standard protocols on use of these resources at specific contact points, lack of training on how to use the resources, and that the resources are not attractive enough for the clients or not contextualized. Service providers get better reception when counseling is linked to a commodity or any takeaway for the clients; this also affects workers' motivation to counsel. Key informants from all countries noted that more skilled workers, like doctors and nurses, invariably focus on curative services and less on counseling. Graduate training courses for doctors and nurses have limited theory and practical sessions on nutrition (39). This was corroborated by key informants from Bangladesh, India, Nepal and Maldives.

The short contact time with clients and lack of privacy at outreach sites are severe limitations in delivering MIYCN counseling services (40). In settings where home visits or community group meetings are also unlikely, such as in areas that are hard to reach, highly conservative, and/or experiencing a severe shortage of frontline workers, there is practically no opportunity for face-to-face interaction; thus, options for technology-enabled MIYCN messaging and mass media become very relevant. There are no dedicated



platforms for male engagement in MIYCN counseling, except in Sri Lanka. Most supervisors are constrained to travel to all planned sites due to limited transport allowances but there is opportunity to prioritize visits and devise methods of group supervision.

MIYCN counseling content and materials

In most countries, one to two departments within the Ministry of Health lead development of MIYCN counseling materials. Donor agencies and development partners are engaged in development of these materials. Seventy (70) of the 96 (73%) materials for pregnant women, 60 of the 86 (70%) for breastfeeding mothers and 69 of 95 (73%) for mother/caregivers of children six to 23 months were in paper format. Under 15% of these were materials for clients to take home. With increasing access to technology, web-based information and audio-visual content is gaining relevance and reach. Technology based solutions directly for clients were noted in Maldives and in experimental stage in Bihar, India. In Maldives, nutrition information for first 1,000 days is available through *Yagooth* mobile application. In Bihar an application based game *Chatkaarey B* enables users to access information on family nutrition. Both applications are available through Google Play Store. In Nepal, series of engaging videos on first 1,000 days nutrition with special focus on male engagement were developed under the *Banchin Ama* (Mother says) campaign. Video campaigns are also available through various national programs in Bangladesh, Bhutan, India, Maldives and Pakistan (Table 10).

Maternal nutrition messages for pregnant women and breastfeeding mothers mostly relate to healthy eating, specifically, eating locally available diverse foods; 66% of materials for pregnant women and 49% for breastfeeding mothers carried these messages. However, physical activity, weight gain and rest in pregnancy, and consumption of IFA and calcium supplements are much less covered (9 to 21 of 96 materials reviewed). An innovation from Telangana, India is inclusion of a page with 180 dots in the Mother and Child card to enable pregnant women to track daily IFA tablet consumption. Messaging on gestational weight gain in most countries (except

Maldives) follows standard 10–12 kg weight gain recommendation without consideration of pre-pregnancy BMI or other nutritional status parameters for pregnant women, like mid-upper arm circumference. Gestational age-specific messaging is missing across all countries except Maldives and is present in some materials from India and Bangladesh (Tables 11, 12).

Standard messages on breastfeeding, specifically early initiation of breastfeeding and exclusive breastfeeding, are well covered in most countries and in materials for all target groups. However, fewer materials provide information on correct positioning and responsive feeding. Complementary feeding messages on timely initiation and age-appropriateness had better coverage than responsive feeding and feeding during illness. Age-appropriate complementary feeding messages covered feeding quantity, frequency, consistency, and diversity of foods for infants 6–8 months, 9–11 months, and 12 to 23 months. However, messages on importance of GMP and nutritional assessment-based counseling were limited to 17% of the 95 materials for children six–23 months. Messages on prevention and guidance on management of nutritional risks for all target groups had limited coverage across countries (Tables 11, 12).

Counseling materials from five of the seven countries – Bangladesh, India, Maldives, Nepal and Sri Lanka – depicted men caring for pregnant women, mothers, and children, did not enforce stereotypical roles, and showed women as skilled care and counseling providers (Supplementary Table S3). Except India, MIYCN counseling materials targeting local leaders as influencers were lacking. Most printed counseling materials from all countries, except Maldives and Sri Lanka, predominantly focused on rural audiences. No MIYCN counseling materials contextualized for urban settings, including the more vulnerable urban poor, were identified in these countries.

Information systems for MIYCN counseling

All countries include indicators on ANC, institutional deliveries, and PNC contact points that have the potential to deliver MIYCN counseling services. However, contact points for infants and children are reported

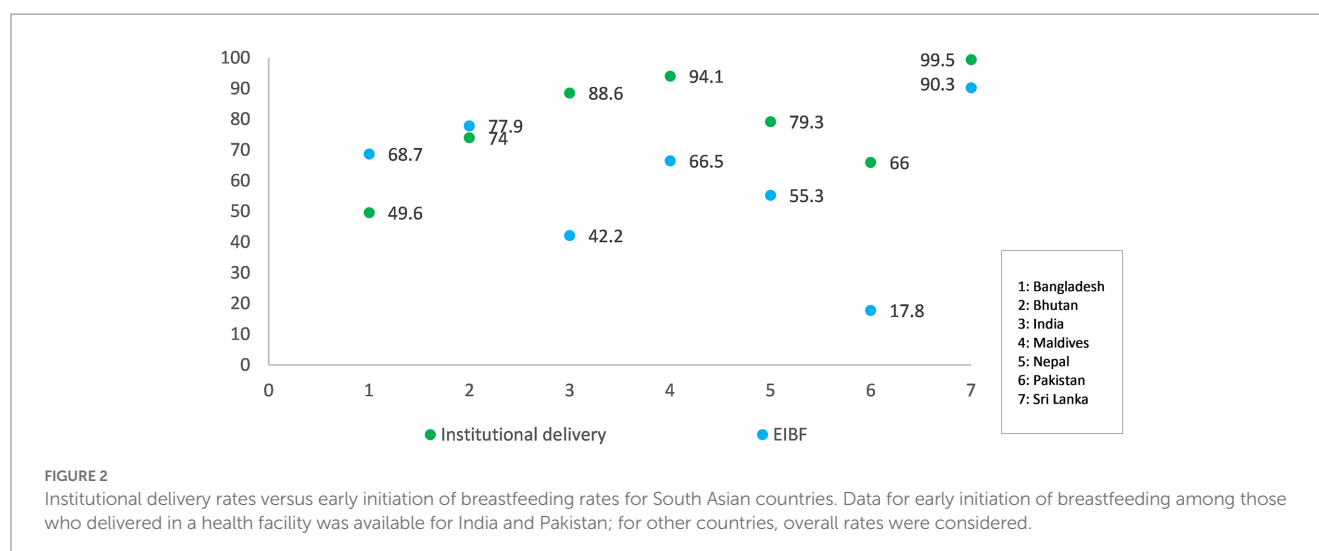
TABLE 6 Odds of consuming 100+ IFA tablets in pregnancy by background characteristics, receipt of at least four ANC contacts, and women's access to mid-mass media.

N	BGH		BHN		IND		MAL		NPL		PAK		SL	
	5,012	95% CI	887	95% CI	122,458	95% CI	1,693	95% CI	2,761	95% CI	6,276	95% CI	4,635	95% CI
Rural vs. Urban	1.1	0.9–1.3	1.3	0.4–4.9	1.4***	1.3–1.4	NA		0.9	0.7–1.1	1.4***	1.2–1.8	1.1	0.6–2.0
Age < 20 yrs. vs. ≥ 20 yrs	1.1	0.9–1.3	1.7	0.7–4.3	1.0	0.9–1.0			1.4**	1.0–1.9	1.4	0.6–1.3	0.3	0.0–2.2
Wealth quintile poorest vs														
poorer	0.9	0.7–1.1	0.8	0.3–2.1	1.2***	1.1–1.2	0.8	0.5–1.3	1.0	0.7–1.3	1.1	0.8–1.6	1.2	0.7–2.1
middle	1.2	0.9–1.5	1.3	0.4–4.6	1.2***	1.2–1.3	0.7	0.4–1.1	1.0	0.7–1.5	1.0	0.7–1.4	1.4	0.7–2.5
richer	1.3**	1.0–1.6	1.5	0.3–7.7	1.4***	1.3–1.5	0.7	0.4–1.2	0.8	0.6–1.2	1.4**	1.0–2.0	1.7*	1.0–3.3
richest	1.9***	1.5–2.5	0.8	0.2–3.4	1.7***	1.6–1.8	1.0	0.6–1.6	1.2	0.8–1.8	2.3***	1.6–3.3	1.3	0.7–2.5
At least 4ANC = yes	3.4**	2.9–3.9	25.2***	12.5–50.6	2.3***	2.2–2.4	2.7***	1.7–4.2	4.8***	3.8–6.0	4.6***	3.6–6.0	7.0***	3.6–13.5
Public vs. private sector provider	0.9	0.8–1.1	NA		0.8***	0.8–0.9	1.2	0.8–1.8	0.7**	0.5–0.9	1.4***	1.1–1.8	1.6**	1.1–2.4
Skilled vs. unskilled health care provider	0.8*	0.6–1.10	NA		0.8***	0.8–0.9	NA		0.6	0.1–2.7	0.3	0.1–1.4	0.2	0.1–0.4
Own mobile phone = yes	1.1	1.0–1.3	NA		1.0	1.0–1.1	1.3	0.5–3.1	1.5***	1.2–1.9	1.0	0.8–1.3	1.1	0.7–1.7
Read newspaper at least once a week = yes	2.0***	1.3–3.1	NA		1.1*	1.0–1.1	1.2	1.0–2.2	2.6**	1.2–5.6	1.6**	1.1–2.5	1.6**	1.0–2.4
Listen to radio at least once a week = yes	1.6**	1.0–2.5	NA		0.8*	0.7–0.8	0.8	0.6–1.4	1.6***	1.3–2.1	0.9	0.6–1.5	1.1	0.8–1.6
Watch television at least once a week = yes	0.9	0.8–1.1	NA		1.4***	1.3–1.4	1.6**	1.0–2.4	1.2	0.9–1.6	1.0	0.8–1.2	1.8***	1.2–2.7
Total number of influencers	6		1		11		2		6		6		5	

