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Fatigue and quality of sleep jointly influence the association between physical activity and health-related quality of life in patients with chronic kidney disease: a cross-sectional study

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Introduction: Fatigue is a prevalent and burdensome symptom in Chronic Kidney Disease (CKD), with major impact on Health-Related Quality of Life (HRQoL). Physical activity has been linked to improvements in both fatigue and HRQoL. This study examined whether physical activity relates to HRQoL indirectly through fatigue and whether this relationship is moderated by sleep quality.

Methods: A total of 465 CKD patients (mean age = 53.78 years; 50% female) participated in the study. Fatigue, physical activity, HRQoL, and sleep quality were assessed and compared to general population norms and across treatment modalities using t-tests and ANCOVAs. Mediation, moderation, and moderated mediation analyses were conducted.

Results: CKD patients reported lower physical activity levels, HRQoL, and sleep quality, and higher fatigue than the general population (all *ps* < .001). Among treatment groups, transplant recipients showed the most favorable outcomes, while patients without renal replacement therapy reported the poorest. Higher levels of physical activity were associated with better HRQoL indirectly through fatigue, with small to moderate effect sizes. Stronger associations observed in those reporting better sleep quality.

Discussion: These findings indicate that physical activity is associated with better HRQoL in CKD patients through its relationship with fatigue, particularly among those with good sleep quality. Future research should explore fatigue across CKD stages to optimize interventions that target both physical activity and sleep.

KEYWORDS

chronic kidney disease, fatigue, sleep, physical activity, HRQoL, renal transplantation, renal replacement therapy, dialysis

Introduction

Fatigue appears to be the main complaint in chronic kidney disease (CKD). In a healthy population, fatigue is reported in 5% to 45% of the cases (1). The prevalence of (chronic) fatigue in CKD is substantially higher and varies depending on the study from about 50% to 89% in hemodialysis (HD) (2). Very few studies focused however on peritoneal dialysis and transplant populations (3). Given its prevalence and burdensome nature, fatigue has been identified as a highly prioritized symptom to treat and investigate (4).

The biopsychosocial model of fatigue in CKD patients (5) hypothesizes fatigue is precipitated by physiological factors [uremia, anemia, blood pressure, inflammation (2, 6, 7)] and may be perpetuated by psycho-behavioral [psychological distress, sleep disturbances, physical activity, smoking, and cognitions (2)], and social factors (e.g. social support). However, specific determinants and causal mechanisms of fatigue in CKD patients are not well understood due to its complex multifaceted etiology (2, 8, 9) and the lack of longitudinal studies (2).

Fatigue has a profound direct and indirect negative effect on individuals' functioning and quality of life. Consequences of fatigue are directly reflected in impaired functionality (10), disease progression, increased risk of hospitalization (11), and lower physical and mental Health-Related Quality of Life (HRQoL) (2, 12–14). Indirectly, fatigue may predict mortality through distress, impaired functioning and its consequences (15). It should, however, be noted that both fatigue and HRQoL differ by CKD treatment and modality (16, 17).

Poor sleep quality proved to be associated with more fatigue in patients on maintenance hemodialysis, while prolonged fatigue in these patients was associated with mortality (13). According to a review in hemodialysis patients, fatigue is especially related to poor physical HRQoL (18). Fatigue in patients with CKD, especially in patients on long-term dialysis, also leads to muscle wasting, resulting in inactivity or reduced physical activity which are in turn related to mortality (19, 20).

Experiential evidence shows physical activity decreases fatigue in CKD patients (9) and improves HRQoL (21). It is hypothesized physical activity has a positive, multifaceted effect (9) on fatigue due to its beneficial effect on pathophysiologic mechanisms of fatigue in CKD populations such as improved mental health, a positive effect on the cardiovascular and muscular system and reduced inflammation (9, 22, 23) which are evident across the whole spectrum of CKD (19). In addition, a systematic review by Zhao et al. (24), based on 13 randomized controlled trials, demonstrated that exercise interventions have a positive impact on fatigue as well as on both physical and mental HRQoL in CKD. Therefore, physical activity could be a promising target to alleviate fatigue in this population (9).

Sleep has an important regenerative and restorative function in an individual's health (25). Unhealthy sleep, characterized as inappropriate length or quality, results in a myriad of negative consequences such as impaired daily functioning, poor quality of life (26), reduced well-being (25), and disease progression (27). Diminished sleep quality is assumed to be a significant determinant of fatigue in CKD patients (13, 28, 29).

