Implementation and use of patient-reported outcome measures in routine nephrology care

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Itching in dialysis patients: impact on health-related quality of life and interactions with sleep problems and psychological symptoms – results from the RENINE/PROMs registry

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Abstract

Background: Itching (pruritus) is common in dialysis patients, but little is known about its impact on health-related quality of life (HRQOL), sleep problems and psychological symptoms. This study investigates the impact of itching in dialysis patients by looking into the persistence of itching, the effect of itching on the course of HRQOL, and the combined effect of itching with sleep problems and with psychological symptoms on HRQOL.

Methods: Data were obtained from the RENINE/PROMs registry and included 2978 dialysis patients who completed patient-reported outcome measures between 2018-2020. Itching, sleep problems and psychological symptoms were assessed with the DSI, and HRQOL with the SF-12. Effects of itching on HRQOL and interactions with sleep problems and psychological symptoms were investigated cross-sectionally and longitudinally, using linear regression and linear mixed models.

Results: Half of the patients experienced itching and in 70% of them, itching was persistent. Itching was associated with a lower physical and mental HRQOL (-3.35 [95%CI: -4.12;-2.59] and -3.79 [95%CI: -4.56;-3.03]). HRQOL remained stable during two years and trajectories did not differ between patients with or without itching. Sleep problems (70% vs 52%) and psychological symptoms (36% vs 19%) were more common in patients with itching. These symptoms had an additional negative effect on HRQOL, but did not interact with itching.

Conclusions: The persistence of itching, its impact on HRQOL over time, and the additional effect on HRQOL of sleep problems and psychological symptoms, emphasize the need for recognition and effective treatment of itching to reduce symptom burden and improve HRQOL.

Introduction

Patients with end-stage kidney disease (ESKD) experience numerous physical and emotional disease-related symptoms, such as fatigue, muscle cramps, itching, sleep problems and depressive symptoms.[1, 2] The heavy symptom burden has a disruptive impact on individuals' lives and has been shown to be associated with the impaired health-related quality of life (HRQOL) in this population.[3, 4]

A common and highly distressing symptom is chronic kidney disease-associated pruritus, better known as itching. Itching is experienced by both hemodialysis (HD) and peritoneal dialysis (PD) patients with a prevalence of approximately 50%.[1, 2, 5, 6] Itching was found to be one of the ten most burdensome symptoms experienced by dialysis patients[2] and is considered a main research priority by patients with ESKD, their caregivers and healthcare professionals.[7] The pathogenesis of itching in dialysis patients is not yet fully understood, but several factors seem to influence the occurrence or burden of itching, including abnormal calcium, phosphate and parathyroid hormone levels, opioid imbalance, peripheral neuropathy, dialysis efficiency and a dry skin.[5, 6] Furthermore, itching has been associated with adverse clinical outcomes, such as hospitalization and mortality, and poor patient-reported outcomes, such as a decreased HRQOL, psychological symptoms (e.g. depressive symptoms) and sleep problems.[5, 6, 8, 9] Large cohort studies have found that HRQOL, depressive symptoms and sleep quality were worse with more severe itching in dialysis patients [8, 9]; these associations suggest a causal effect of itching on HRQOL. However, information about the impact of itching on the course of HRQOL over time is lacking. Moreover, although itching is often accompanied with sleep problems and psychological symptoms, no literature is currently available about the extent to which the combinations of these symptoms affect patients' physical and mental HRQOL.

Insight into the impact of itching on HRQOL and into the combined effect of itching with sleep problems and with psychological symptoms in the association with HRQOL, could help to better understand patients' outcomes and ultimately to reduce symptom burden and increase HRQOL. Therefore, the aim of this study is to investigate the impact of itching in patients receiving dialysis treatment by looking into the persistence of itching over time, the relationship between itching and HRQOL, and the combined effect of itching with sleep problems and psychological symptoms on HRQOL. These associations will be examined both cross-sectionally and longitudinally, using data from routine Dutch dialysis care.

Methods

Study design and population

Data were obtained from RENINE (Registratie Nierfunctievervanging Nederland: www.nefrovisie.nl/renine), the nationwide Dutch renal registry of patients receiving kidney replacement therapy. The registry collects information on demographics and clinical characteristics which are registered every 3 months. In addition, patient-reported outcome measures (PROMs) were introduced into routine dialysis care in September 2016 as part of a pilot study in 16 Dutch dialysis centres and have now been implemented nationally since November 2018.[2] The PROMs were selected in collaboration with patients and experts[10], and include the 12-item Short Form Health Survey (SF-12)[11] to assess HRQOL and the Dialysis Symptom Index (DSI)[12] to assess symptom burden. PROMs-invitations are distributed 1-2 times per year in all patients receiving dialysis treatment (i.e. total prevalent dialysis population). To ensure inclusion of all hospitals and a consistent follow-up period, data from 2018-2020 were used for this study. All dialysis patients that completed the PROMs at least once in this period were included in the analysis.

All patients included in RENINE gave consent to collect and use their data for scientific research purposes. Additionally, the current study protocol was reviewed and approved by the scientific committees of Nefrovisie and of the clinical epidemiology department at Leiden University Medical Centre (LUMC). The study is reported according to the Strengthening the Reporting of Observational studies in Epidemiology (STROBE) guidelines[13] with the extension of the REporting of studies Conducted using Observational Routinely collected health Data (RECORD) statement[14].

Itching, sleep problems and psychological symptoms

The DSI is a 30-item kidney disease specific questionnaire to assess physical and emotional symptom burden. Patients were asked to report the presence of 30 symptoms (yes/no) during the past week and, if present, the burden of each symptom on a 5-point Likert scale ranging from 1 'not at all' to 5 'very much' bothersome.[12] Two overall scores were calculated: 1) the total number of symptoms present (0-30 symptoms), and 2) the total symptom burden score (score range 0-150), which is the sum of burden on individual symptoms whereby missing items were assumed absent (i.e. burden score: 0).[2, 15]

The symptoms of interest in this study – itching, sleep problems and psychological symptoms – were assessed by means of the DSI. Itching was reported using a single item assessing whether itching was experienced in the past week and, if present, how bothersome this was. For the main analysis, patients were stratified

based on the presence of itching (yes/no) at baseline (i.e. the patient's first PROM measurement). The burden score of itching ranges from 0 to 5, with higher scores indicating a higher burden.
Sleep problems were assessed using two symptoms, namely 'trouble falling asleep' and 'trouble staying asleep'. Sleep problems were defined as at least one of these two symptoms being present. The burden score of sleep problems ranges from 0 to 10, with higher scores indicating a higher burden.
The psychological cluster includes the following five symptoms: 'worrying', 'feeling nervous', 'feeling irritable', 'feeling sad' and 'feeling anxious'. Psychological symptoms were considered present when at least three out of these five symptoms were experienced by the patient. The total burden score of psychological symptoms ranges from 0 to 25, with higher scores indicating a higher burden.

Health-related quality of life

The SF-12 is a generic health questionnaire consisting of 12 questions assessing the following 8 domains of HRQOL: physical functioning, role physical, bodily pain, general health, vitality, social functioning, role emotional and mental health. These domains contribute (in different proportions) to the scoring of a physical component summary (hereafter referred to as 'physical HRQOL') and a mental component summary (hereafter referred to as 'mental HRQOL'). HRQOL scores range from 0 to 100, with higher scores indicating a better physical and mental HRQOL.[11]

Population characteristics

Demographics and clinical characteristics were: age, sex, primary kidney disease (PKD) according to European Renal Association codes[16], socio-economic status (SES, classified as low, middle and high using standard deviation [SD] scores based on zip code), dialysis modality (haemodialysis [HD] or peritoneal dialysis [PD]), number of dialysis sessions and hours per week in HD, time since dialysis initiation, kidney transplantation in the past (yes/no), residual glomerular filtration rate (rGFR, ml/min/1.73m^2), single pool Kt/V per dialysis session in HD patients, total Kt/V per week in PD patients, haemoglobin (mmol/L), ferritin (µg/L), transferrin saturation (%), albumin-adjusted calcium (mmol/L), phosphate (mmol/L), parathyroid hormone (pmol/L).

Statistical analysis

Baseline was defined as the patient's first PROMs-measurement. Baseline characteristics of the dialysis population, stratified for the experience of itching (yes/

no) are presented as frequencies with percentages for categorical variables, as mean with SD for normally distributed continuous variables and as median with interquartile range (IQR) for skewed continuous variables. The prevalence and persistence of itching over time are shown graphically based on calendar time (prevalence of itching over time) and on patients' follow-up time stratified for itching at baseline (persistence of itching over time).