* $p < 0.1$, ** $p < 0.05$, *** $p < 0.01$. NA, Not available. *At least one ANC. Grey: Insufficient sample size.

in fewer countries, namely, Bangladesh, India, Maldives, and Sri Lanka. Key informants raised concerns on the quality of reporting in all countries, except Sri Lanka. Coverage of all MIYCN counseling indicators is limited, with only four of the seven countries – Bangladesh, India, Maldives, and Sri Lanka – having data on counseling services for maternal nutrition, breastfeeding, and GMP. In these four countries,

counseling contacts, such as number of antenatal classes and GMP sessions in Sri Lanka and outreach fixed-day services and home visits organized by health and nutrition workers in India, are tracked. However, only in India and partially in Bangladesh, are these data available disaggregated by provider to assess service reach of community-based versus facility-based providers. Individual client tracking is possible in



both Bangladesh and India. In Bangladesh, clients registered at community clinics can be tracked, while in India, individual tracking is possible for clients registered under the national nutrition program, Integrated Child Development Services (ICDS), through the Poshan Tracker, as well as for those registered for ANC in the reproductive child health portal. In Telangana, India, the Nutrition and Health Tracking System has been in operation since 2016 to monitor receipt of services by every registered pregnant woman, breastfeeding mother and child under-six and reaching at-risk cases timely with required services. Bangladesh is the only country to have reporting on both coverage and quality of MIYCN counseling through the World Bank-supported Disbursement Linked Indicators (DLI) reporting. Two counseling indicators are covered, namely (1) any nutrition counseling in pregnancy and (2) counseling, including checking on the status of exclusive breastfeeding and complementary feeding. Checklists to review quality of counseling were introduced but implemented in pilot geographies only.

All countries use District Health Information System2 (DHIS2). However, in none of the countries is the system computerized end-to-end. Data are reported from the lowest tier of health facilities and consolidated at sub-national levels before reporting at the National level. In all countries, reporting by community health workers associated with the lowest tier health facility is done manually. DHIS2 is a health information system; hence, modules on nutrition themes need to be created for the software. Recently, in collaboration with UNICEF, DHIS2 released the NUT digital data pack, which bridges the gap in availability of nutrition-focused modules.

To generate data on quality of counseling for local decision making, mApps for use by community health workers and their supervisors have been successfully tested in Bangladesh and India. As data on MIYCN counseling has limited availability, not much can be said on its usage to strengthen MIYCN programming at country level.

Financing for MIYCN counseling

It was challenging to get information on costing or status of funding for MIYCN counseling in South Asian countries. Four papers were sourced through key informants covering Bangladesh, India, Nepal, and Sri Lanka. The spread of MIYCN counseling services across several programs made it challenging to infer status of MIYCN

counseling financing. An India study provided cost estimates for scaled-up MIYCN counseling services compared with food supplementation, health services, micronutrient supplementation, deworming and maternity benefit schemes. Attempts to review budgets and expenditure for trainings which include MIYCN counseling did not yield usable information.

Discussion

This analysis provides insights into specific areas to strengthen MIYCN counseling related to (1) policy, (2) workforce, (3) counseling content and materials, and (4) information systems. The analysis on coverage, continuity, intensity, and quality of MIYCN counseling for these seven countries provides the status of MIYCN counseling and facilitates interpretation of findings on the four system inputs listed above.

The analysis highlights gaps in adapting global recommendations on counseling on seven themes. These seven themes are: (1) diet guidance by gestational age (unavailable in Bhutan, Nepal, Pakistan, Sri Lanka), (2) pre-pregnancy BMI-based gestational weight gain counseling (unavailable in all countries except Maldives), (3) specificity of type and duration of physical activity in pregnancy and during breastfeeding (unavailable in all countries except Maldives), (4) IFA dosage, consumption and managing side-effects in breastfeeding mothers and children (child IFA supplementation counseling relevant for Bhutan, India, Maldives, Nepal and Pakistan; unavailable in all except India), (5) counseling undernourished pregnant women and breastfeeding mothers (screening for thinness unavailable in Bhutan, India), (6) community-based management of uncomplicated SAM and MAM and (7) management of overweight and obesity among all target groups (unavailable in all countries except Maldives and Sri Lanka) (18–26).

At least four ANC contacts with skilled or unskilled providers can be made more impactful to improve maternal nutrition counseling. Having the first ANC contact in the first trimester of pregnancy can improve the earlier reach of counseling, particularly in Bangladesh, Bhutan, and Pakistan. At least four ANC contacts have no correlation with early initiation of breastfeeding in four of the seven countries: Bangladesh, Nepal, Pakistan, and Sri Lanka (OR 1.0, 1.2, 1.0, 1.0, respectively). Counseling and support for breastfeeding

TABLE 7 Odds of exclusive breastfeeding by background characteristics, receipt of PNC within 48 h of birth, and women's access to mid-mass media.

N	BGH		BHN		IND		MAL		NPL		PAK		SL	
	5,012	95% CI	887	95% CI	122,458	95% CI	1,693	95% CI	2,761	95% CI	6,276	95% CI	4,635	95% CI
Rural vs. Urban	0.8	0.6–1.1	1.3	0.1–13.5	0.8***	0.7–0.8	NA		0.7	0.5–1.2	0.8	0.5–1.1	1.2	0.6–2.6
Age < 20 yrs. vs. ≥ 20 yrs	1.1	0.8–1.6			0.8**	0.7–1.0			1.0	0.6–1.7	1.4	0.8–2.5	0.8	0.2–4.1
Wealth quintile poorest vs														
Poorer	1.2	0.8–1.9			0.9**	0.8–1.0	0.8	0.3–2.1	0.7	0.3–1.4	1.0	0.6–1.7	1.3	0.5–3.5
Middle	1.1	0.6–1.8			0.9**	0.8–1.0	0.5	0.2–1.4	1.1	0.5–2.4	0.9	0.6–1.6	1.5	0.6–3.6
Richer	1.2	0.7–2.0			0.9	0.8–1.0	0.9	0.2–2.0	0.7	0.3–1.5	0.8	0.5–1.4	1.8	0.7–4.9
Richest	1.2	0.7–2.1			0.8***	0.7–0.9	0.6	0.3–2.4	0.8	0.3–2.0	0.7	0.4–1.2	1.3	0.5–3.5
Received PNC < 48 h = yes	0.6	0.3–1.5			1.4***	1.2–1.6	0.7	0.3–1.9	1.3	0.2–7.5	3.2*	1.0–10.3	3.1*	1.0–10.7
Public vs. private sector provider	0.9	0.5–1.4			0.9***	0.8–0.9	1.3	0.5–3.4	0.8	0.4–1.9	1.1	0.7–1.7	0.5	0.2–1.4
Skilled vs. unskilled health care provider	0.7	0.4–1.1			1.1***	1.0–1.2	NA		0.8	0.4–1.6	1.4*	1.0–2.2	NA	
Own mobile phone = yes	0.9	0.7–1.3	NA		1.1*	1.0–1.3			0.8	0.5–1.5	0.9	0.6–1.3	0.6	0.2–1.8
Read newspaper at least once a week = yes	2.1	0.8–5.8	NA		1.0	0.9–1.2	1.2	0.6–2.5	1.2	0.3–4.3	2.1*	1.0–4.5	0.4**	0.2–0.8
Listen to radio at least once a week = yes	0.4	0.1–1.2	NA		0.9	0.7–1.1	0.7	0.3–1.4	1.6	0.9–2.8	1.2	0.6–2.4	0.9	0.5–1.7
Watch television at least once a week = yes	1.0	0.7–1.4	NA		1.1**	1.0–1.2	0.7	0.2–1.8	1.0	0.6–1.7	1.0	0.7–1.4	0.5*	0.2–1.0
Total number of influencers	0		0		10		0		0		3		3	