Evidence suggests that physical activity benefits both fatigue and HRQoL in patients with CKD, and studies in healthy populations indicate that the association between physical activity and fatigue depends on sleep quality (30, 31). Yet, despite the high prevalence of fatigue and its association with poor sleep in CKD, little research has examined how these factors jointly shape the relationship between physical activity and HRQoL, leaving an important gap in understanding their combined roles.

Based on previous studies in healthy and CKD samples, we hypothesize that physical activity is indirectly associated with better physical and mental HRQoL through lower fatigue, and that this indirect association is stronger among CKD patients reporting better sleep quality.

The current study focuses on the following research questions (RQs):

- RQ-A: Compare fatigue, sleep, physical activity, and physical and mental HRQoL between patients with CKD and the general population.
- RQ-B: Compare fatigue, sleep, physical activity, and physical and mental HRQoL between treatment modalities within the CKD population.
- RQ-C: Investigate whether fatigue mediates the relationship between physical activity and physical and mental HRQoL.
- RQ-D: Investigate whether sleep moderates the relationship between physical activity and fatigue.
- RQ-E: If RQ-C and RQ-D are confirmed, examine whether sleep moderates the indirect relationship—mediated by fatigue—between physical activity and HRQoL.

Materials and methods

Study design

The study employed a cross-sectional design. Patients were recruited through the official German national patient association for kidney disease (Bundesverband Niere e.V.), in cooperation with Fresenius Medical Care Germany. An information letter, informed consent form, and the study questionnaire were published in the association's quarterly journal *Der Nierenpatient*. Patients could detach the questionnaire from the journal, sign the informed consent form prior to completing it, and return both anonymously in a prepaid envelope to the patient association. Alternatively, after providing informed consent, participants had the option to complete the survey online via the survey tool LimeSurvey. Thus, participants could choose their preferred mode of participation and were given ten weeks to respond following publication in the journal. Inclusion criteria were age ≥ 18 years, a diagnosis of CKD, and residence in Germany. CKD status and treatment modality were self-reported.

A power analysis was conducted using GPower (32). Under a significant level of .05, a power of 95%, in total four covariates and

medium effect size, a minimum of total 357 participants was required.

Ethical approval for the study was obtained from the Psychology Research Ethics Committee of Leiden University (proposal number CEP 18-0516/257). Data will be shared upon reasonable request to the first author.

Measures

The Short Form (SF)-12 (33) was used to assess physical and mental HRQoL. Twelve statements with varying response categories were converted into physical and mental standardized values. From the standardized values, a norm-based T-score is calculated for the physical and mental component, with higher scores indicating a better HRQoL. The SF-12 demonstrated good reliability, construct validity, and responsiveness (34) and test-retest reliability was supported in clinical patients (35).

Physical activity was assessed with the International Physical Activity Questionnaire-Short Form (IPAQ-SF), a valid and reliable tool (36) providing information on the time spent on moderate and vigorous-intensive physical activity, walking and sitting.

Fatigue was measured using the 20-item Multidimensional Fatigue Inventory (MFI-20) (37), consisting of five scales: general fatigue, physical fatigue, mental fatigue, reduced activity, and reduced motivation. A total MFI score can also be computed. Items were scored on a five-point scale (1 = not true, ..., 5 = true). Reversely stated items were recoded and a higher score indicates more fatigue. The instrument has adequate reliability and validity (38). In the current study, reliability is good for all subscales ($\alpha = 0.77$ – 0.84) except for reduced motivation ($\alpha = 0.61$), which has acceptable internal consistency reliability.

Sleep quality was assessed with the 4-item sleep scale of the Kidney Disease Quality of Life - Short Form (KDQOL-SF) (39). Participants rated their sleep quality on a 0 to 10 scale (0 = bad, ..., 10 = excellent) and three statements on other sleep problems in the last four weeks using a 6-point scale (1 = never, ..., 6 = always). Scores were transformed and summed on a 0 to 100 scale. In the current study, internal consistency reliability is good ($\alpha = 0.75$). Quantity of sleep was measured by self-reported effective sleeping time in hours.