The main analyses were performed both cross-sectionally and longitudinally, so that all patients and all PROMs-measurements could be included in the analyses, and to expand on existing (mainly cross-sectional) literature.[5] The cross-sectional analysis was performed at baseline and includes all patients in the study population (n=2978 patients). The longitudinal analysis includes all PROMs-measurements (n=5042), with 1218 (40.9%) patients having multiple PROMs-measurements. Of the individuals that had only one PROMs-measurement (n=1760), 1032 (58.6%) patients started with PROMs in 2020 and 322 (18.3%) patients died, which prevented follow-up data being available. The main analyses were performed crude and adjusted for the following potential baseline confounders: age, sex, PKD, SES, dialysis modality, time since dialysis initiation and kidney transplantation in past. The symptoms, HRQOL and potential confounding variables included in the main analyses had no or less than two percent missing values.

Cross-sectionally, the association between the presence of itching and physical and mental HRQOL was investigated using linear regression analysis. Furthermore, in two separate linear regression models, a cross-product interaction term for itching (yes/no) and sleep problems (yes/no) and for itching and psychological symptoms (yes/no) was included to assess the interaction effects of these symptoms in the association with HRQOL.

The associations described above were also investigated longitudinally using linear mixed models. By using this statistical method, all measurements from all individuals could be included, as the model takes account of a varying number of follow-up measurements across individuals and even single measurements can be included in the estimation of the trajectory over time at population level.[17] The presence of itching at baseline was included in the model as fixed independent variable, time as random variable, and the continuous physical and mental HRQOL over time as dependent variable. The interaction between time and itching was included, indicating the annual change in HRQOL for individuals with itching compared to individuals without itching.

Sensitivity analyses were conducted to assess the robustness of our main results. Both the cross-sectional and the longitudinal analyses were repeated using the continuous burden score of itching, sleep problems and psychological symptoms.

The analyses were also performed with the symptoms classified based on low or high burden, e.g. no or mild itching (burden score: 0-2) versus moderate to severe itching (burden score: 3-5), and similar categories for sleep problems and psychological symptoms. Furthermore, the analyses were repeated comparing persistent itching (i.e. presence of itching reported both at baseline and at the first follow-up measurement) with no or non-persistent itching. Last, analyses were performed using 2019-2020 data, to only include measurements from the official start of the PROMs registry at November 2018.
All statistical analyses were performed using SPSS version 25.0 (IBM, Armonk, NY, USA).

Results

Population characteristics

Table 1 presents the characteristics of all patients (n=2978) that completed the PROMs at least once in 2018-2020, stratified for the presence of itching at baseline. Itching was present in approximately half of the patients and was more common in individuals receiving PD (59.4%) compared to HD (48.7%). (See also Supplement A for the population characteristics stratified by dialysis modality). Patients with itching were more often male, had a higher SES and more often diabetes as primary kidney disease, compared to patients without itching. No differences were observed in calcium, phosphate and parathyroid hormone levels. The total symptom burden was higher in patients who experienced itching, with on average 14 symptoms with a median (IQR) total burden score of 35 (23-51), compared to 8 symptoms with a median (IQR) total burden score of 19 (10-32) in patients who did not experience itching. Patients with itching had more often a dry skin compared to patients without itching (73% versus 43%, resp.). Sleep problems were experienced by 70% of the patients with itching and by 52% of the patients without itching. Psychological symptoms occurred in 36% of the patients with itching compared to 19% in patients without itching.

Table 1. Characteristics of dialysis patients, stratified by presence of itching (yes/no) at baseline

	Total dialysis population (n=2978)	Patients with itching (n=1493, 50.1%)	Patients without itching (n=1485, 49.9%)
Age (years)	67.3 (14.1)	67.4 (14.0)	67.3 (14.2)
Sex (male)	1827 (61.4)	927 (62.1)	900 (60.7)
SES			
Low	1430 (48.4)	711 (48.0)	719 (48.8)
Middle	907 (30.7)	435 (29.4)	472 (32.1)
High	617 (20.9)	336 (22.7)	281 (19.1)
Primary kidney disease			
Glomerulonephritis/sclerosis	333 (11.2)	160 (10.7)	173 (11.7)
Pyelonephritis	140 (4.7)	68 (4.6)	72 (4.9)
Polycystic kidney disease	171 (5.7)	86 (5.8)	85 (5.7)
Hypertension/renal vascular disease	809 (27.2)	411 (27.5)	398 (26.8)
Diabetes mellitus type 1/2	601 (20.2)	320 (21.4)	281 (18.9)
Miscellaneous	535 (18.0)	257 (17.2)	278 (18.7)
Unknown	387 (13.0)	191 (12.8)	196 (13.2)
Dialysis modality			
HD	2583 (87.9)	1258 (85.6)	1325 (90.1)
PD	357 (12.1)	212 (14.4)	145 (9.9)
Dialysis sessions per week (HD)			
< 3	266 (12.8)	125 (12.3)	141 (13.2)
3	1672 (80.3)	817 (80.6)	855 (80.1)
> 3	144 (6.9)	72 (7.1)	72 (6.7)
Dialysis hours per week (HD)	11.2 (4.3)	11.1 (3.8)	11.4 (4.8)
Time since dialysis initiation (months)	15 (3-43)	14 (3-41)	17 (3-46)
Kidney transplantation in past (yes)	327 (11.2)	162 (11.1)	165 (11.3)
rGFR (mL/min/1.73m^2)	4.7 (2.0-7.6)	5.0 (2.0-8.0)	4.5 (2.1-7.1)
Single pool Kt/V in HD	1.47 (0.53)	1.46 (0.54)	1.48 (0.52)
Total Kt/V in PD	2.63 (1.06)	2.70 (1.10)	2.52 (0.99)
Haemoglobin (mmol/L)	6.8 (0.9)	6.8 (0.9)	6.8 (0.9)

Ferritin (µg/L)	318 (168-534)	300 (153-517)	330 (187-547)
Transferrin saturation (%)	22.3 (10.5)	21.8 (10.4)	22.8 (10.6)
Calcium (mmol/L)[#]	2.31 (0.19)	2.31 (0.19)	2.31 (0.18)
Phosphate (mmol/L)	1.59 (0.48)	1.62 (0.49)	1.57 (0.47)
Parathyroid hormone (pmol/L)	30 (17-51)	30 (17-52)	30 (17-50)
Symptom burden			
Total number of symptoms (0-30)	11.0 (6.4)	13.7 (6.2)	8.3 (5.3)
Total symptom burden score (0-150)	27 (14-42)	35 (23-51)	19 (10-32)
Dry skin (yes)	1726 (58.0)	1091 (73.1)	635 (42.8)
Sleep problems			
Sleep problems (yes)[^]	1816 (61.0)	1044 (69.9)	772 (52.0)
Trouble falling asleep (yes)	1312 (44.1)	798 (53.4)	514 (34.6)
Trouble staying asleep (yes)	1549 (52.0)	907 (60.8)	642 (43.2)
Psychological symptoms			
Psychological symptoms (yes)[$]	820 (27.5)	534 (35.8)	286 (19.3)
Worrying (yes)	1195 (40.1)	708 (47.4)	487 (32.8)
Feeling nervous (yes)	816 (27.4)	517 (34.6)	299 (20.1)
Feeling irritable (yes)	843 (28.3)	558 (37.4)	285 (19.2)
Feeling sad (yes)	1088 (36.5)	669 (44.8)	419 (28.2)
Feeling anxious (yes)	647 (21.7)	425 (28.5)	222 (14.9)

Values are shown in n (%), mean (SD) or median (IQR).
Missing values for age: n=3 (0.10%), sex: n=2 (0.07%), SES: n=24 (0.81%), primary kidney disease: n=2 (0.07%), dialysis modality: n=38 (1.29%), dialysis sessions per week (HD): n=501 (19.4%), dialysis hours per week (HD): n=505 (19.6%), time since dialysis initiation: n=58 (1.99%), kidney transplantation in past: n=58 (1.99%), residual GFR: n=1977 (66.4%), single pool Kt/V in HD: n=647 (25.0%), Total Kt/V in PD: n=221 (61.9%), haemoglobin: n=286 (9.60%), ferritin: n=416 (14.0%), transferrin saturation: n=993 (33.3%) calcium: n=369 (12.4%), phosphate: n=280 (9.40%), parathyroid hormone: n=522 (17.5%).
[#] Albumin-adjusted calcium.
[^] Sleep problems are considered present if at least one of the two symptoms are experienced by the patient.
[$] Psychological symptoms are considered present if three out of the five symptoms are experienced by the patient.
Abbreviations: SES, social economic status; HD, haemodialysis; PD, peritoneal dialysis; rGFR, residual glomerular filtration rate.