* $p < 0.1$, ** $p < 0.05$, *** $p < 0.01$. NA, Not available. *At least one ANC. Grey: Insufficient sample size.

immediately after birth is deficient across South Asia except in Sri Lanka. Despite increasing institutional delivery rates, the proportion of mothers initiating breastfeeding within an hour of birth is lower across all countries, except Bangladesh (29–36). Some reasons for delayed initiation of breastfeeding in institutional deliveries especially in the private sector could be the lack of

implementation support for early initiation of breastfeeding in health facilities, including rooming-in, limited training of health staff on criticality of early initiation of breastfeeding and how to support mothers to breastfeed, and increased c-section rates coupled with a lack of guidance and systems to initiate breastfeeding early after c-section (41, 42). South Asian countries need to review counseling

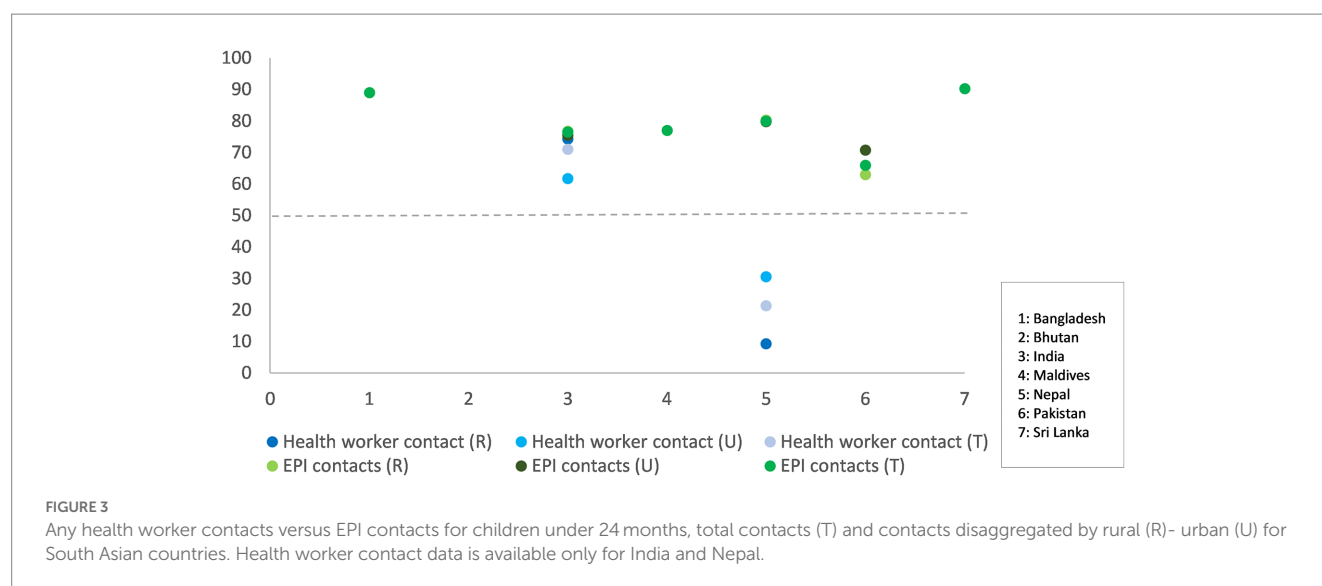


TABLE 8 Odds of infants and children 6–24 months receiving minimum diverse diet by background characteristics, receipt of health worker contact, and mother's access to mid-mass media.

	BGH	BHN	IND		MAL	NPL		PAK	SL
N	3,490		84,579	95% CI		2,761	95% CI		3,008
Rural vs. Urban	NA	NA	1.2***	1.1–1.2	NA	1.0	0.8–1.3	NA	NA
Age < 20 yrs. vs. ≥ 20 yrs	NA	NA	1.1	1.0–1.2	NA	1.0	0.7–1.5	NA	NA
Wealth quintile poorest vs									
Poorer	NA	NA	1.0	0.9–1.1	NA	1.0	0.6–1.4	NA	NA
Middle	NA	NA	1.1*	1.0–1.2	NA	0.9	0.6–1.4	NA	NA
Richer	NA	NA	1.1***	1.0–1.2	NA	1.8***	1.2–2.8	NA	NA
Richest	NA	NA	1.2***	1.0–1.3	NA	1.9**	1.1–3.1	NA	NA
Contacted by health care provider = yes	NA	NA	1.3***	1.2–1.4	NA	1.0	0.8–1.4	NA	NA
Public vs. private sector provider	NA	NA	1.0	0.9–1.0	NA	1.0	0.6–1.5	NA	NA
Skilled vs. unskilled health care provider	NA	NA	0.9*	0.8–0.9	NA	1.0	0.7–1.5	NA	NA
Own mobile phone = yes	NA	NA	1.0	0.9–1.1	NA	1.4***	1.0–1.8	NA	NA
Read newspaper at least once a week = yes	NA	NA	1.2*	1.1–1.3	NA	2.8***	1.4–5.8	NA	NA
Listen to radio at least once a week = yes	NA	NA	1.5***	1.4–1.8	NA	1.3	0.9–1.7	NA	NA
Watch television at least once a week = yes	NA	NA	1.1*	1.0–1.1	NA	1.3*	1.0–1.7	NA	NA
Total number of influencers			9			5			

* $p < 0.1$, ** $p < 0.05$, *** $p < 0.01$. NA, Not available. Blank: Non-significant association.

TABLE 9 Selected features of MIYCN counseling providers under the PHC programs, across South Asia.

	Bangladesh		Bhutan	India			Maldives	Nepal	Pakistan	Sri Lanka
Community and outreach										
CHW expected to counsel on nutrition	FWA	HA	VHW	AWW	ASHA	ANM (at subcenter)	NA	FCHV	LHW	PHM
Nutrition counseling role in job description	Yes	Partial	Yes	Yes	Yes	Yes	NA	Yes	Yes	Yes
Ideal population norm (Rural)	1: 4,500	1:6,000	1:250	1:400–800 ‡	1:1,000	1:5,000	NA	1:150–1,000	1:1,000–1,500	1:3,000
Actual population ratio (Rural)	1: 8,324	1: 10,570	1:372	1:780	1:1,030	1:5,000	NA	1:509	1:1,789*	1:3,876*
Total number (Rural)	20,908	15,420	1,190	1,166,617	883,062	187,557	NA	46,088	92,849*	5,716*
CHW available in urban areas	No	No	No	Yes	Yes	(At PHC)	NA	Yes	Yes	Yes
Ideal population norm	NA	NA	NA	1:800	1:1,000–2,500		NA	1:500–1,000	1:1,500 (slums)	1:3,000
Actual population norm				-	-	-	NA	1:1,170	-	-
Total number	NA	NA	NA	136,000	56,916	20,937 (at PHC)	NA	5,328	-	-
Duration of pre-service training	21 days	21 days	7 days	26 days	8 + 20 days	18 + 6 months	NA	18 days	15 months	6 months
In-service training on nutrition counseling	Yes	Yes	No	Yes	Yes	No	NA	Yes	Yes	Yes
Supervisory structure defined	Yes (FPI)	Yes (AHI/ HI)	Yes (Health Assistants)	Yes (Anganwadi supervisor)	Yes (ASHA facilitator)	Yes (Sr. Nurse or MO)	NA	Yes (AHW/ ANM)	Yes (LHS)	Yes (Supervising PHM)
PHC facilities										
Cadre expected to counsel on nutrition	FWV	CHCP, SAM management unit staff	Health Assistants	NA	NA	ANM, SN, MO	ACHO, CHO, FHO	AHW, ANM, Sr. nurses, MO, HA	LHS, WMO SAM management unit staff	PHN, MO
Receive in-service nutrition training	No	Yes	No	-	-	Yes	Yes (IYCF only)	Yes (AHW, ANM, HA)	Yes	Yes
Cover urban areas	No	No	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes

*1: 400 for mini Anganwadi and 1:800 for Anganwadi in rural or urban. In hard to reach areas norm is 1: 300–800 for Anganwadi and 1: 150–300 for mini Anganwadi. *Numbers of community-based workers are total for rural and urban. Actual population coverage cannot be estimated due to lack of disaggregated rural–urban numbers.

TABLE 10 Review of counseling materials relevant for pregnant women (T = Total).