Statistical analysis

Normative data of the healthy German population on physical and mental HRQoL (40), physical activity (41), fatigue (42) and sleep quantity (43), was compared with the sample data of the study (RQ-A). For the total sample and across gender groups, the average HRQoL score was tested against the population mean using one-sample T-tests. A one-sample Wilcoxon signed-rank test was used to evaluate physical activity against the reported median of the German population. Norm scores for fatigue were reported across age and gender, and were compared within each subgroup using two-samples T-tests. No norm-reference data was available on sleep

quality. For the purpose of comparison, sleep quantity (effective sleeping time) of CKD patients was transformed into the categories “short”, “optimal” and “long” as Schlack and colleagues (43) only provided categorical reference data. This study’s sample distribution was tested against their reported percentages using a multinomial goodness-of-fit Chi-squared test. As measure of effect size, the Cohen’s *d* was used when applying T-tests (≥ 0.20 as “small”; ≥ 0.50 as “medium”; ≥ 0.8 as “large”); phi was used when a Chi-squared test was conducted (0.10 ~ small; 0.30 ~ medium; 0.50 ~ large). To control for multiple testing, *p*-values were adjusted using Bonferroni corrections.

For the multivariate analyses, a logarithmic transformation was applied to the physical activity variable in accordance with the recommendations of Tabachnick and Fidell (44). To compare fatigue, sleep, physical activity, and physical and mental HRQoL between treatment modalities, ANCOVAs were conducted. The PROCESS macro developed by Hayes (45) was used to test mediation (RQ-C), moderation, and moderated mediation (RQ-D and RQ-E). These analyses, were performed for each aspect of fatigue separately to avoid issues of collinearity among the different MFI (sub)scales. All multivariate analyses were controlled for gender, age, comorbidity, and disease duration. For each model, the assumptions of linearity, homoscedasticity, and normality of residuals were inspected using residual-versus-fitted plots and partial regression plots. Variance Inflation Factor values indicated no problems with multicollinearity (all VIFs < 2). Missing data were handled using pairwise deletion, so that all available data for each analysis could be included.

Statistical analyses were conducted using IBM SPSS Statistics version 22 with the PROCESS macro version 4.2 (45).

Results

Subjects

A total of 465 patients participated in the study. The average age was 53.78 years (*SD* = 15.00); 50.3 percent were women. Demographic and medical characteristics of the patient sample can be found in Table 1.

Norm-comparisons of CKD patients with the German population

In the CKD patient group, the mean HRQoL scores were significantly lower than the normative means for the physical (*M* = 39.32 vs. 51.40) and mental component (*M* = 45.55 vs. 49.30). The associated effect size was medium to large for the physical (*d* = -1.13), and small for the mental component (*d* = -0.33). The same pattern of differences was found within the female and male subsamples, respectively (all *ps* < .001).

Physical activity was significantly lower in the patient group than in the general population. The median score in the patient sample was 2091 (IQR = 3412), which is significantly lower than the

TABLE 1 Demographic and medical characteristics of the sample (N = 465).

Demographic characteristics		n	%	M	SD	Minimum	Maximum
Age				53.78	15.00	14	87
Gender	Male	229	49.7%				
	Female	232	50.3%				
Occupation	Student	27	5.9%				
	Employee	157	34.1%				
	Retiree	228	49.6%				
	Unemployed	10	2.2%				
	Other	38	8.3%				
Medical background information		<i>n</i>	%	<i>Median</i>	<i>IQR</i>	<i>Minimum</i>	<i>Maximum</i>
Disease duration (in years)				22.5	14	0	60
Comorbidities	None present	91	19.7%				
	Present	372	80.3%				
Treatment	Transplantation	112	26.2%				
	Hemodialysis	239	55.8%				
	Peritoneal dialysis	28	6.5%				
	Patients without RRT	49	11.4%				
	Unknown	37	8.0%				

RRT, Renal Replacement Therapy; IQR, Interquartile Range.

median of 5070 reported by Rütten et al. (41) ($p < .001$). The CKD sample mean ($M = 3249.7$, $SD = 3925.1$) was also substantially lower than the reported population mean ($M = 8534.2$, $SD = 9024.5$).

An overview of norm comparisons of the MFI subscales, stratified by gender and age, is presented in Figure 1. Higher fatigue was reported in the sample of CKD patients, except for reduced motivation and mental fatigue for the oldest group of women and mental fatigue for the oldest group of men. With respect to the age-groups, the largest differences were found in younger men and women (≤ 40 years; Cohen's $d = 1.02$ – 1.97). With respect to gender, a similar pattern was found for females and males. With respect to the MFI-subscales, overall, the largest differences were found for general fatigue ($d = 0.71$ – 1.97), followed by reduced activity ($d = 0.62$ – 1.97) and physical fatigue ($d = 0.55$ – 1.68); the differences for reduced motivation ($d = 0.24$ – 1.44) and mental fatigue ($d = 0.13$ – 1.21) were smaller.