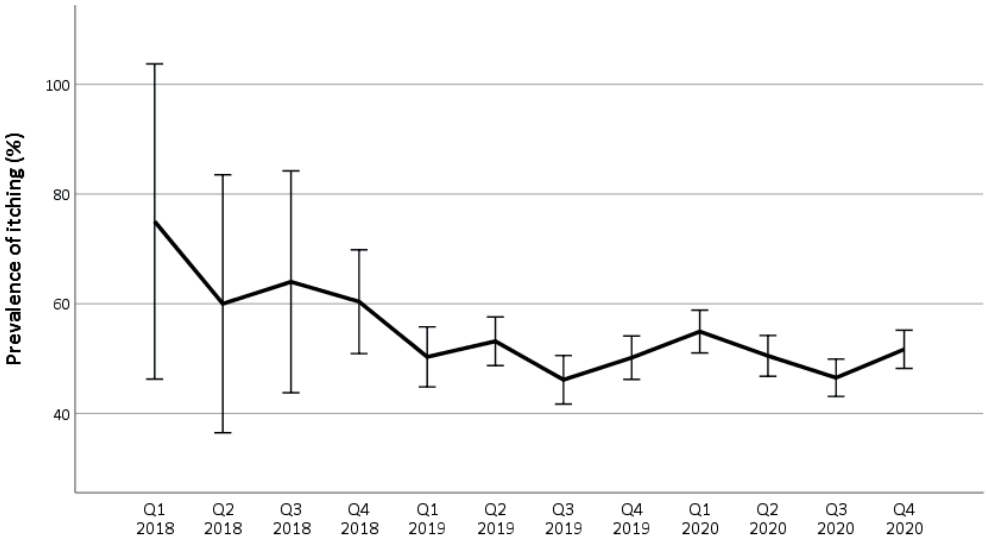

Figure 1a. Prevalence of itching (yes/no) over study period (calendar time).
Percentage of dialysis patients who experience itching (solid line) with 95% confidence intervals (bars) at each quartile in 2018-2020. Note that Q1-Q3 2018 includes a small number of patients (n=12, n=20, n=25, resp.), as the PROMs registry officially started from November 2018. Some patients already participated in Q1-Q3 2018 for scientific research purposes.

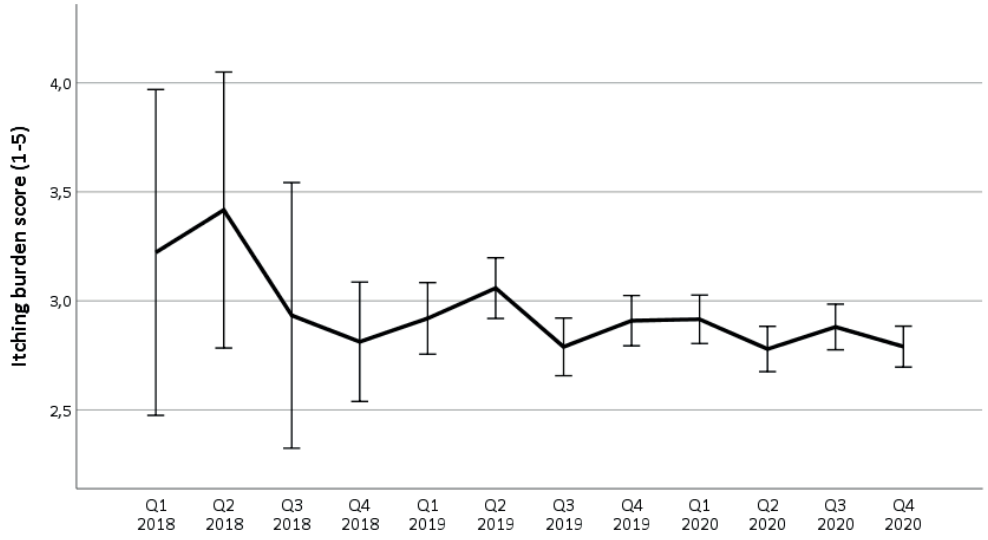

Figure 1b. Burden of itching (scale: 1-5) over study period (calendar time) in patients who experienced itching.
Average itching burden score (solid line) with 95% confidence intervals (bars) in dialysis patients who experienced itching at each quartile in 2018-2020. Note that Q1-Q3 2018 includes a small number of patients (n=12, n=20, n=25, resp.), as the PROMs registry officially started from November 2018. Some patients already participated in Q1-Q3 2018 for scientific research purposes.

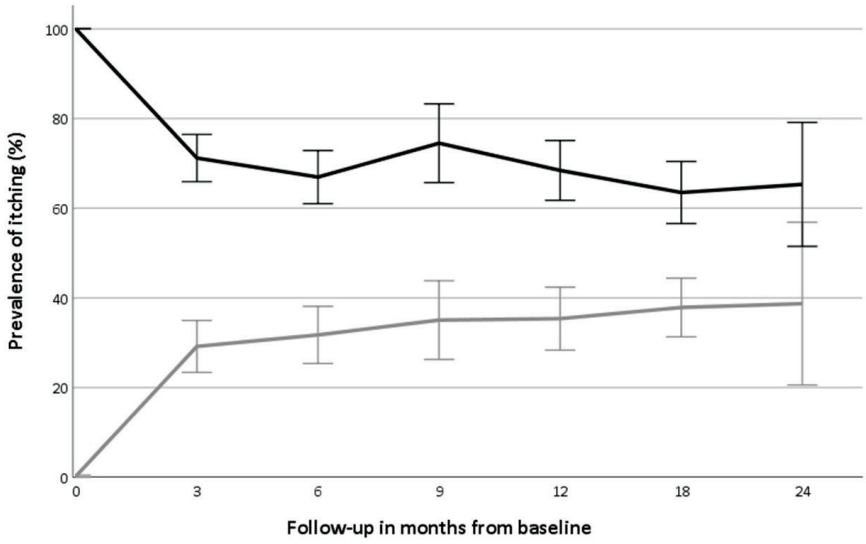

Figure 2. Persistence of itching during follow-up in patients with itching (black) and patients without itching (grey) at baseline.

Black solid line (black bars) shows the percentage (95% Confidence Interval [CI]) of dialysis patients in which itching is persistent during follow-up since baseline. Grey solid line (grey bars) shows the percentage (95% CI) of dialysis patients in which itching was newly developed during follow-up since baseline. Note that the average time between follow-up measurements was 6.7 months, meaning that the number of patients that contribute data fluctuates across the time-points in the graph.

Prevalence and persistence of itching over time

In total, 1218 patients have multiple PROMs-measurements (median: 2, IQR: 2-3 measurements), with on average 6.7 months (SD: 5.0) between baseline and the second PROMs-measurement. Throughout the whole study period, the prevalence of itching is around 50% with a moderate burden (mean burden scores between 2.8 and 3.4 on 1-5 scale) (Figure 1a/b). No clear differences in prevalence or burden of itching could be detected between the yearly quartiles (i.e. no seasonal effects). Figure 2 shows that itching persisted over time in approximately 70% of the patients that experienced itching at baseline. Of the patients without itching at baseline, 30-40% developed itching during follow-up. Sleep problems and psychological symptoms also persisted over time in the majority of the patients (see Supplement B).

Table 2. Cross-sectional effects of the presence of itching (yes/no), combined with sleep problems and psychological symptoms, on physical and mental HRQOL

	Physical HRQOL		Mental HRQOL	
	Coef. (95%CI)	p-value	Coef. (95%CI)	p-value
Itching				
Model 1, unadjusted	-3.36 (-4.13; -2.59)	<0.001	-3.82 (-4.58; -3.06)	<0.001
Model 2, adjusted^	-3.35 (-4.12; -2.59)	<0.001	-3.79 (-4.56; -3.03)	<0.001
Itching and sleep problems (Model 3$)				
Itching	-3.38 (-4.62; -2.13)	<0.001	-2.38 (-3.61; -1.15)	<0.001
Sleep problems	-3.85 (-4.92; -2.78)	<0.001	-3.37 (-4.42; -2.31)	<0.001
Itching * sleep problems	1.00 (-0.58; 2.58)	0.214#	-1.18 (-2.74; 0.38)	0.139#
Itching and psychological symptoms (Model 4$)				
Itching	-2.81 (-3.70; -1.92)	<0.001	-2.35 (-3.15; -1.56)	<0.001
Psychological symptoms	-3.51 (-4.87; -2.15)	<0.001	-11.34 (-12.56; -10.13)	<0.001
Itching * psychological symptoms	0.03 (-1.72; 1.79)	0.971#	1.01 (-0.56; 2.58)	0.208#

^ *Adjusted for age, sex, primary kidney disease, socio-economic status, dialysis modality, time since dialysis initiation and kidney transplantation in past.*
$ *Model 3 and 4 build on model 2 and include the interaction with sleep problems and psychological symptoms, respectively.*
# *P-value for interaction.*

Association between itching and HRQOL at baseline

Mean (SD) physical and mental HRQOL scores in the total dialysis population were 35.8 (10.4) and 48.1 (10.4), respectively. Table 2 shows the cross-sectional effects of itching, combined with sleep problems and psychological symptoms, on physical and mental HRQOL. Patients with itching experienced a lower physical (-3.35 [95% Confidence Interval (CI): -4.12 to -2.59; p<0.001]) and mental HRQOL (-3.79 [95% CI: -4.56 to -3.03; p<0.001]), compared to patients without itching. Sleep problems and psychological symptoms had an additional negative effect on HRQOL. No interaction was observed between itching and sleep problems or psychological symptoms in the association with HRQOL. Table 3a shows the average physical and mental HRQOL in patients with itching, sleep problems, or a combination of both. Table 3b shows the average physical and mental HRQOL in patients with itching, psychological symptoms, or a combination of both.