		BGH	BHN	IND	MAL	NPL	PAK	SRL	T
Total number of materials reviewed		23	13	41	6	4	5	4	96
Print materials		16	4	33	5	3	5	4	70
for Display, demonstration		11	4	32	3	3	2	4	59
as Take aways		05	0	1	2	0	3	0	11
Videos and other e-materials		7	9	8	1	1	0	0	26
Themes		Number of materials							
Healthy eating	Consume variety of locally available foods	19	2	33	4	3	0	2	63
	Consume fortified foods (iodized salt and others)	1	0	25	3	0	0	1	30
Keeping physically active	Attain or maintain a healthy weight and/or prevent excessive weight gain	6	3	8	2*	2	0	0	21
	Take adequate rest	5	1	10	2	2	0	1	21
	Avoid heavy workload	3	0	8	0	0	0	1	12
In undernourished populations, increasing daily energy and protein intake	Increase number of meals using locally available foods (Special reference to thin women)	0	NA	17	NA	NA	NA	NA	17
	Consume food supplement provided through government programs	0	NA	8	NA	NA	NA	1	9
Daily oral iron and folic acid supplementation	Importance of daily consumption	7	1	19	3	2	1	1	34
	How to take supplements	3	1	18	2	2	0	0	28
	How to manage side effects	1	0	14	2	0	0	0	17
In populations with low dietary calcium intake, daily calcium supplementation	Importance of daily consumption	4	1	10	NA	0	0	1	16
	How to take supplements	4	1	8	NA	0	0	0	13
Reducing caffeine intake	Reduce frequency of caffeinated drinks	1	0	6	2	0	0	0	9
	Avoid tea/coffee with meals	2	1	13	2	0	0	0	18
Breastfeeding	Importance of breastfeeding	13	4	21	3	3	3	1	47
	Immediate and uninterrupted skin-to-skin contact after birth	5	2	10	3	3	3	1	27
	Early initiation of breastfeeding	13	2	21	3	3	3	1	46
	Correct positioning and attachment	5	3	10	3	2	3	1	27
	Exclusive breastfeeding till completion of 6 months of age	13	4	17	3	3	3	1	44
	Responsive breastfeeding	2	2	5	3	2	3	1	18
	Risks of giving formula, breast milk substitutes, using bottles, teats and pacifiers	3	2	12	0	0	0	0	17
Counseling on handwashing, food hygiene	Handwashing at critical times	4	0	9	1	2	2	0	18
Messages customized to gestational age		2	0	4	1	0	0	0	7

*MAL- Gestational weight gain counseling as per IOM BMI based classification.

There were two types of materials reviewed-Printed (paper format) and videos/e materials. Under printed materials there were two sub-categories-Display and take away. Values against two main types of materials are bold to distinguish from the sub-categories.

TABLE 11 Review of counseling materials relevant for breastfeeding mothers (T = Total).

		BGH	BHN	IND	MAL	NPL	PAK	SRL	T
Total number of materials reviewed		16	17	35	4	3	8	3	86
Print materials		11	6	27	3	2	8	3	60
for Display, demonstration		8	6	26	3	2	2	3	50
as Take aways		3	0	1	0	0	6	0	10
Videos and other e-materials		5	11	8	1	1	0	0	26
Themes									
Healthy eating	Consume variety of locally available foods	11	3	21	3	3	0	1	42
	Consume fortified foods (iodized salt and others)	1	0	15	3	1	0	0	20
Keeping physically active	Limit time spent sedentary	0	1	0	2	0	0	0	3
	Do at least 150 min of physical activity throughout the week	0	0	0	1*	0	0	0	1
In undernourished populations, increasing daily energy and protein intake	Increase number of meals using locally available foods	0	NA	8	NA	NA	NA	NA	8
	Consume food supplement provided through government programs	0	NA	6	NA	NA	NA	1	7
Daily oral iron and folic acid supplementation	Importance of daily consumption	4	1	15	NA	2	1	0	23
	How to take supplements	2	1	16	NA	2	0	0	20
	How to manage side effects	0	0	6	NA	1	0	0	7
Reducing caffeine intake	Reduce frequency of caffeinated drinks	0	0	0	2	0	0	0	2
	Avoid tea/coffee with meals	0	1	8	2	0	0	0	11
Breastfeeding	Importance of breastfeeding	6	4	22	3	4	6	1	46
	Immediate and uninterrupted skin-to-skin contact after birth	4	2	11	3	4	4	1	29
	Early initiation of breastfeeding	6	2	20	3	4	4	1	40
	Correct positioning and attachment	5	3	12	3	4	3	1	31
	Exclusive breastfeeding until 6 months of age	6	4	21	3	4	4	1	43
	Responsive breastfeeding	1	2	15	3	4	3	1	29
	Overcoming problems in breastfeeding	3	0	4	1	1	0	0	9
	Risks of giving formula, breast milk substitutes, using bottles, teats and pacifiers	2	2	17	0	1	0	1	23
Counseling on handwashing and food hygiene	Handwashing at critical times	3	0	11	1	2	2	0	19
Dietary advice and information on factors associated with constipation	Consumption of high fiber foods and fluids	1	0	4	1	0	0	0	6

*MAL Duration of activity as 150 min per week specified for all adults.

There were two types of materials reviewed-Printed (paper format) and videos/e materials. Under printed materials there were two sub-categories-Display and take away. Values against two main types of materials are bold to distinguish from the sub-categories.

content related to breastfeeding for pregnant women, reaching more family influencers and strengthening delivery care systems to support early initiation of breastfeeding for both home and institutional

deliveries. GMP services need to be strengthened with referral and follow-up for children with MAM and SAM and have a dedicated management package for children affected by overweight or obesity.

TABLE 12 Review of counseling materials relevant for mothers of children 6–23 months (T = Total).

		BGH	BHN	IND	MAL	NPL	PAK	SRL	T
Total number of materials reviewed		19	17	28	7	6	8	10	95
Print materials		14	6	23	6	3	8	9	69
for Display, demonstration		11	6	22	5	3	3	8	58
as Take aways		3	0	1	1	0	5	1	11
Videos and other e-materials		5	11	5	1	3	0	1	26
Themes									
Timely introduction of complementary feeding	Importance of timely introduction of complementary feeding	10	4	20	3	5	2	5	48
	Feeding techniques	6	4	16	3	5	1	5	40
	Quantity, consistency and frequency of introductory complementary feeding	7	4	16	3	5	1	5	41
Age appropriate complementary feeding	Importance of appropriate complementary feeding	7	4	20	3	5	1	5	45
	Age-appropriate quantity, consistency and frequency of feeding	7	4	20	3	5	1	5	45
	Including locally available diverse foods	9	10	21	5	5	6	6	62
	Responsive feeding	6	4	16	3	3	1	5	38
	Handwashing at critical times	5	11	17	3	5	2	1	44
	Safe preparation, handling and storage of complementary foods	4	11	17	3	4	1	1	41
	Child feeding during illness	4	2	17	2	3	1	1	30
Continued breastfeeding till child is two years and beyond	Continued breastfeeding	5	2	19	2	4	1	5	38
Growth Monitoring Promotion	Nutritional counseling for children under-5 based on assessment	2	0	9	2	2	0	1	16
	Management plan for overweight and obese children under-5 at primary health care facilities	0	0	0	0	0	0	0	0
Assessment and management of wasting	Explaining GMP	3	0	6	2	2	0	1	14
IFA supplement to young children >6 m*	Importance of daily consumption	NA	NA	10	NA	NA	NA	NA	10
	Continued and consistent consumption	NA	NA	10	NA	NA	NA	NA	10
	How to take supplements	NA	NA	10	NA	NA	NA	NA	10
	How to manage side effects	NA	NA	4	NA	NA	NA	NA	4

*Only India has universal IFA supplementation program for this age group.

There were two types of materials reviewed-Printed (paper format) and videos/e materials. Under printed materials there were two sub-categories-Display and take away. Values against two main types of materials are bold to distinguish from the sub-categories.

In Bangladesh, layering GMP services on the established EPI platform is being attempted as recommended in recent health and nutrition program review (43).

The data deficiency on assessing coverage, continuity, intensity and quality for complementary feeding behaviors is a serious concern in five of seven countries, with the exception of India and Nepal. In

India and Nepal, health worker contacts did not correlate with timely initiation of complementary feeding (India OR 1.0, Nepal OR 1.7). This could partly be explained by the quality of data available for these contacts. In India, health worker contact data were not specifically for nutrition counseling, while in Nepal the period of recall for health worker contact was one year opposed to three months for India. In India, health worker contacts did correlate with children being fed a more diverse diet, but the strength of the correlation was the same as that for other influencers such as being an urban resident or belonging to a household in the richest income quintile.

MIYCN counseling is mostly an add-on role for community health workers and assumed role for facility staff who contact pregnant women, breastfeeding mothers, and infants and young children. The review highlights the varying qualification criteria and pre-service trainings for community health workers across the seven countries. Except in Bangladesh and India, most country nutrition training packages for health workers cover IYCF only, and within that, mainly focus on breastfeeding. Countries need training curriculum on maternal nutrition and complementary feeding to cover the full spectrum of counseling under MIYCN. This applies to both community-based and facility-based service providers. As noted in the review, graduate training of nurses and doctors also lack focus on MIYCN counseling, particularly on maternal nutrition. Community health workers face similar socio-cultural-gender barriers as pregnant women and mothers. Training should cover overcoming these barriers and negotiating behavior change with male members of the family.