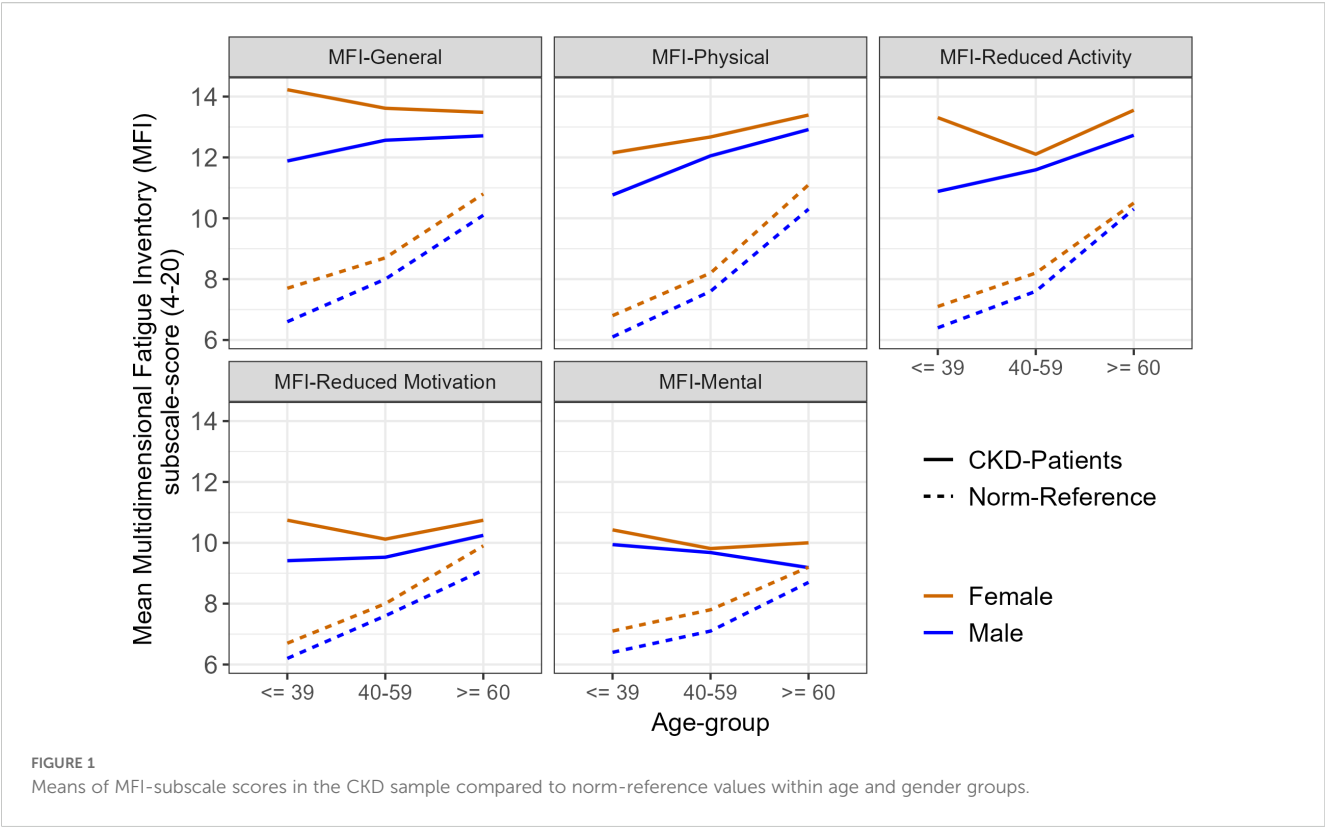
A significant difference in sleeping time was found between the CKD sample and the healthy German population, $\chi^2(2) = 32.52$, $p < .001$; $\phi = 0.27$. Short sleep (≤ 5 hours) was more common in the CKD group (21.1% vs. 12.3%), while optimal sleep was less frequent (72.2% vs. 81.6%). Long sleep (≥ 9 hours) occurred at similar rates (6.2% vs. 6.1%). This pattern was significant for both females, $\chi^2(2) = 36.36$, $p < .001$, $\phi = 0.40$, and males, $\chi^2(2) = 6.05$, $p = .049$, $\phi = 0.17$, with a larger effect for females. Female patients reported optimal sleep less often (68.4%) than male patients (76.6%) compared to the norm (80.5%).

Comparisons across modalities of treatment

Table 2 shows results of mean comparison tests across treatment modalities. Overall, transplant patients had the highest sleep quality, the lowest levels of (general) fatigue and reduced motivation, and the highest mental HRQoL, followed by hemodialysis patients. In contrast, the lowest sleep quality and mental HRQoL, and the highest (general) fatigue was found in the group of patients without RRT. Level of physical activity, physical fatigue, reduced activity, mental fatigue and the physical component of HRQoL was not significantly different across treatment modalities.