Table 3a. Physical and mental HRQOL in patients with itching, sleep problems, or a combination of both.

		Physical HRQOL^		Mental HRQOL^	
Itching	**Sleep problems**	Mean	SD	Mean	SD
no	no	39.44	2.23	51.89	1.79
yes	no	36.01	2.03	49.68	1.69
no	yes	35.58	2.21	48.47	1.83
yes	yes	33.25	2.22	44.89	1.81

^ Adjusted for age, sex, primary kidney disease, socio-economic status, dialysis modality, time since dialysis initiation and kidney transplantation in past.

Table 3b. Physical and mental HRQOL in patients with itching, psychological symptoms, or a combination of both.

		Physical HRQOL^		Mental HRQOL^	
Itching	**Psychological symptoms**	Mean	SD	Mean	SD
no	no	38.12	2.15	52.34	1.46
yes	no	35.33	2.03	50.02	1.40
no	yes	34.51	2.17	40.80	1.54
yes	yes	31.75	2.19	39.46	1.47

^ Adjusted for age, sex, primary kidney disease, socio-economic status, dialysis modality, time since dialysis initiation and kidney transplantation in past.

Association between itching and HRQOL over time

Figures 3a and 3b show the trajectories of physical and mental HRQOL during follow-up, stratified by itching at baseline. Findings from the longitudinal analyses using linear mixed models were similar to the cross-sectional analyses, showing that patients with itching experienced a lower physical and mental HRQOL compared to patients without itching (-3.12 [95% CI: -3.86 to -2.38; p<0.001] and -3.62 [95% CI: -4.35 to -2.88; p<0.001], resp.). No changes in physical and mental HRQOL over time were observed in the total population throughout follow-up (annual change: 0.01 [95% CI: -0.68 to 0.70; p=0.97] and -0.04 [95% CI: -0.75 to 0.67; p=0.91], resp.). No differences in physical and mental HRQOL trajectories were observed between patients with and without itching (extra annual change in patients with itching: 0.10 [95% CI: -0.83 to 1.03; p=0.83] and -0.07 [95% CI: -1.04 to 0.90; p=0.88], resp.). Also longitudinally, in the association with physical and mental HRQOL, there was no significant interaction between itching and sleep problems (p=0.52 and p=0.22, resp.) or itching and psychological symptoms (p=0.66 and p=0.29, resp.).

A post hoc subgroup analysis showed an increase in physical and mental HRQOL when itching disappeared (+0.56; p=0.49 and +1.78; p=0.02, resp.) and a decrease when itching newly occurred (-0.44; p=0.61 and -0.68; p=0.38, resp.) between the patients' first and second PROMs-measurement (see Supplement C).

Sensitivity analyses

All sensitivity analyses yielded results comparable to the main analyses, both cross-sectionally and longitudinally (see Supplement D). Analyses using the continuous burden scores for symptoms showed that physical and mental HRQOL were -1.26 (95% CI: -1.50 to -1.02; p<0.001) and -1.42 (95% CI: -1.65 to -1.18; p<0.001) points lower, respectively, for each point increase in burden of itching. Using the continuous burden scores, the interaction between itching and psychological symptoms in the association with physical and mental HRQOL became statistically significant, though with a similarly small effect. Moderate to severe itching (prevalence: 26.1%) compared to no or mild itching showed a larger decrease in physical and mental HRQOL (-4.20 [95% CI: -5.07 to -3.33; p<0.001] and -4.90 [95% CI: -5.76 to -4.03; p<0.001], resp.). Comparing persistent itching to no or non-persistent itching showed comparable results. Restriction to 2019-2020 data yielded similar results.

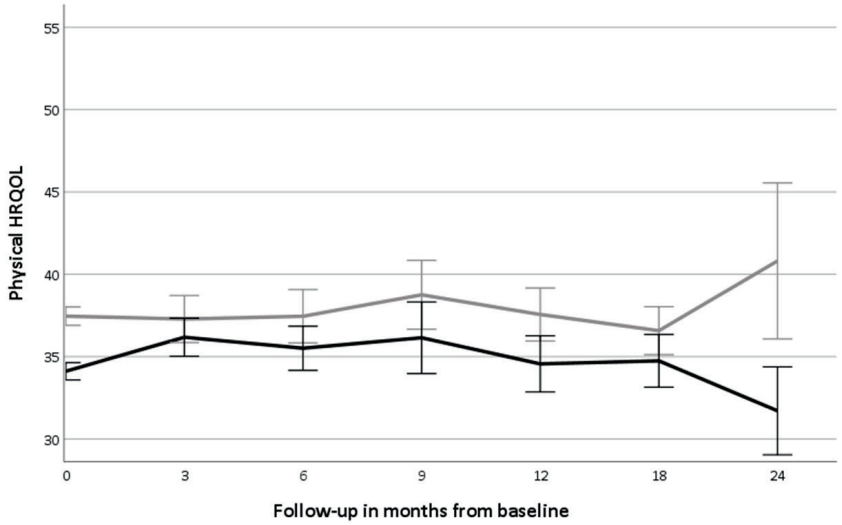

Figure 3a. Trajectory of physical HRQOL during follow-up in patients with itching (black) and patients without itching (grey) at baseline.

Black solid line (black bars) shows the mean physical HRQOL (95% Confidence Interval [CI]) over time in dialysis patients with itching at baseline. Grey solid line (grey bars) shows the mean physical HRQOL (95% CI) over time in dialysis patients without itching at baseline. Note that the average time between follow-up measurements was 6.7 months, meaning that the number of patients that contribute data fluctuates across the timepoints in the graph.

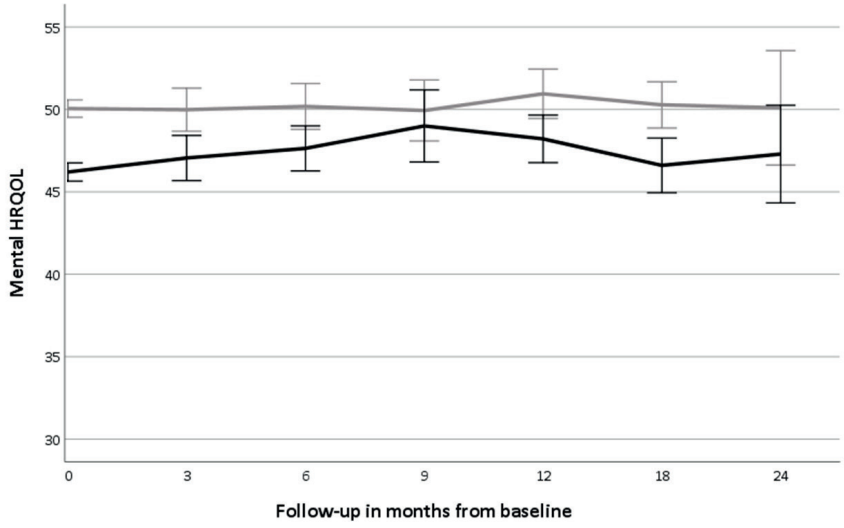

Figure 3b. Trajectory of mental HRQOL during follow-up in patients with itching (black) and patients without itching (grey) at baseline.

Black solid line (black bars) shows the mean mental HRQOL (95% Confidence Interval [CI]) over time in dialysis patients with itching at baseline. Grey solid line (grey bars) shows the mean mental HRQOL (95% CI) over time in dialysis patients without itching at baseline. Note that the average time between follow-up measurements was 6.7 months, meaning that the number of patients that contribute data fluctuates across the timepoints in the graph.