Delays in roll-out of pre-service or entry-level trainings, resource constraints in organizing any refresher trainings, and poor quality of trainings are systemic problems in the region which also affect training on MIYCN counseling. Supervisors can play a critical role to hone service providers' MIYCN counseling skills as there is opportunity to directly observe challenges faced by service providers and provide hands-on, continuing support. Ideally, country training plans should cover joint trainings of service providers and supervisors on MIYCN counseling with supervisors trained on how to provide feedback and support for different types of challenges: technical, community resistance, supply issues, and others. If resource limitations impede the organization of joint trainings, trainings for supervisors should be prioritized. Technology-enabled tools to ease supportive supervision are available for adaptation (44). The Sahyog mobile application for supervisors under ICDS is being used in one of the largest states in India, Uttar Pradesh, and being scaled up in other states. The application enables efficient scheduling of supervision visits; guided observations and observation recording for follow-up with supervisees; learning aids for supervisors and supervisees; and the generating performance data instantly for decision making.

Across countries there is a disproportionate availability of materials with standard messages on breastfeeding and eating foods from diverse food groups. Most of these materials are in print format and suited to rural audiences. Materials need to be contextualized especially for a non-rural audience. While urban poor mainly comprise migrants from rural areas or smaller towns and can relate to content, access to food resources and health care service providers is starkly different for urban poor than rural residents. The urban middle- and higher-income population is influenced by social media, which may provide incorrect information and include aggressive marketing of food products including

for infants. Influence of social media on food preferences was not part of the scope of this study although it is an emerging area of concern. Food items included in counseling materials for complementary feeding should consider costing, problems in sourcing raw ingredients, and cooking time for mother and family. Cooking practices in some countries lean toward use of high fat, sugar, and salt ingredients, which should be checked for in recipes suggested to women and children. There is opportunity to enrich growth charts with standard messages for mother/caregiver based on child's nutritional status (green, yellow or red zone). Beyond use of counseling materials and demonstrations, discussions around important life events like pregnancy announcements or the initiation of complementary feeding have been successful in changing MIYCN behaviors in South Asia due to wider community engagement, the engagement of males, and less dependence on literacy (45, 46).

In the South Asian context, cultural and gender norms in most countries limit access to information for women who are the primary clients for services in the first 1,000 days (47). These norms adversely affect translation of information into practice even when available. However, except for audio-visual materials from Bangladesh and Nepal, messaging was targeted mostly at women. Nuanced material is needed to cover all recommended counseling and reach the full range of target groups, which include families (husband, fathers, parents-in-law) of direct clients as well as community leaders. These family and community influencers shape health and nutrition behaviors, including types of foods consumed and uptake of nutrition services by pregnant women and children. Most countries have done well in developing materials in local languages.

In all countries, MIYCN counseling materials need to be organized by platforms and most appropriate service provider to identify need for any new materials. Service providers have varying qualifications and capacities which need to be considered when developing new materials. How users will be trained on use of new materials should be planned in line with ongoing capacity building efforts on MIYCN. In Bangladesh and India, community volunteers such as self-help group members engaged in MIYCN counseling should be considered when organizing materials by service providers. With the increasing reach of internet service and hardware, web-based counseling through artificial intelligence is gaining momentum. There is opportunity to transform available print materials to electronic or creating new materials for tech-based dissemination.

MIYCN counseling is a service that requires investments in time, capacity building, counseling materials, and organization of events, all of which should be defined across community- and facility-based platforms. Targets for counseling contacts and events especially for community-based platforms are needed in country plans and budgets. Each country has established platforms for delivering counseling services but miss monitoring delivery of counseling services. A curated set of indicators that provide the most relevant data to strengthen counseling services at local level are needed. These indicators should clearly establish the reach of counseling services platforms, especially for infants and young children and as well as an assessment of quality of counseling. Notable counseling related indicators being used in few South Asian countries are on consumption of IFA and increasing dietary diversity in pregnancy, breastfeeding and GMP. Monitoring should include verification of information by direct observations of

behaviors by service providers such as observing breastfeeding or a child feeding session. A few of these indicators may be used for upward reporting.

Limitations

The analysis on coverage, continuity, intensity, and quality of MIYCN counseling is based on proxy indicators of maternal and child contact points due to the unavailability of direct MIYCN counseling indicators. Most countries are working to integrate nutrition services with these contact points. In DHS, the duration of recall for most of these contacts varied from three to five years across countries. To limit bias due to variable recall and have comparable data, the duration of recall was set at three years during analysis. The definition of health worker contacts for infants and children varied for India and Nepal and this data is not comparable. KIIs covered representatives from national government, training institutes, and development partners to gain insights on policy, planning and implementing MIYCN counseling programs at a high level. Service provider and client perspectives on MIYCN counseling were not in scope of this study but are critical for a comprehensive assessment of MIYCN counseling services; country-level assessments should include them as key respondents. In Balochistan, Pakistan, KIIs could not be completed as the areas was inundated with floods during the time of data collection. Counseling materials were sourced from websites and key informants. These do not cover the whole range of materials available, especially in larger countries (Bangladesh, India, and Pakistan). Awareness generation materials meant exclusively for dissemination through mass media and social networks were not included in this study.

Recommendations

Based on these findings, countries in South Asia need to review guidelines on MIYCN counseling to align with global recommendations. Country policy and planning should recognize MIYCN counseling as a service with defined set of activities, across different platforms. MIYCN counseling roles need to be rationalized against job responsibilities, qualifications, and training of service providers. Training curriculum needs to be updated for all cadres required to provide MIYCN counseling as per global recommendations. Health worker trainings on MIYCN counseling need to be backed with supportive supervision by skilled supervisors. Counseling materials need to be mapped for coverage of content and target groups, types of users, and format to determine need for any additional materials. Use of counseling materials needs to be restructured to deliver the right message, by the right provider, and at the right time. Countries need to establish a system to monitor MIYCN counseling services and set accountability mechanisms to deliver counseling as is done to deliver nutrition commodities.

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Data availability statement

Publicly available datasets were analyzed in this study. This data can be found here: <https://dhsprogram.com/data/available-datasets.cfm>.

Author contributions

AB, VS, ZM, SG, and TF were involved in conceptualization and methodology. AB and SG supervised data collection. AB and KS were involved in data analysis. AB, VS, and TF led the drafting of the manuscript. VS, ZM, and TF were involved in funding acquisition and project administration. All authors provided technical input, read, and agreed to the published version of the manuscript.

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Conflict of interest

The authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

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Supplementary material

The Supplementary material for this article can be found online at: <https://www.frontiersin.org/articles/10.3389/fnut.2023.1205620/full#supplementary-material>

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EDITED BY

Sunita Taneja,
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REVIEWED BY

Savita Sapra,
Society for Applied Studies, India
Tomas Yeheyis,
Hawassa University, Ethiopia
Chutima Roomruangwong,
Chulalongkorn University, Thailand
B. Sheeba,
JSS Academy of Higher Education and
Research, India

*CORRESPONDENCE

Markos Desalegn
✉ markosdesalegn@gmail.com

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Antenatal depression and associated factors among pregnant women attending antenatal care at public health facilities in the Gida Ayana district, Oromia Region, West Ethiopia, in 2022

Lelisa Oljira¹, Eba Abdissa², Matiyos Lema¹, Emiru Merdassa¹,
Jira Wakoya Feyisa¹ and Markos Desalegn^{1*}

¹Department of Public Health, Institute of Health Sciences, Wollega University, Nekemte, Ethiopia,

²Department of Psychiatry Nursing, School of Nursing, Institute of Health Sciences, Wollega University, Nekemte, Ethiopia

Background: Though antenatal depression (AND) has a risk of maternal and fetal morbidity and mortality, it is a neglected component of pregnancy care in Ethiopia. Research evidence is compulsory in different parts of the country to alleviate this problem. Thus, this study was needed to assess antenatal depression and its associated factors, which can help antenatal care (ANC) providers and program coordinators focus on the mental health of pregnant mothers.

Objectives: This study aimed to assess antenatal depression and associated factors among pregnant women attending ANC at public health facilities in the Gida Ayana district, Oromia Region, West Ethiopia, in 2022.

Methods: A facility-based cross-sectional study was conducted among 370 pregnant women attending ANC at public health facilities. Systematic random sampling techniques were used to select study participants. A standard (validated) tool, the Edinburgh Postnatal Depression Scale, was also used to assess antenatal depression. The collected data were coded, entered into Epi-data software version 4.6, and analyzed by SPSS version 23. Multivariable logistic regression analyses were used to identify associated factors with a p -value <0.05 .

Results: In this study, the prevalence of antenatal depression was 62 (16.8%; 95% CI: 13, 20.5). Being single in marital status (AOR = 3, 95% CI: 1.5, 6.2), having an unplanned pregnancy (AOR = 2.7, 95% CI: 1.45, 5.1), and having partner conflict (AOR = 3.49, 95% CI: 1.79, 6.8) were the factors associated with antenatal depression.