Fatigue as a mediator of the effect of physical activity on HRQoL

In Table 3 (Panel A), the results of the mediation analysis are presented. The indirect effects were all significantly positive. Patients who were physically more active, had a lower level of fatigue, which in turn was related to better physical and mental HRQoL. For physical quality of life, physical fatigue showed the strongest indirect association ($\beta = 0.195$); for the mental component of HRQoL, total fatigue showed the largest indirect association ($\beta = 0.243$). The smallest indirect effects were found for reduced motivation and mental fatigue. To illustrate the mediating effect of fatigue, results for general fatigue (MFI-G) are presented in Figure 2.



Sleep as a moderator of the effect of physical activity on fatigue

Panel B (Table 3) gives an overview of the moderating effects of sleep quality and sleep quantity. For patients reporting better sleep quality, the association between physical activity and

physical fatigue was stronger, indicating a moderating effect of sleep quality (see Figure 3, left). A similar moderating effect was observed for the MFI subscale measuring reduced activity: patients with better sleep quality and higher physical activity levels showed more favorable scores on this subscale (see Figure 3, right). By contrast, sleep quantity did not

TABLE 2 Differences between treatment modalities for physical activity, sleep, fatigue and health-related quality of life.

Variable	Procedure								Mean comparison		
	Transplantation		Hemo-dialysis		Peritoneal dialysis		Patients without RRT		ANCOVA test result		
	M	SD	M	SD	M	SD	M	SD	F-value	p	Eta ²
Physical Activity	7.56	1.18	7.49	1.22	7.66	0.93	7.20	1.34	0.40	0.75	0.004
Sleep quality	63.24	19.20	57.56	19.03	53.70	23.12	51.41	19.50	2.93*	0.03	0.023
MFI-G	12.17	4.29	13.18	3.79	13.85	3.66	14.63	3.39	4.01**	0.008	0.032
MFI-Physical	11.60	4.55	12.69	4.04	12.89	3.21	13.30	3.82	2.51	0.06	0.020
MFI-RA	11.50	4.42	12.73	3.87	12.46	3.36	12.96	3.94	2.23	0.08	0.018
MFI-RM	9.22	3.70	10.39	3.56	10.70	2.45	10.40	2.99	3.78*	0.01	0.030
MFI-M	9.23	4.12	9.70	3.93	9.86	3.92	10.37	3.57	1.38	0.25	0.011
MFI-tot	53.68	18.51	58.67	16.03	59.78	13.49	61.56	14.32	3.54*	0.02	0.030
SF-12 Physical	41.07	10.52	38.35	10.49	40.41	10.00	39.57	11.72	1.45	0.23	0.012
SF-12 Mental	48.06	11.51	45.23	11.13	46.48	11.74	43.30	10.44	2.87*	0.04	0.023

**p <.01, *p <.05; ANCOVA, Analysis of Covariance; MFI, Multidimensional Fatigue Inventory; RRT, Renal Replacement Therapy; MFI subscales: MFI-G, General; MFI-P, Physical; MFI-RA, Reduced Activity; MFI-RM, Reduced Motivation; MFI-M, Mental; MFI-tot, Total; SF-12 Physical, Physical Health-Related Quality of Life; SF-12 Mental, Mental Health-Related Quality of Life; Eta², measure of effect size. ANCOVAs were controlled for effect of age, gender, comorbidity and disease duration.

TABLE 3 Indirect effects of physical activity on HRQoL for each of the fatigue scales as mediator.