Discussion

This nationwide Dutch study investigated the impact of itching (pruritus) on HRQOL and interactions with sleep problems and psychological symptoms in patients receiving dialysis treatment. Half of the dialysis patients experienced itching and in 70% of them, itching was persistent over time. Individuals with itching experienced a lower physical and mental HRQOL. This is the first study showing that HRQOL remained stable during the two years of follow-up and HRQOL trajectories did not differ between patients with or without itching. Furthermore, we found that sleep problems and psychological symptoms were more common in individuals who also experienced itching. These symptoms had an additional negative effect on physical and mental HRQOL, but did not interact with itching (i.e. the combination of both symptoms did not result in a significantly lower or higher HRQOL than the sum of individual effects).

The high prevalence of itching and its persistence over time demonstrate that itching is a major problem in patients receiving dialysis treatment. Although the estimated prevalence varies between 20-90% across studies[5], for instance due to differences in populations and in definitions of itching, it is clear that itching affects many dialysis patients' lives, especially given that itching appeared to be persistent in many patients. In line with our results, two other studies found that itching was persistent for >1 year in 50-69% of the dialysis patients.[18, 19] The reason why itching was persistent in some patients and not in others, remained unclear. According to one of the studies, differences could not be explained by whether or not the patients received treatment for their itching, as itching was often underestimated and left untreated.[18] Therefore, more research is needed to identify patients with persistent itching in order to treat them in a timely manner.

The impact of itching on patients' lives is clearly reflected in the decreased HRQOL scores. In line with existing literature, physical and mental HRQOL were around three to four points lower in patients who experienced itching compared to those without itching, and HRQOL scores decreased further with more severe itching.[8, 9, 20-22] Information regarding the relevance of this difference according to dialysis patients is lacking[23], but comparable differences in HRQOL have been considered important in other populations.[24-26] In addition to the existing literature, this study also investigated the impact of itching on the course of HRQOL and showed that the difference in HRQOL between individuals with and without itching persisted over time. A possible explanation for this result is that itching also persisted over time in the majority of the patients. However, in contrast to what might be expected based on previous research about the effect of itching on clinical outcomes over time (e.g. mortality and hospitalizations)[5, 8, 27, 28], this study showed no faster

deterioration of HRQOL in patients with (persistent) itching during two years of follow-up. Future research should investigate these relationships using a longer follow-up period.

Findings from our study confirm that sleep problems and psychological symptoms often co-occur with itching.[6, 8, 29-31] Results from previous studies suggest that sleep problems and psychological symptoms may partly explain the effect of itching on HRQOL.[5, 20, 30] Our study does not contradict this suggestion, but it does show that sleep problems and psychological symptoms also independently affect HRQOL, in addition to the effect that itching has on HRQOL. Since these symptoms often co-occur in dialysis patients, many individuals have to deal with a substantially decreased HRQOL.

Our findings emphasize the importance of an effective treatment for itching in dialysis patients. Although unadjusted for potential confounding, findings from two observational studies suggest that HRQOL improves when itching disappears.[18, 19] A post hoc analysis in our data also showed an improved physical HRQOL ($p<0.05$) and mental HRQOL (p=ns) when itching disappeared. Additionally, several treatment trials showed that a reduced itching intensity may already result in improved HRQOL scores and sleep quality.[5] Furthermore, literature suggests that a better management of itching and HRQOL might even result in improved clinical outcomes, such as mortality and hospitalizations.[5, 8, 27, 28] The need for and the potential benefits of a treatment for itching are thus evident. However, effective treatment of itching in dialysis patients appeared challenging: some treatment options are available (e.g. prevention of hyperphosphatemia, adequate dialysis dose, ultraviolet-B light therapy, gabapentin and several emollient creams), but seem to have limited efficacy or side effects.[5, 6, 32]

With this study, we aim to provide insight in and awareness of the high prevalence and impact of itching, as this may still be underestimated.[33, 34] We believe that our research can contribute to existing knowledge in particular due to the longitudinal design using national data from routine dialysis care. As PROMs are part of and used for routine care, patients are more likely to participate (compared to research purposes only), which enhances the generalizability of our results. On the downside, due to this design the study mainly includes prevalent dialysis patients, which means that patients have been followed from different points in their trajectory (e.g. differences in time since start of dialysis). However, we do not believe this has affected the relationship between itching and HRQOL. Another limitation of this study is that no information was available on treatments that may have induced or reduced itching. It is therefore unclear how treatment may have affected the results (e.g. is the prevalence and persistence of itching this high despite treat-

ment of itching?) or to what extent available treatment options may decrease the burden of itching in dialysis patients. Furthermore, additional knowledge about factors that may influence itching is needed, and may be informative for treatment choices, for example to tailor the dialysis schedule or nutritional advice. Taken together, current findings show that itching is a major problem in dialysis patients and call for further research to effectively identify and treat (persistent) itching to reduce symptom burden and improve HRQOL.

Of course, to reduce the burden of itching in dialysis patients, attention must be paid to itching on the individual patient level. Literature suggests however that itching remains underreported and therefore undertreated due to a lack of knowledge and assessment during consultations.[34] We believe that the use of PROMs in routine dialysis care improves the reporting, and prompts discussion of patients' experiences and treatment options.[2] Current findings can be used to better inform patients and may enhance shared decision making.

In conclusion, the high prevalence and persistence of itching, its impact on HRQOL over time, and the additional effect on HRQOL of the often co-occurring sleep problems and psychological symptoms, emphasize the need for recognition and effective treatment of itching to reduce symptom burden and improve HRQOL in dialysis patients. No individual prognoses can be derived from our study, but the findings may be used in shared decision making. We hope that this study provided insight into and awareness of the major impact that itching can have, to enable early recognition and treatment of itching.

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Supplemental Material for Chapter 6

A. Population characteristics in patients receiving haemodialysis and peritoneal dialysis

Table S1 presents the characteristics of all haemodialysis and peritoneal dialysis patients that completed the PROMs at least once in 2018-2020, stratified for the presence of itching at baseline.

Table S1. Characteristics of haemodialysis and peritoneal dialysis patients, stratified by presence of itching (yes/no) at baseline

	Haemodialysis patients		Peritoneal dialysis patients	
	with itching (n=1258, 48.7%)	**without itching** (n=1325, 51.3%)	**with itching** (n=212, 59.4%)	**without itching** (n=145, 40.6%)
Age (years)	67.8 (14.2)	67.5 (14.1)	65.6 (12.8)	65.3 (15.4)
Sex (male)	775 (61.6)	804 (60.7)	135 (63.7)	85 (58.6)
SES				
Low	632 (50.5)	660 (50.2)	72 (34.6)	57 (39.3)
Middle	353 (28.2)	410 (31.2)	75 (36.1)	58 (40.0)
High	266 (21.3)	245 (18.6)	61 (29.3)	30 (20.7)
Primary kidney disease				
Glomerulonephritis/sclerosis	128 (10.2)	154 (11.6)	28 (13.2)	18 (12.4)
Pyelonephritis	60 (4.8)	63 (4.8)	6 (2.8)	9 (6.2)
Polycystic kidney disease	72 (5.7)	73 (5.5)	13 (6.1)	11 (7.6)
Hypertension/ renal vascular disease	336 (26.7)	351 (26.5)	70 (33.0)	46 (31.8)
Diabetes mellitus type 1/2	278 (22.1)	256 (19.4)	37 (17.4)	23 (15.9)
Miscellaneous	223 (17.7)	258 (19.5)	30 (14.2)	18 (12.4)
Unknown	161 (12.8)	170 (12.8)	28 (13.2)	20 (13.8)
Time since dialysis initiation (months)	17 (3-44)	19 (3-49)	4 (1-17)	3 (1-14)