Conclusion: About one in five pregnant women has antenatal depression. Being single, having an unplanned pregnancy, and having a dissatisfied relationship with a sexual partner were the factors associated with antenatal depression. Therefore, women or partners are expected to plan pregnancy, and the dissemination of health information related to an unplanned pregnancy needs to be intensified by health providers. The partner ought to avoid conflict during the pregnancy, and healthcare providers or families are needed to support the single or widowed pregnant women. Further prospective cohort studies are needed to ascertain the effect of antenatal depression on fetal–maternal outcomes.

KEYWORDS

perinatal, antenatal, depression, women, antenatal care, pregnant

1. Background

Prenatal depression is a circumstance that labels a range of physical and emotional changes encountered by women during pregnancy (1, 2). Some of these symptoms include fatigue, crying, hopelessness, anxiety, changes in appetite, sleeping difficulty, a lack of interest in daily activities, and suicide (1, 2). The mental health of women in the reproductive age group is becoming a significant public health problem both in developing and developed countries (3).

Globally, ~280 million people suffer from depression annually (4). The prevalence of antenatal depression ranges from 15 to 65% around the globe (5). According to a study conducted in one of the sub-Saharan countries, Ghana, the prevalence of antenatal depression was 19.7%, while 14.1% of them were confirmed to have suicidal ideation (6). Evidence showed that the prevalence of prenatal depression in Ethiopia was 24.2% until 2018 (7). In the West Shawa zone of Oromia, the prevalence of prenatal depression was 32.3% (8).

Antenatal depression is the leading cause of disability, poor performance, suicide, premature death, discrimination, and stigma among pregnant women it affects (4, 9). It also has negative effects on the fetus, including low birth weight and preterm birth, which carry a great risk of neonatal death (10). Furthermore, antenatal depression is a confirmed risk factor for stunting in a child born from a pregnancy suffering from antenatal depression (11). In addition, a surviving child born to a woman affected by antenatal depression has a high risk of developing lifelong mental impairments (12). Moreover, antenatal depression is associated with severe pregnancy complications, including preeclampsia, a high rate of cesarean delivery, birth asphyxia, and postpartum psychosis, among others (6, 13, 14). Despite its severity and seriousness, it was the most neglected element of antenatal care (13–17).

The factors associated with antenatal depression include lack of basic needs and safety, low-income level, poor social status, unplanned pregnancy, spousal violence, sexual harassment, personal and family history of mental disorder, substance abuse, marital status, being HIV positive, poor social support, bad obstetric history, fear of labor pain, and lack of ANC, among others (4–17). Even though most of the identified risk factors for antenatal depression are believed to be preventable by appropriate, timely action, failure to recognize them and delays in seeking healthcare result in further expenses to treat the complications that result every year (5).

In Ethiopia, the Program for Improving Mental Health Care (PRIME) and the Emerging Mental Health System in Low- and Middle-Income Countries (Emerald) have been working to improve maternal mental health (18, 19). The program for improving mental healthcare aimed to scale up mental health

service integration through evidence generation (18), whereas the Emerging Mental Health System in Low- and Middle-Income Countries (Emerald) aimed to improve the effectiveness of mental health service delivery by identifying health system obstacles and their solutions (19).

Despite this, antenatal depression is still a critical public health problem due to its intergenerational impact on mothers, infants, and children (20). One-third to one-fifth of women in developing countries have a significant mental health problem during pregnancy and after delivery (21, 22). Overall, the prevalence of antenatal depression varies among previous studies conducted in different parts of the world and different areas of Ethiopia. Furthermore, the factors reported as associated with antenatal depression among different studies were mostly not consistent with each other.

To the best of the knowledge of the investigator, the prevalence of antenatal depression and the factors associated with it were not studied in the East Wollega Zone, especially in the Gida Ayana district. There is no guideline to assess and treat AND in Ethiopia, and it is a neglected component of antenatal care. More importantly, since antenatal depression is a neglected component of antenatal care and leads to tremendous health, social, and economic negative consequences, adding more research evidence on the issue is necessary to arouse the focus of policymakers to solve the problem. Thus, this study was aimed at filling the existing gap.

2. Methods

2.1. Study area, period, and design

A facility-based cross-sectional study design was conducted from 1 March to 10 April 2022. The study was conducted in the Gida Ayana District, East Wollega Zone, Oromia region, west Ethiopia. The total population of the district was 158,635 people, of whom 79,878 were men and 78,757 were women. The district has 29 kebeles and 29,644 households. The district has 22 health posts, six public health centers, one public general hospital, and 26 private clinics (23).

2.2. Participants

All pregnant women in the Gida Ayana District were the source population, whereas pregnant women attending antenatal care at selected public health facilities in Gida Ayana District during the study period were the study population. All pregnant women attending antenatal care at the public health facilities of Gida Ayana district during this study period were included, whereas pregnant women who had a severe illness and those unable to communicate verbally were excluded from the study.

2.3. Sample size determinations

A single population proportion formula was used to determine the sample size for the prevalence of AND. The assumptions were as follows: a 95% confidence interval, a 5% margin of error, a 32.3%

Abbreviations: ANC, antenatal care; AND, antenatal depression; AOR, adjusted odds ratio; BSc, Bachelor of Science; CI, confidence interval; FANC, focused antenatal care; FMOH, Federal Ministry of Health; HI, health institution; LAMI, low and middle income; PNC, postnatal care; PI, principal investigator; IF, variance inflation factor; SD, standard deviation; SPSS, Statistical Package for Social Sciences; HIV, human immune virus.

expected proportion of antenatal depression from a previous study done in the West Shawa Zone (8), and a 10% non-response rate were considered. Here, n_o = sample size; ρ = proportion from the previous study; d = desired degree of precision; Z = level of confidence desired, at a 95% confidence level.

$$n_o = \frac{(Z\alpha/2)^2 \times \rho(1 - \rho)}{d^2}$$

The double population proportion formula was employed to estimate the sample size for factors associated with antenatal depression using EPI INFO version 7. Considering previous abortion as an associated factor in prenatal depression, the power of the study was 80% (95% CI), the ratio of unexposed to non-exposed was 1, the proportion among exposed was 47.8%, and the proportion among non-exposed was 27.3% (24). This assumption yields a sample size of 215, which is less than the one estimated for the prevalence of antenatal depression. Therefore, the sample size calculated for the prevalence of AND was used as the maximum sample size of 370 after adding a 10% non-response rate.

2.4. Sampling technique

A systematic random sampling method was employed to pick the study participants. The district has six public health centers and one public general hospital, and all of them were included in the study. Based on the record of the last 6 months, the average number of antenatal mothers expected to attend all the public health facilities during the data collection period was identified. Then the sample was proportionally allocated to each health facility based on their respective client flow. The individual client was approached by calculating the sampling interval " $k = N/n$," where " N " is the total number of mothers expected to attend ANC at each health facility during the data collection period and " n " is the proportionally allocated sample size for each health facility. Thus, the sampling interval " k " becomes 1.4, which was rounded to 2 for all health facilities [Ayana Health Center (67/49), Angara Gute Health Center (74/54), Jangir Health Center (42/31), Gaba Jimata Health Center (35/24), Andode Dicho Health Center (42/31), Warabo Health Center (44/32), and Gida Ayana General Hospital (205/149)]. The first respondent was selected randomly, and the subsequent respondents were selected from every other mother visiting the health facility for ANC.

2.5. Data collection tools and procedures

A face-to-face interviewer-administered structured questionnaire was used to collect the data. The questionnaire has five parts: socio-demographic characteristics, obstetric characteristics, predisposing factors (behavioral pattern and history of depression), social support, domestic violence, and antenatal depression measurements were adapted (15, 16, 20). The tool was prepared in English and translated into Afaan Oromo, and back again to English by different professionals in both Afaan Oromo and English to maintain uniformity.

The Edinburgh Postnatal Depression Scale (EPDS), a 10-item self-reporting questionnaire that has been validated for screening antenatal depression, was also used to assess antenatal depression (AND) (25).

Two experienced female midwives and two supervisors participated in data collection for 5 weeks. The supervisors led the data collectors during the data collection procedure. Ahead of data collection, both the supervisors and data collectors were given training on the objective of the study, the content of the tool, and an approach to respondents during data collection. Supervisors checked the accuracy and completeness of the data and submitted it to the principal investigator. The principal investigator oversaw the whole data collection process.

2.6. Data quality control

Training the supervisors and female data collectors was performed to ensure the quality of the data. A pilot test was done ahead of actual data collection among 5% of the sample size in the Guto Gida district of Uke, the health center, which has almost the same socio-demographic as the population of the study area. The amendment was made to the questionnaire based on the results of the pilot test. During and before data collection, the data collected by the data collectors have been checked for completeness and truthfulness daily by immediate supervisors.

2.7. Study variables

Dependent variable: antenatal depression among women attending ANC.