Panel A: mediation	Physical component score				Mental component score			
MFI scale	Effect ^A	SE _{Boot}	95% CI	β	Effect ^A	SE _{Boot}	95% CI	β
General	1.09*	0.19	(0.74; 1.50)	0.133	1.61*	0.27	(1.09; 2.15)	0.180
Physical	1.63*	0.25	(1.17; 2.15)	0.195	1.87*	0.28	(1.37; 2.45)	0.206
Reduced Activity	1.16*	0.23	(0.73; 1.65)	0.140	1.40*	0.28	(0.90; 2.00)	0.157
Reduced Motivation	0.45*	0.14	(0.20; 0.73)	0.054	1.22*	0.27	(0.69; 1.76)	0.135
Mental	0.30*	0.12	(0.10; 0.57)	0.036	1.07*	0.32	(0.46; 1.71)	0.119
Total	1.29*	0.22	(0.86; 1.76)	0.153	2.23*	0.33	(1.58; 2.88)	0.243
Panel B: moderation								
Moderator	Sleep Quality				Sleep Quantity			
MFI scale	F-value	p	R ² change		F-value	p	R ² change	
General	1.73	0.19	0.004		0.73	0.40	0.002	
Physical	5.38*	0.02	0.011		1.44	0.23	0.004	
Reduced Activity	4.92*	0.03	0.012		2.18	0.14	0.006	
Reduced Motivation	2.39	0.12	0.006		1.81	0.18	0.005	
Mental	0.09	0.76	<0.001		0.63	0.43	0.002	
Total	2.22	0.14	0.005		0.62	0.43	0.002	
Panel C: moderated mediation (sleep quality)								
	Physical Component Score				Mental Component Score			
MFI scale	Effect ^B	SE _{Boot}	95% CI		Effect ^B	SE _{Boot}	95% CI	
General	0.012	0.009	(-0.006; 0.030)		0.017	0.013	(-0.008; 0.043)	
Physical	0.024*	0.010	(0.007; 0.046)		0.026*	0.011	(0.007; 0.050)	
Reduced Activity	0.019*	0.009	(0.004; 0.038)		0.022*	0.010	(0.004; 0.043)	
Reduced Motivation	0.008	0.005	(-0.002; 0.019)		0.020	0.013	(-0.005; 0.048)	
Mental	-0.001	0.005	(-0.011; 0.008)		-0.005	0.015	(-0.032; 0.027)	
Total	0.014	0.009	(-0.002; 0.033)		0.023	0.014	(-0.003; 0.054)	

* $p < .05$; β , standardized indirect effect; CI, Confidence Interval; SE_{Boot}, bootstrapped standard error; MFI, Multidimensional Fatigue Inventory; HRQoL, Health-Related Quality of Life. ^A indirect effect of Physical Activity on Quality of Life through the fatigue; ^B index of moderated mediation by sleep quality. All models controlled for Comorbidity, Gender, Age and Disease Duration.

significantly moderate the association between physical activity and fatigue.

Sleep quality as a moderator of the indirect effect of physical activity on physical and mental HRQoL via fatigue

The results of the analysis are shown in Table 3 (Panel C). The indirect association between physical activity and physical and mental HRQoL via physical fatigue was moderated by sleep quality. Specifically, for patients with better sleep quality, the negative association between physical activity and physical fatigue was stronger, which in turn was related to higher HRQoL. A similar

moderated mediation was observed for the MFI subscale measuring reduced activity: patients with higher sleep quality and greater physical activity reported less reduced activity, which was associated with higher physical and mental HRQoL.

Discussion

The results of the current study indicate that CKD patients report lower mental and physical HRQoL compared to a sample from the general population, with the largest difference observed for physical HRQoL. CKD patients also report lower levels of physical activity and higher levels of fatigue. The greatest differences in fatigue were found among patients younger than 40 years. In

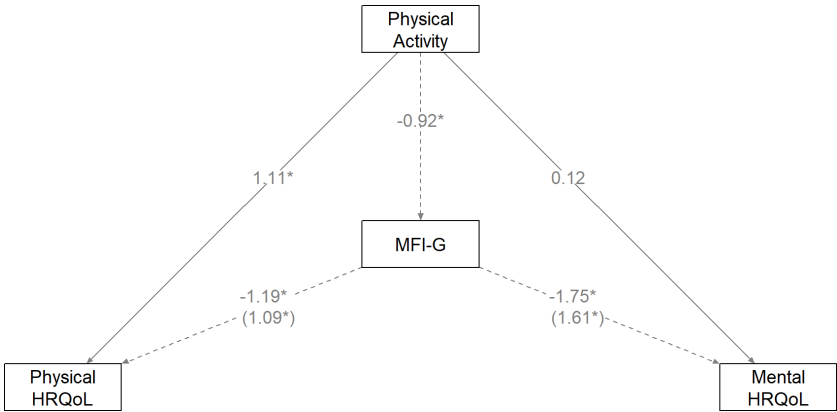


FIGURE 2
Unstandardized path coefficients of the mediating effect of fatigue (MFI-total) on the effect of physical activity on (the physical and mental component of) Health-Related Quality of Life (HRQoL). The indirect effects are shown in parenthesis (* $p < .05$).

addition, a larger proportion of participants in our sample reported short sleep duration (less than five hours per night) compared to data from the general population.