Kidney transplantation in past (yes)	148 (11.8)	157 (11.9)	14 (6.7)	8 (5.6)
rGFR (mL/min/1.73m²)	5.0 (2.0-8.0)	4.6 (2.1-7.1)	5.2 (2.0-7.1)	4.0 (3.0-5.5)
Kt/V@	1.46 (0.54)	1.48 (0.52)	2.70 (1.10)	2.52 (0.99)
Haemoglobin (mmol/L)	6.8 (0.9)	6.8 (0.9)	6.9 (0.9)	6.9 (0.9)
Ferritin (µg/L)	316 (167-532)	340 (194-550)	178 (86-383)	226 (113-483)
Transferrin saturation (%)	21.8 (10.4)	22.6 (10.6)	22.0 (10.1)	25.3 (10.5)
Calcium (mmol/L)#	2.30 (0.19)	2.30 (0.18)	2.32 (0.18)	2.32 (0.20)
Phosphate (mmol/L)	1.63 (0.51)	1.57 (0.47)	1.55 (0.36)	1.53 (0.43)
Parathyroid hormone (pmol/L)	31 (18-54)	30 (17-51)	25 (15-40)	27 (18-40)
Symptom burden				
Total number of symptoms (0-30)	13.7 (6.2)	8.2 (5.4)	13.3 (6.1)	8.3 (4.5)
Total symptom burden score (0-150)	35 (23-52)	19 (9-32)	33 (23-46)	19 (11-31)
Dry skin (yes)	907 (72.2)	574 (44.2)	167 (78.8)	56 (40.3)
Sleep problems				
Sleep problems (yes)^	875 (69.6)	694 (52.4)	152 (71.7)	71 (49.0)
Trouble falling asleep (yes)	674 (53.6)	468 (35.3)	110 (51.9)	42 (29.0)
Trouble staying asleep (yes)	758 (60.3)	579 (43.7)	135 (63.7)	56 (38.6)
Psychological symptoms				
Psychological symptoms (yes)$	464 (36.9)	262 (19.8)	61 (28.8)	22 (15.2)
Worrying (yes)	611 (48.6)	439 (33.1)	85 (40.1)	44 (30.3)
Feeling nervous (yes)	454 (36.1)	270 (20.4)	55 (25.9)	26 (17.9)

Feeling irritable (yes)	473 (37.6)	254 (19.2)	75 (35.4)	28 (19.3)
Feeling sad (yes)	571 (45.4)	387 (29.2)	86 (40.6)	29 (20.2)
Feeling anxious (yes)	374 (29.7)	204 (15.4)	44 (20.8)	15 (10.3)

Values are shown in n (%), mean (SD) or median (IQR).
[@] Single pool Kt/V in haemodialysis and total Kt/V in peritoneal dialysis.
[#] Albumin-adjusted calcium.
[^] Sleep problems are considered present if at least one of the two symptoms are experienced by the patient.
[$] Psychological symptoms are considered present if three out of the five symptoms are experienced by the patient.
Abbreviations: SES, social economic status; rGFR, residual glomerular filtration rate.

B. Persistence of sleep problems and psychological symptoms

PERSISTENCE OF SLEEP PROBLEMS

The persistence of sleep problems is shown graphically based on patients' follow-up time, stratified for sleep problems at baseline (Figure S1a) and for itching at baseline (Figure S1b).

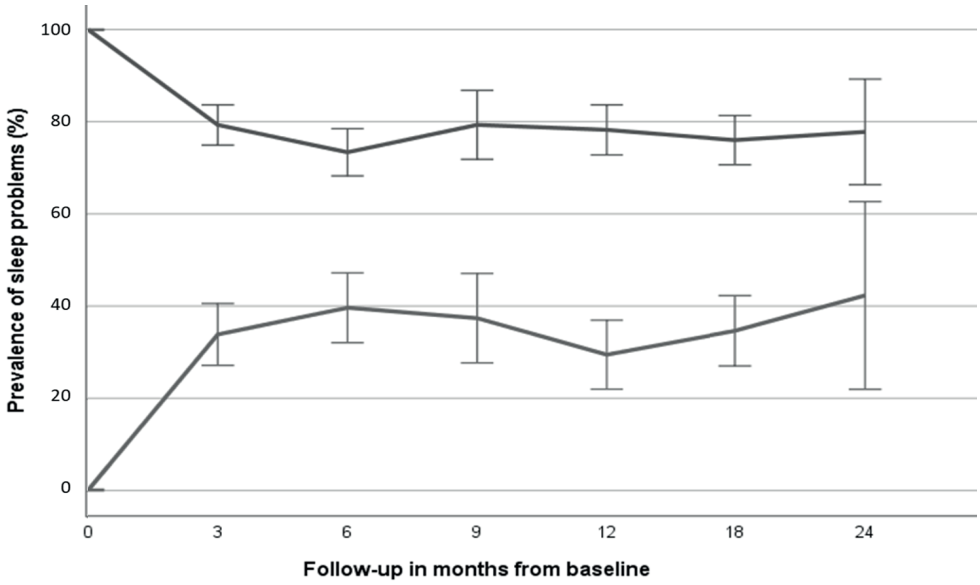

Figure S1a. Persistence of sleep problems during follow-up in patients with sleep problems (upper line) and patients without sleep problems (lower line) at baseline.
Upper solid line (upper bars) shows the percentage (95% Confidence Interval [CI]) of dialysis patients in which sleep problems are persistent during follow-up since baseline. Lower solid line (lower bars) shows the percentage (95% CI) of dialysis patients in which sleep problems were newly developed during follow-up since baseline.

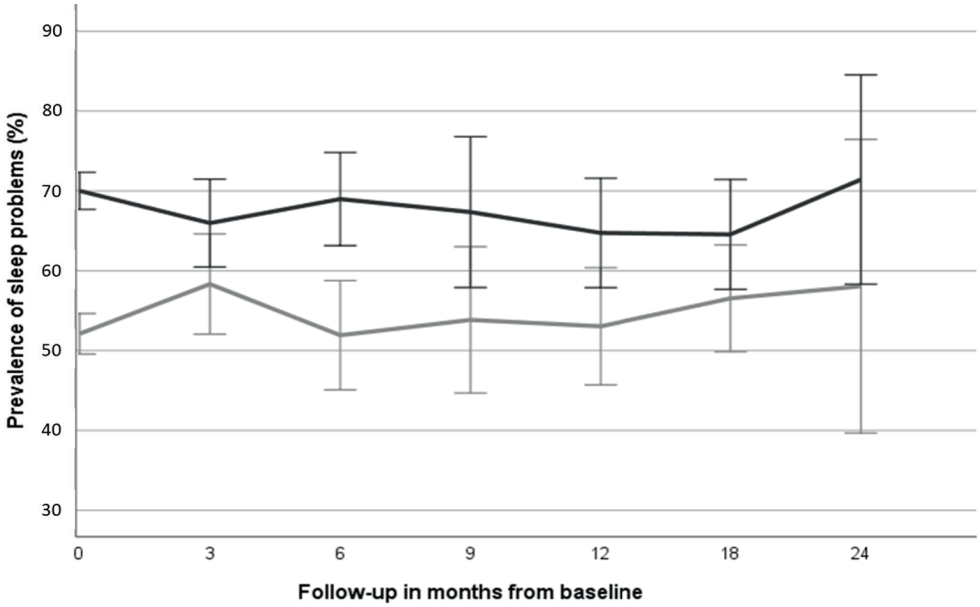

Figure S1b. Persistence of sleep problems during follow-up in patients with itching (upper line) and patients without itching (lower line) at baseline.

Solid lines (bars) show the percentages (95% Confidence Intervals [CI]) in which sleep problems are present during follow-up, stratified for patients with itching (upper line) and without itching (lower line) at baseline. Note that itching is persistent in approximately 70% of the dialysis patients.

PERSISTENCE OF PSYCHOLOGICAL SYMPTOMS

The persistence of psychological symptoms is shown graphically based on patients' follow-up time, stratified for psychological symptoms at baseline (Figure S2a) and itching at baseline (Figure S2b).

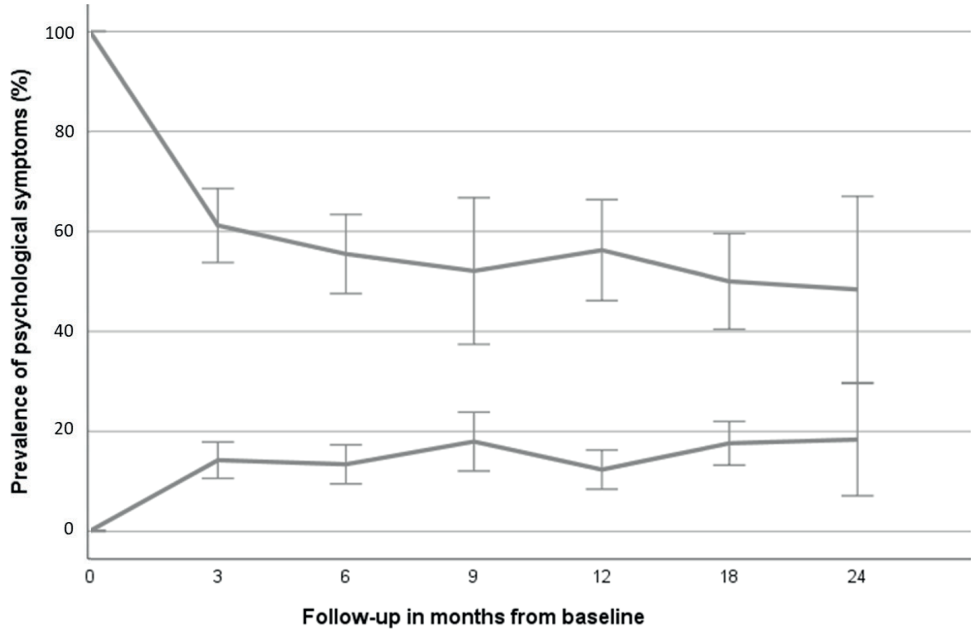

Figure S2a. Persistence of psychological symptoms during follow-up in patients with psychological symptoms (upper line) and patients without psychological symptoms (lower line) at baseline.