Independent variables: socio-demographic variables: age of the mother, maternal educational level, residence, family income, marital status, occupational status, ethnicity, and religion.

Obstetric-related variables: history of spontaneous abortion, stillbirth, congenital malformation, gravity, parity, unplanned pregnancy, stressful life events during pregnancy, experienced death of the baby, HIV status, and undesired fetal sex.

History of depression: personal history of depression and family history of depression.

Social support status and domestic violence experience: marital conflict, conflict with husband during the current pregnancy, the nature of the relationship with the husband, intimate partner violence, and status of social support.

Behavioral pattern: husband and self-status regarding substance abuse (smoking cigar rate, chat chewing, and drinking alcohol).

2.8. Operational definitions

Antenatal depression: the scale consisted of 10 short statements. A mother checks off one of the four possible answers that are closest to how she has felt during the past week. Most mothers easily complete the scale in <5 min. Responses were scored 0, 1, 2, and 3 based on the seriousness of the symptom. Items 3, 5,

and 10 were reverse scored (i.e., 3, 2, 1, and 0). The total score was found by adding together the scores for each of the 10 items. Then the respondents who had a sum score ≥ 13 were regarded as having antenatal depression, and the rest were regarded as not having antenatal depression (26).

Social support: social support is considered the support the pregnant woman gains from her husband, neighbor, and relevant others, such as relatives. It was measured by the single item that asks for the respondents' self-report of whether they are satisfied or not with the social support they gain when they need it (27).

Intimate partner violence is defined as a behavior by an intimate partner or ex-partner that causes physical, sexual, or psychological harm, including physical aggression, sexual coercion, psychological abuse, and controlling behaviors (28). Thus, it was measured by using a single item that asks for the respondents' self-report of whether they had any form of intimate partner violence to respond as either yes or no.

Substance abuse: it was measured by the participant's self-report (as "yes" or "no") of whether they or their husband or sexual partner drinks alcohol, chews chat, and/or smokes cigars during their recent pregnancy without specifying the frequency by which they take the substances (5).

Relationship status: the respondents were asked, "Have you ever had any conflict with your partner during the current pregnancy?" with a response of "yes" or "no" in this study. Based on this, the respondent's response was dichotomized as "partner conflict" for a "yes" response and "no partner conflict" for a "no" response.

2.9. Data processing and analysis

The collected data were coded and cleaned to identify missing values, outliers, and inconsistencies. The coded data were checked for completeness, entered into EPI INFO, and exported to SPSS version 23 for statistical analysis. Descriptive statistics were presented using frequency and percentages in tables and figures. In bivariate analysis, candidate variables were identified with a p -value < 0.25 . In multivariable logistic regression, variables with a p -value of 0.05 were determined to be factors associated with antenatal depression. In addition, the odds ratio and 95% confidence interval were used to determine the strength of the association. Hosmer–Lemeshow goodness-of-fit test was used, and the result showed a p -value of > 0.05 , indicating that the model was a good fit. To investigate collinearity, a diagnostic test was run across all independent variables. The VIF was < 10 , indicating that there was no severe multi-collinearity among the independent variables.

3. Results

3.1. Socio-demographic characteristics of the respondents

All the study participants in this study were interviewed and responded to, with a response rate of 100%. The mean and standard deviation of the participant's age were 27.956.14, respectively, while the range was between 17 and 43. A significantly higher proportion (285, or 77%) of the study's participants was married. Furthermore,

TABLE 1 Socio-demographic characteristics of women who were attending ANC visit in public health facilities of Gida Ayana district, West Ethiopia, 2022 ($n = 370$).

Variables	Categories	Frequency	Percentage (%)
Age	≤ 19	23	6.2
	20–29	211	57
	≥ 30	136	36.8
Marital status	Single	51	13.8
	Married	285	77
	Divorced	21	5.7
	Widowed	13	3.5
Religion	Protestant	184	49.7
	Orthodox	114	30.8
	Muslim	69	18.6
	Others*	3	0.9
Ethnicity	Oromo	336	90.8
	Amhara	26	7
	Others**	8	2.2
Residence	Rural	156	42.2
	Urban	214	57.8
Educational status	Able to read and write	77	20.8
	Unable to read and write	87	23.5
	Primary	48	13
	Secondary	93	25.1
	College/university	65	17.6
Occupational status	House wife	174	47
	Merchant	62	16.8
	Self-employed	53	14.3
	Government employee	81	21.9
Household monthly income	$< 2,500$	180	48.6
	$\geq 2,500$	190	51.4

*Catholic, and Adventist.

**Tigre and Gurage.

the majority of 336 (90.8%) of the respondents were from the Oromo ethnic group, followed by the Amhara ethnic group at 26 (7%; Table 1).

3.2. Obstetric characteristics of the respondents

Approximately three-fourths (72.4%) of the respondents had two to five pregnancies or gravidity. In this study area, approximately a quarter (87, 23.5%) of the respondents had

TABLE 2 Obstetric characteristics of women who were attending ANC visit in public health facilities of Gida Ayana district, West Ethiopia, 2022 (*n* = 370).

Variables	Categories	Frequency	Percentage (%)
Gravidity	Primigravida	48	13
	2–5	268	72.4
	≥6	54	14.6
Parity	Nullipara	48	13
	2–5	307	83
	≥6	15	4
Current pregnancy status	Planned	189	51.1
	Not planned	181	48.9
Know their HIV status during the current pregnancy	Yes	270	73
	No	100	27
Attending their ANC as per appointment	Yes	154	41.6
	No	216	58.4
Had any complication during the current pregnancy	Yes	75	20.3
	No	295	79.7
Had fear of giving birth of the current pregnancy	Yes	96	25.9
	No	274	74.1
Had known the sex of their current fetus	Yes	39	10.5
	No	331	89.5
History of spontaneous abortion	Yes	87	23.5
	No	283	76.5

experienced spontaneous abortion, and the other 40 (10.8%) of the respondents had experienced stillbirth, whereas 47 (12.7%) of the respondents had experienced the death of their baby (Table 2).

3.3. Behavioral patterns, social support status, and domestic violence experience among the respondents

Almost all the respondents had no history of smoking cigarettes (368, 99.5%), chewing chat (365, 98.6%), or drinking alcohol (355, 95.9%). In this study area, ~70 (18.9%) and 44 (11.9%) of pregnant women have experienced intimate partner violence (IPV) during their current pregnancy, respectively. Approximately one-fourth

(23.2%) of the pregnant women in this study area had experienced marital conflict at least once in their marriage. Concerning their relationship status with their spouse or sexual partner, the majority (294, or 79.5) of them had a happy relationship. Approximately 250 (67.6%) of the participants had support from family or a partner during the current pregnancy.

3.4. Edinburgh Postnatal Depression Scale assessment of the respondents

Approximately 50% of the 181 (48.9) study participants laughed and saw the funny side of things all of the time in the last week. Fifty-three of the present 186 (50.30) study participants were anxious or worried for no good reason in the last week (Table 3). Based on this depression scale assessment, 62 (16.8%; 95% CI: 13, 20.5) of the study participants had antenatal depression.

3.5. Factors associated with antenatal depression among the respondents

In bivariable analysis, age, marital status, residence, monthly income, having ever had a spontaneous abortion, fear of giving birth, or having had any complications recently, current status, pregnancy status, and status of relationship with a partner were found to be candidate variables for the multivariable logistic regression model.

Three variables were statistically significantly associated with the outcome variable in the final model of multivariable logistic regression. Thus, the variables that had a significant statistical association in the multivariable logistic regression analysis were marital status, whether the current pregnancy was planned, and the respondents' status of relationship with their sexual partner. The odds of having antenatal depression among single women were three times higher compared to married women (AOR = 3, 95% CI: 1.5, 6.2). Furthermore, the odds of having antenatal depression among the women who had unplanned pregnancies were 2.7 times higher compared to the women who had planned pregnancies (AOR = 2.7, 95% CI: 1.45, 5.1). In addition, the odds of having antenatal depression among the women who had an unsatisfactory relationship with their sexual partner were 3.49 times higher compared to the women who had a satisfactory relationship with their sexual partner (AOR = 3.49, 95% CI: 1.79, 6.8; Table 4).

4. Discussion

Approximately one-fifth (16.8%) of the pregnant women attending ANC services at the public health facilities in Gida Ayana district had antenatal depression. Being single in marital status, having an unplanned pregnancy, and having a dissatisfied relationship with the sexual partner were identified as factors associated with antenatal depression in this study area.

A significant proportion of pregnant women in this study had antenatal depression, which was lower than the result of the study done in Addis Ababa, Ethiopia, where the prevalence of

TABLE 3 Edinburgh Postnatal Depression Scale assessment among women who were attending ANC visit in public health facilities of Gida Ayana district, West Ethiopia.