A comparison between the different treatment modalities shows that transplant patients report the best sleep quality, the least fatigue (with respect to general fatigue and reduced motivation) and the best mental HRQoL, followed by the hemodialysis patients. Patients without RRT are doing worse on each of these dimensions. No differences were found for degree of physical activity, the physical component of quality of life, and the other dimensions of fatigue.

Results further indicate that higher physical activity is linked to lower fatigue, which in turn is associated with better mental and physical HRQoL. For the mental component, the strongest indirect association was with total fatigue, whereas for the physical component it was with physical fatigue. The association between higher physical activity and lower fatigue (physical fatigue and reduced activity), which in turn is related to higher HRQoL, appeared more pronounced in patients reporting better sleep

quality, with somewhat stronger effects for mental than for physical HRQoL.

The finding that CKD patients experience more fatigue than the general population is consistent with the existing literature on the subject (2, 3). However, the present study shows that the largest differences between CKD patients and the general population occur in a younger age group, an effect that, to our knowledge, has not been described before. A possible explanation for our finding is that younger patients may experience a heavier impact of the disease on their functioning and, as a consequence, hold more negative thoughts about their condition and related symptoms, which in turn may cause them to experience more severe fatigue. The latter is consistent with the biopsychosocial model of fatigue in CKD patients, which implies that psychological factors, including cognitions, play an important role in the perpetuation of fatigue (2, 5).

The comparison of the different treatment modalities shows that transplant patients do better whereas patients without RRT do worse than the other subgroups in a number of respects. The

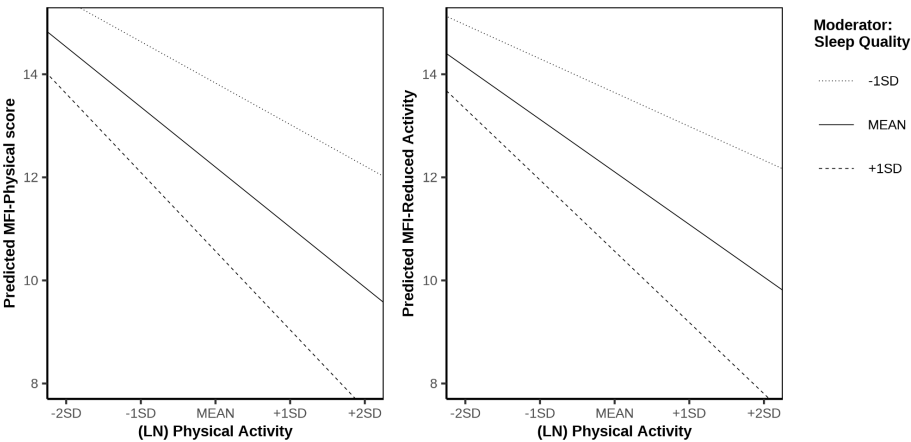


FIGURE 3
Interaction plots of physical activity $\times$ sleep quality on the MFI-physical subscale (left) and physical activity $\times$ sleep quality on the MFI-reduced activity subscale score (right).

finding regarding transplant patients is consistent with previous studies (17, 46). That patients not yet on RRT do worse may seem counterintuitive. It can however be explained by the fact that these patients already experience symptoms due to deteriorating kidney function but are not yet receiving treatment that can adequately alleviate these symptoms (47). The null findings for degree of physical activity, the physical component of quality of life, and the other dimensions of fatigue may indicate that such differences truly do not exist between treatment modalities, or they may reflect limitations of the study. In particular, some subgroups (e.g., patients on peritoneal dialysis or not yet on RRT) were relatively small, which reduces statistical power and sensitivity to detect potential differences. It is therefore possible that the study was underpowered to capture more subtle contrasts. Nevertheless, future research with larger and more balanced samples across treatment modalities will be important to clarify whether such group differences are truly absent or simply not detected in the current study.

Previous research has reported positive associations between physical activity and both fatigue (9) and quality of life in CKD patients (21). In addition, fatigue in CKD patients has been shown to be associated with lower quality of life (18). However, to our knowledge, this is the first study to examine these relationships together and to suggest that fatigue may serve as a pathway linking physical activity with quality of life, that is, the association between physical activity and HRQoL may be explained, at least in part, by fatigue.

Although earlier studies have shown that poorer sleep quality is associated with higher patient-reported fatigue (13, 28, 29), as well as lower quality of life (23) in CKD patients, the question of whether sleep quality modifies the relationship between physical activity, fatigue, and HRQoL has not previously been examined. The present study's finding that the strength of the association between physical activity and fatigue (and thereby HRQoL) appears to vary depending on sleep quality is therefore noteworthy and aligns with findings in non-clinical populations (30, 31).