Upper solid line (upper bars) shows the percentage (95% Confidence Interval [CI]) of dialysis patients in which psychological symptoms are persistent during follow-up since baseline. Lower solid line (lower bars) shows the percentage (95% CI) of dialysis patients in which psychological symptoms were newly developed during follow-up since baseline.

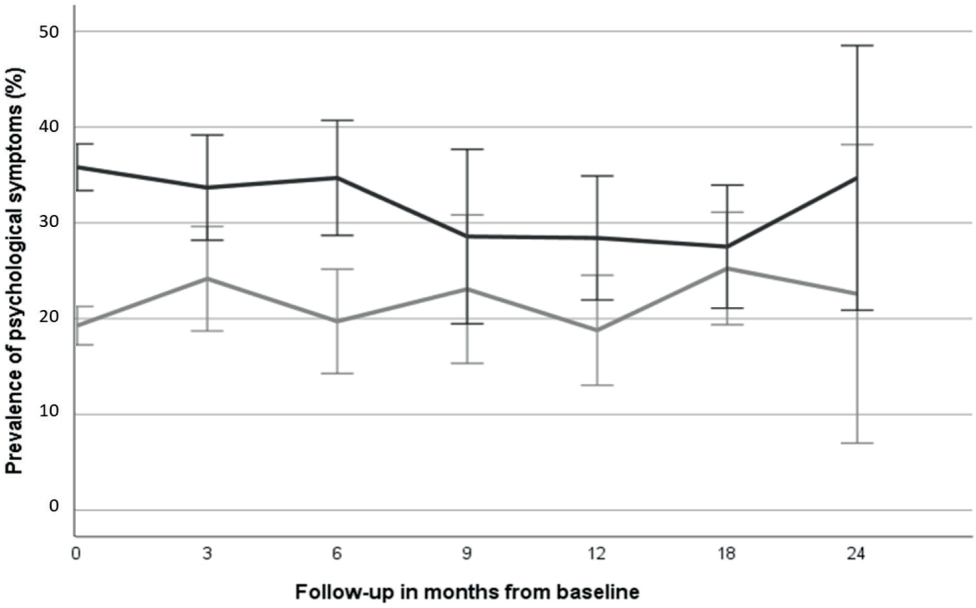

Figure S2b. Persistence of psychological symptoms during follow-up in patients with itching (upper line) and patients without itching (lower line) at baseline.
Solid lines (bars) show the percentages (95% Confidence Intervals [CI]) in which psychological symptoms are present during follow-up, stratified for patients with itching (upper line) and without itching (lower line) at baseline. Note that itching is persistent in approximately 70% of the dialysis patients.

C. Change in itching and HRQOL

A post hoc analysis was performed on the change in HRQOL in dialysis patients where itching disappeared (n=185; 15.2%) and where itching newly occurred (n=181; 14.9%) between their first and second PROMs measurement (see Table S2).

Table S2. Change in physical and mental HRQOL in dialysis patients where itching disappeared or newly occurred

	Δ Physical HRQOL	p-value*	Δ Mental HRQOL	p-value*
Itching disappeared	+ 0.56	0.489	+ 1.78	0.023
Itching newly occurred	- 0.44	0.613	- 0.68	0.380

** p-value based on paired samples t-test.*

D. Sensitivity analyses

BURDEN OF ITCHING AND HRQOL

The main analyses were also performed using the continuous burden scores for itching (range: 0-5), sleep problems (range: 0-10) and psychological symptoms (range: 0-25). A burden score of 0 refers to the symptom being absent and a higher score indicates the level of symptom burden that is experienced by the patient. Table S3 shows the cross-sectional effects of the burden of itching, combined with the burden of sleep problems and psychological symptoms, on physical and mental HRQOL.

Table S3. Cross-sectional effects of the burden of itching, combined with the burden of sleep problems and psychological symptoms, on physical and mental HRQOL

	Physical HRQOL		Mental HRQOL	
	Coef. (95%CI)	p-value	Coef. (95%CI)	p-value
Itching[§]				
Model 1, unadjusted	-1.29 (-1.52; -1.05)	<0.001	-1.45 (-1.69; -1.22)	<0.001
Model 2, adjusted[^]	-1.26 (-1.50; -1.02)	<0.001	-1.42 (-1.65; -1.18)	<0.001
Itching and sleep problems[§] (Model 3[$])				
Itching	-1.18 (-1.52; -0.83)	<0.001	-1.05 (-1.39; -0.71)	<0.001
Sleep problems	-0.72 (-0.90; -0.54)	<0.001	-0.87 (-1.05; -0.70)	<0.001
Itching * sleep problems	0.07 (-0.00; 0.14)	0.063[#]	0.02 (-0.05; 0.09)	0.557[#]
Itching and psychological symptoms[§] (Model 4[$])				
Itching	-1.21 (-1.52; -0.90)	<0.001	-0.77 (-1.02; -0.52)	<0.001
Psychological symptoms	-0.44 (-0.55; -0.33)	<0.001	-1.29 (-1.38; -1.20)	<0.001
Itching * psychological symptoms	0.05 (0.01; 0.09)	0.018[#]	0.06 (0.03; 0.09)	<0.001[#]

[§] Burden of itching on a 0-5 scale, burden of sleep problems on a 0-10 scale and burden of psychological symptoms on a 0-25 scale, with higher scores indicating a higher burden.

[^] Adjusted for age, sex, primary kidney disease, socio-economic status, dialysis modality, time since dialysis initiation and kidney transplantation in past.

[$] Model 3 and 4 build on model 2 and include the interaction with sleep problems and psychological symptoms, respectively.

[#] P-value for interaction.

Findings from the longitudinal analyses using linear mixed models were similar to the cross-sectional analyses, showing a monotonic association between burden of itching and HRQOL. Physical and mental HRQOL was -1.19 (95% CI: -1.41 to -0.96; p<0.001) and -1.37 (95% CI: -1.59 to -1.14; p<0.001) points lower, respectively, for each point increase in burden of itching. No significant changes in physical and mental HRQOL were observed in the total population during follow-up (annual change: -0.23 [95% CI: -0.88 to 0.41; p=0.48] and 0.02 [95% CI: -0.65 to 0.69; p=0.95], resp.). No differences in physical and mental HRQOL trajectories were observed for higher burden of itching (extra annual change for each point increase in burden of itching: 0.13 [95% CI: -0.16 to 0.41; p=0.40] and -0.01 [95% CI: -0.31 to 0.29; p=0.92], resp.). There was no significant interaction between the burden of itching and sleep problems in the association with physical and mental HRQOL (p=0.13 and p=0.89, resp.). The interaction between burden of itching and psychological symptoms in the association with physical and mental HRQOL became statistically significant (p=0.04 and p<0.001, resp.), though with a similarly small effect.

MODERATE TO SEVERE ITCHING AND HRQOL

The main analyses were also performed with the symptoms classified based on low or high burden: no or mild itching (burden score: 0-2) versus moderate to severe itching (burden score: 3-5), combined with no or mild sleep problems (burden score: 0-4) versus moderate to severe sleep problems (burden score: 5-10) and with no or mild psychological symptoms (burden score: 0-10) versus moderate to severe psychological symptoms (burden score: 10-25).

In total, 773 (26.1%) patients had moderate to severe itching, 814 (27.3%) patients had moderate to severe sleep problems and 380 (12.8%) patients had moderate to severe psychological symptoms.

Table S4 shows the cross-sectional effects of moderate to severe itching, combined with moderate to severe sleep problems and psychological symptoms, on physical and mental HRQOL.