Variables	Categories	Frequency	Percent (%)
In the last week I have been able to laugh and see the funny side of things?	Yes, all of the time	181	48.9
	Yes, most of the time	150	40.5
	No, not very often	22	5.9
	No, not at all	17	4.6
In the last week I have looked forward with enjoyment to things	Yes, all of the time	149	52.4
	Yes, most of the time	133	35.9
	No, not very often	27	7.3
	No, not at all	16	4.3
In the last week I have blamed myself unnecessarily when things went wrong	Yes, most of the time	177	47.8
	Yes, some of the time	108	29.2
	Not very often	64	17.3
	No, neve	21	5.7
In the last week I have been anxious or worried for no good reason	Yes, all of the time	186	50.3
	Yes, most of the time	114	30.8
	No, not very often	48	13
	No, not at all	22	5.9
In the last week I have felt scared or panicky for no very good reason	Yes, most of the time	189	51.1
	Yes, some of the time	108	29.2
	Not very often	47	12.7
	No, neve	726	7
In the last week I have things been getting on top of me	Yes, most of the time	216	58.4
	Yes, some of the time	82	22.2
	Not very often	55	14.9
	No, neve	17	4.6
In the last week I have been so unhappy that I have had difficulty sleeping	Yes, most of the time	182	49.2
	Yes, some of the time	82	22.2

(Continued)

TABLE 3 (Continued)

Variables	Categories	Frequency	Percent (%)
	Not very often	92	24.9
	No, neve	14	3.8
In the last week I have felt sad or miserable	Yes, most of the time	163	44.1
	Yes, some of the time	103	27.8
	Not very often	89	24.1
	No, neve	15	4.1
In the last week I have been so unhappy that I have been crying	Yes, most of the time	226	61.1
	Yes, some of the time	85	23
	Not very often	44	11.9
	No, neve	15	4.1
In the last week the thought of harming myself has occurred to me	Yes, most of the time	241	65.1
	Yes, some of the time	86	23.2
	Not very often	26	7
	No, neve	17	4.6

antenatal depression was 24.94% (26). In addition, the magnitude of antenatal depression was lower than that of the study conducted in West Shawa (32.3%) (8), Maichew, north Ethiopia (31.1%) (29), Badewacho, south Ethiopia (23.3%) (30), and Gondar Hospital, northwest Ethiopia (23%). The possible reason for the difference could be due to differences in the study period and differences in socio-economic or cultural characteristics among the study areas. On the other hand, the lower magnitude of antenatal depression in this area could also be due to less intimate partner violence (11.9%) during the current pregnancy, and the majority of the participants in this study area were multi-gravida (72.4%), which is related to a lower risk of antenatal depression.

The magnitude of antenatal depression in the current study was similar to the finding of the study done in Jimma town (16.6%) (1) and Dubti Hospital (17.9%) (14), and this similarity could be due to close geographical proximity and similar health system factors, and the cultures of communities within Ethiopia seem to complement each other. However, the other study from the northeast of Ethiopia, Northwest Debre Tabor Town, revealed a lower prevalence of antenatal depression of 11.8% (25) than the current finding. This could be because this study area was a conflict area where there could be catastrophic events, which could increase the risk of prenatal depression (31). Being single in marital status was associated with antenatal depression in the current study. This finding is consistent with the findings of the study done in Northwest Ethiopia and Southwest Ethiopia,

TABLE 4 Multivariable logistic regression analyses of factors associated with antenatal depression among pregnant women who were attending ANC in Gida Ayana district, West Ethiopia, 2022 ($n = 370$).

Variables	Categories	Had antenatal depression		COR (95 % CI)	AOR (95%, CI)
		Yes (N, %)	No (N, %)		
Age	≤19	7 (30.4)	16 (69.6)	1.85 (0.69, 4.96)	2.42 (0.75, 7.76)
	20–29	29 (13.7)	182 (86.3)	0.67 (0.38, 1.20)	0.7 (0.36, 1.38)
	≥30	26 (19.1)	110 (80.9)	1	1
Marital status	Single	17 (33.3)	34 (66.7)	3.15 (1.6, 6.18)	3 (1.5, 6.2)*
	Divorced/widowed	6 (17.6)	28 (82.4)	1.35 (0.53, 3.48)	0.46 (0.16, 1.3)
	Married	39 (13.7)	246 (86.3)	1	1
Ever had spontaneous abortion	Yes	20 (23)	67 (77)	0.584 (0.32, 1.06)	0.757 (0.39, 1.47)
	No	42 (14.8)	241 (85.2)	1	1
Had fear of giving birth	Yes	24 (25)	72 (75)	2.07 (1.16, 3.68)	1.75 (0.86, 3.58)
	No	38 (13.9)	236 (84.1)	1	1
Had any complication recently	Yes	18 (24)	57 (76)	0.55 (0.299, 1.03)	1.002 (0.46, 2.2)
	No	44 (24.9)	251 (85.1)	1	1
Current pregnancy status	Unplanned	44 (24.3)	137 (75.6)	3.05 (1.69, 5.5)	2.7 (1.45, 5.1)*
	Planned	18 (9.5)	171 (90.5)	1	1
Status of relationship with partner	Unsatisfactory	25 (32.9)	51 (67.1)	3.4 (1.9, 6.14)	3.49 (1.79, 6.8)*
	Satisfactory	37 (12.6)	257 (87.4)	1	1

*Indicates statistical significance at p -value < 0.05 .

AOR, adjusted odds ratio; CI, confidence interval; COR, crude odds ratio.

where being single was associated with higher odds of antenatal depression (12, 30). The possible reason for the similarity could be that unmarried pregnant women lack the necessary support from their male partner and most probably face social stigma that leads them to develop antenatal depression (32).

Having an unplanned pregnancy was also positively associated with higher odds of antenatal depression in this study area. This finding was consistent with the findings of the studies (12, 17, 32). The women who had unplanned pregnancies are at risk of developing antenatal depression. The possible reason behind this is that it is obvious that if the pregnancy was not planned, the woman may be challenged to cope with any challenges that she may face during the pregnancy because “an unplanned pregnancy may have a long-lasting negative impact on a woman’s perinatal mental health” (33).

Being in a dissatisfying relationship with a sexual partner was positively associated with higher odds of antenatal depression. This finding is in line with the findings of the study done in the Hadiya zone of south Ethiopia and Maichew, north Ethiopia (29, 30). The possible reason behind this could be that pregnant women with a dissatisfied relationship with their sexual partner are at increased risk of having antenatal depression (32). Evidence suggests that lower marital quality is highly associated with lower levels of life satisfaction and higher levels of depressive symptoms (33, 34).

The findings of this study are an input for healthcare providers and other relevant stakeholders at different levels

to give due attention to preventing and treating antenatal depression during antenatal care visits. However, this study was not without limitations. First, this study was a facility-based study, which could miss pregnant women who were not attending antenatal care services at public facilities. On the other hand, the study used a cross-sectional study design, which cannot establish the temporal relationship between the independent variables and the outcome variable. Third, the study used a sole quantitative method that could not explore the concerns of pregnant women, spouses, family, the community, and the care provider about antenatal depression. In addition, contributing factors such as social support, intimate partner violence, substance abuse, and the relationship status of pregnant women could have been more comprehensively investigated through detailed inquiries or questionnaires.

5. Conclusion

Approximately one in five pregnant women in this study area had antenatal depression. Being single in marital status, having an unplanned pregnancy, and having a dissatisfied relationship with a sexual partner or spouse were possible factors associated with antenatal depression among pregnant women in this study area. Therefore, women and their partners ought to recognize that quality information, education, and family

planning services can minimize the risk of unwanted pregnancy. Healthcare providers ought to intensify health information dissemination about the advantages of contraceptive methods in combating the risk of unplanned pregnancies. The spouses should avoid conflict during pregnancy. Single or unmarried pregnant women are better supported by family, community, and health professionals to minimize the actual or perceived social stigma. Orientation and in-service training should be provided for obstetric care providers regarding the detection, control, and prevention of antenatal depression to minimize further complications. Prospective cohort studies are needed to ascertain the effect of antenatal depression on fetal and maternal outcomes.

Data availability statement

The raw data supporting the conclusions of this article will be made available by the authors, without undue reservation.

Ethics statement

The Helsinki Declaration of Health Research ethical standard was applied to undertake this study (35). Ethical approval was obtained from the Institutional Review Board of Wollega University, Institute of Health. A support letter was obtained from the Gida Ayana district health office. Each health facility administrator was communicated with using the ethical approval letter and the support letter of their district. The study participants have been informed of the objective of the study, the right to discontinue or refuse to participate in the study, and the confidentiality of their responses. Written informed consent was obtained from each study participant before starting the data collection.

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Author contributions

LO and MD were involved in conducting the study, data analysis, report writing, and the main manuscript text development. EA, ML, EM, and JW were involved in editing the report and manuscript text development. Furthermore, they took part in preparing Tables 1–4. All authors reviewed the manuscript. All authors contributed to the article and approved the submitted version.

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Conflict of interest

The authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

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