Strengths and weaknesses

A major strength of the study is that physical activity, fatigue, and sleep, factors that are all known to influence HRQoL as well as disease progression and mortality in CKD patients (18, 20, 27), were examined together. Another strength is the inclusion of a heterogeneous CKD population, consisting of patients on hemodialysis, peritoneal dialysis, and kidney transplantation, as well as patients not yet receiving RRT. This contrasts with most prior studies, which have typically focused only on hemodialysis populations.

At the same time, several limitations should be acknowledged. First, while mediation and moderation analyses provide valuable insights into potential pathways, the cross-sectional design of the study does not allow conclusions regarding temporal sequence or causality. Longitudinal studies are needed to establish causal inferences. Second, recruitment took place via a patient association newsletter and an anonymous online survey, which may have introduced self-selection bias, for example, by attracting more

motivated or health-literate patients. This, in turn, may limit the generalizability of our findings. Third, physical activity was measured using the IPAQ-SF, a widely used tool, but one known to overestimate activity and subject to recall bias. Similarly, sleep was assessed with the abbreviated 4-item KDQOL sleep scale, which may not fully capture all dimensions of sleep quality. Fourth, all measures in the study - including CKD status and treatment modality - were self-reported; no objective measures such as actigraphy for activity (using an accelerometer) or polysomnography for sleep were employed. Additional medical information such as CKD stage and medication use was not available, nor were bloodwork and clinical data (e.g., hemoglobin, eGFR), as the study was conducted anonymously in collaboration with a patient organization. This limits the ability to account for important medical confounders; for instance, anemia or uremic toxins may contribute to fatigue independently of physical activity or sleep. Finally, some CKD subgroups were relatively small, which may have reduced the sensitivity to detect subtle differences across treatment modalities.

Suggestions for future research and potential clinical implications

Beyond statistical significance, the present findings also have clinical relevance. Fatigue and sleep quality emerged as important factors associated with physical activity and HRQoL in patients with CKD. Although some of the observed effect sizes were modest, they highlight domains directly relevant to patients' daily functioning and well-being. For example, even small improvements in sleep quality may strengthen the association between physical activity and reduced fatigue, which can translate into better energy levels, adherence to treatment, and overall quality of life. Building on this, the results suggest that interventions incorporating physical activity could be a promising strategy to address both fatigue and quality of life in CKD patients.

At the same time, prescribing exercise to fatigued patients with poor sleep quality may be challenging in practice. Tailored approaches that account for sleep quality, and that integrate sleep-focused strategies before or alongside physical activity, may therefore be more feasible. While previous studies have established that fatigue is related to lower QoL and that exercise is associated with reduced fatigue in CKD (24), the present study extends this work by examining mediated and moderated associations. These findings underscore the relevance of fatigue as a potential pathway and sleep quality as a potential modifier in the relationship between physical activity and HRQoL. To investigate these relationships more rigorously, it will be important to conduct longitudinal studies to further examine the observed associations and to establish temporal sequence and causality. In addition, the use of objective measures for physical activity and sleep would strengthen the validity of future findings. Subsequently, intervention studies are needed to test whether interventions targeting sleep and physical activity have the desired effect on reducing fatigue.

The results also show a substantial gap in fatigue between younger CKD patients and their peers in the general population, suggesting that younger patients may be a primary target group for

intervention development. Moreover, the impact of untreated fatigue on later treatment outcomes has not yet been adequately studied from earlier stages of CKD through to renal replacement therapy. Addressing this gap would allow for the more targeted development of interventions across the disease trajectory.

For future research, it will be important to include biological indicators of renal function in addition to the psychosocial variables examined here. This would make it possible to investigate a broader range of factors within the biopsychosocial model of fatigue in CKD patients.

Data availability statement

The datasets presented in this article are not readily available because they contain potentially identifiable participant information. Requests to access the datasets should be directed to the corresponding author.

Ethics statement

The studies involving humans were approved by the Psychology Research Ethics Committee of Leiden University (nr. of proposal CEP 18-0516/257). The studies were conducted in accordance with the local legislation and institutional requirements. Written informed consent for participation was not required from the participants or the participants' legal guardians/next of kin in accordance with the national legislation and institutional requirements.

Author contributions

VDG: Investigation, Methodology, Conceptualization, Writing – original draft. DW: Data curation, Methodology, Formal Analysis, Writing – original draft. VP: Data curation, Writing – review & editing, Formal Analysis. KC: Writing – review & editing, Investigation.

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Conflict of interest

Author KC was employed by the company Fresenius Medical Care Deutschland GmbH.

The remaining 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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