Findings from the longitudinal analyses using linear mixed models were similar to the cross-sectional analyses, showing that patients with moderate to severe itching experienced a lower physical and mental HRQOL compared to patients with no or mild itching (-3.98 [95% CI: -4.82 to -3.14; p<0.001] and -4.66 [95% CI: -5.49 to -3.83; p<0.001], resp.). No significant changes in physical and mental HRQOL were observed in the total population during follow-up (annual change: 0.22 [95% CI: -0.73 to 1.16; p=0.66] and -0.19 [95% CI: -1.17 to 0.78; p=0.70], resp.). No differences in physical and mental HRQOL trajectories were observed between pa-

tients with moderate to severe itching and no or mild itching (extra annual change in patients with moderate to severe itching: 0.37 [95% CI: -0.71 to 1.44; p=0.50] and -0.26 [95% CI: -1.37 to 0.85; p=0.65], resp.). Also longitudinally, in the association with physical and mental HRQOL, there was no significant interaction between moderate to severe itching and sleep problems (p=0.30 and p=0.35, resp.) or moderate to severe itching and psychological symptoms (p=0.63 and p=0.71, resp.).

Table S4. Cross-sectional effects of moderate to severe itching, combined with moderate to severe sleep problems and psychological symptoms, on physical and mental HRQOL

	Physical HRQOL		Mental HRQOL	
	Coef. (95%CI)	p-value	Coef. (95%CI)	p-value
Itching				
Model 1, unadjusted	-4.33 (-5.20; -3.46)	<0.001	-4.98 (-5.85; -4.12)	<0.001
Model 2, adjusted^	-4.20 (-5.07; -3.33)	<0.001	-4.90 (-5.76; -4.03)	<0.001
Itching and sleep problems (Model 3$)				
Itching	-3.88 (-4.99; -2.77)	<0.001	-4.31 (-5.40; -3.22)	<0.001
Sleep problems	-3.55 (-4.63; -2.47)	<0.001	-5.07 (-6.13; -4.02)	<0.001
Itching * sleep problems	1.11 (-0.74; 2.95)	0.239#	1.30 (-0.51; 3.11)	0.158#
Itching and psychological symptoms (Model 4$)				
Itching	-3.90 (-4.87; -2.93)	<0.001	-3.04 (-3.92; -2.17)	<0.001
Psychological symptoms	-3.57 (-5.13; -2.02)	<0.001	-13.21 (-14.62; -11.80)	<0.001
Itching * psychological symptoms	0.94 (-1.40; 3.28)	0.432#	0.28 (-1.84; 2.40)	0.794#

^ *Adjusted for age, sex, primary kidney disease, socio-economic status, dialysis modality, time since dialysis initiation and kidney transplantation in past.*
$ *Model 3 and 4 build on model 2 and include the interaction with sleep problems and psychological symptoms, respectively.*
# *P-value for interaction.*

PERSISTENT ITCHING AND HRQOL

The main analyses were repeated in individuals with multiple PROMs measurements (n=1218) to compare persistent itching with no or non-persistent itching. Persistent itching was defined as the presence of itching at baseline and at the first follow-up measurement. In total, 430 (35.3%) patients had persistent itching.
Table S5 shows the cross-sectional effects of persistent itching, combined with sleep problems and psychological symptoms, on physical and mental HRQOL.

Table S5. Cross-sectional effects of persistent itching, combined with sleep problems and psychological symptoms, on physical and mental HRQOL

	Physical HRQOL		Mental HRQOL	
	Coef. (95%CI)	p-value	Coef. (95%CI)	p-value
Itching				
Model 1, unadjusted	-2.97 (-4.22; -1.72)	<0.001	-3.57 (-4.81; -2.34)	<0.001
Model 2, adjusted^	-3.27 (-4.55; -2.00)	<0.001	-3.29 (-4.53; -2.04)	<0.001
Itching and sleep problems (Model 3$)				
Itching	-4.07 (-6.20; -1.94)	<0.001	-2.72 (-4.80; -0.64)	0.010
Sleep problems	-3.26 (-4.77; -1.75)	<0.001	-3.01 (-4.48; -1.54)	<0.001
Itching * sleep problems	1.78 (-0.87; 4.42)	0.187#	-0.25 (-2.83; 2.33)	0.851#
Itching and psychological symptoms (Model 4$)				
Itching	-2.45 (-3.98; -0.92)	0.002	-1.74 (-3.10; -0.38)	0.012
Psychological symptoms	-3.56 (-5.41; -1.72)	<0.001	-10.58 (-12.21; -8.94)	<0.001
Itching * psychological symptoms	-0.52 (-3.27; 2.23)	0.709#	0.78 (-1.66; 3.21)	0.532#

^ *Adjusted for age, sex, primary kidney disease, socio-economic status, dialysis modality, time since dialysis initiation and kidney transplantation in past.*
$ *Model 3 and 4 build on model 2 and include the interaction with sleep problems and psychological symptoms, respectively.*
# *P-value for interaction.*

Findings from the longitudinal analyses using linear mixed models were similar to the cross-sectional analyses, showing that patients with persistent itching experienced a lower physical and mental HRQOL compared to patients with no or non-persistent itching (-2.99 [95% CI: -4.14 to -1.82; p<0.001] and -3.46 [95% CI: -4.59 to -2.32; p<0.001], resp.). No significant changes in physical and mental HRQOL were observed in the total population during follow-up (annual change: -0.73 [95% CI: -1.61 to 0.16; p=0.11] and -0.48 [95% CI: -1.42 to 0.46; p=0.31], resp.). No differences in physical and mental HRQOL trajectories were observed between patients with persistent itching and no or non-persistent itching (extra annual change in patients with persistent itching: -0.64 [95% CI: -1.66 to 0.38; p=0.22] and 0.12 [95% CI: -0.96 to 1.20; p=0.83], resp.). Also longitudinally, in the association with physical and mental HRQOL, there was no significant interaction between persistent itching and sleep problems (p=0.88 and p=0.86, resp.) or persistent itching and psychological symptoms (p=0.49 and p=1.00, resp.).

ITCHING AND HRQOL USING 2019-2020 DATA

The main analyses were repeated using data from 2019 (n=1416) and 2020 (n=1436), to only include measurements from the official start of the PROMs registry at November 2018.

Table S6 shows the cross-sectional effects of the presence of itching, combined with sleep problems and psychological symptoms, on physical and mental HRQOL. Findings from the longitudinal analyses using linear mixed models were similar to the cross-sectional analyses, showing that patients with itching experienced a lower physical and mental HRQOL compared to patients without itching (-3.12 [95% CI: -3.86 to -2.37; p<0.001] and -3.61 [95% CI: -4.35 to -2.87; p<0.001], resp.). No significant changes in physical and mental HRQOL were observed in the total population during follow-up (annual change: 0.29 [95% CI: -0.45 to 1.02; p=0.45] and 0.09 [95% CI: -0.66 to 0.83; p=0.82], resp.). No differences in physical and mental HRQOL trajectories were observed between patients with and without itching (extra annual change in patients with itching: 0.38 [95% CI: -0.61 to 1.37; p=0.45] and 0.05 [95% CI: -0.96 to 1.06; p=0.92], resp.). Also longitudinally, in the association with physical and mental HRQOL, there was no significant interaction between itching and sleep problems (p=0.49 and p=0.34, resp.) or itching and psychological symptoms (p=0.54 and p=0.18, resp.).

Table S6. Cross-sectional effects of the presence of itching, combined with sleep problems and psychological symptoms, on physical and mental HRQOL (2019-2020)

	Physical HRQOL		Mental HRQOL	
	Coef. (95%CI)	p-value	Coef. (95%CI)	p-value
Itching				
Model 1, unadjusted	-3.28 (-4.05; -2.50)	<0.001	-3.85 (-4.61; -3.08)	<0.001
Model 2, adjusted^	-3.32 (-4.10; -2.55)	<0.001	-3.84 (-4.61; -3.08)	<0.001
Itching and sleep problems (Model 3$)				
Itching	-3.28 (-4.54; -2.03)	<0.001	-2.58 (-3.81; -1.34)	<0.001
Sleep problems	-3.75 (-4.82; -2.68)	<0.001	-3.28 (-4.35; -2.22)	<0.001
Itching * sleep problems	0.90 (-0.68; 2.49)	0.264#	-0.97 (-2.54; 0.61)	0.228#
Itching and psychological symptoms (Model 4$)				
Itching	-2.73 (-3.63; -1.83)	<0.001	-2.40 (-3.20; -1.60)	<0.001
Psychological symptoms	-3.27 (-4.65; -1.90)	<0.001	-11.56 (-12.78; -10.33)	<0.001
Itching * psychological symptoms	-0.16 (-1.94; 1.61)	0.859#	1.30 (-0.27; 2.88)	0.105#

^ *Adjusted for age, sex, primary kidney disease, socio-economic status, dialysis modality, time since dialysis initiation and kidney transplantation in past.*
$ *Model 3 and 4 build on model 2 and include the interaction with sleep problems and psychological symptoms, respectively.*
# *P-value for interaction.*