

SUPPLEMENT

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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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

1. 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).

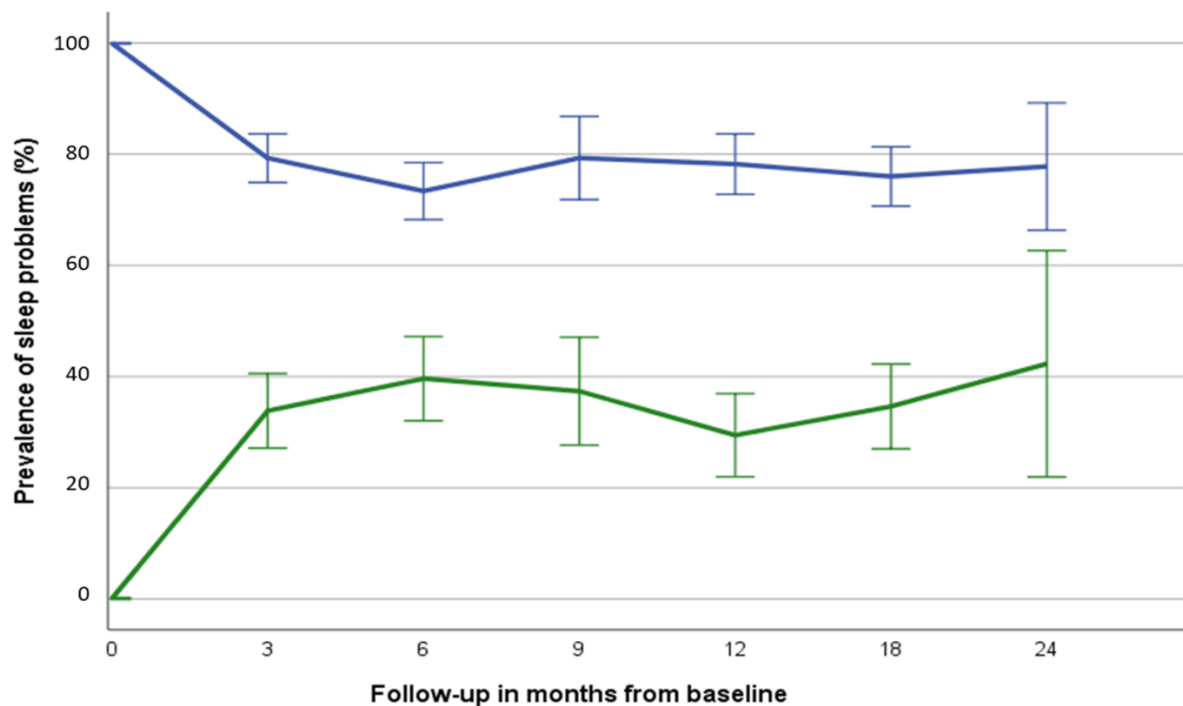


Figure S1a. Persistence of sleep problems during follow-up in patients with sleep problems (blue) and patients without sleep problems (green) at baseline.

Blue solid line (blue bars) shows the percentage (95% Confidence Interval [CI]) of dialysis patients in which sleep problems are persistent during follow-up since baseline. Green solid line (green bars) shows the percentage (95% CI) of dialysis patients in which sleep problems were newly developed during follow-up since baseline.

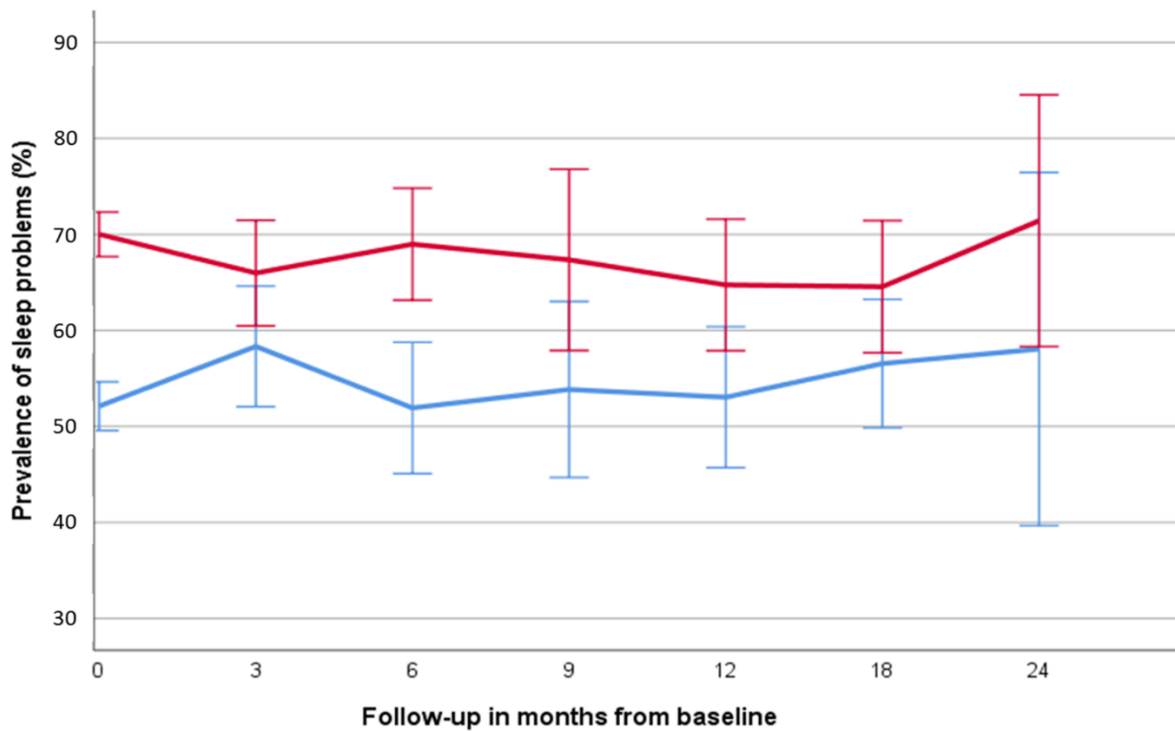


Figure S1b. Persistence of sleep problems during follow-up in patients with itching (red) and patients without itching (blue) at baseline.

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

2. 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).

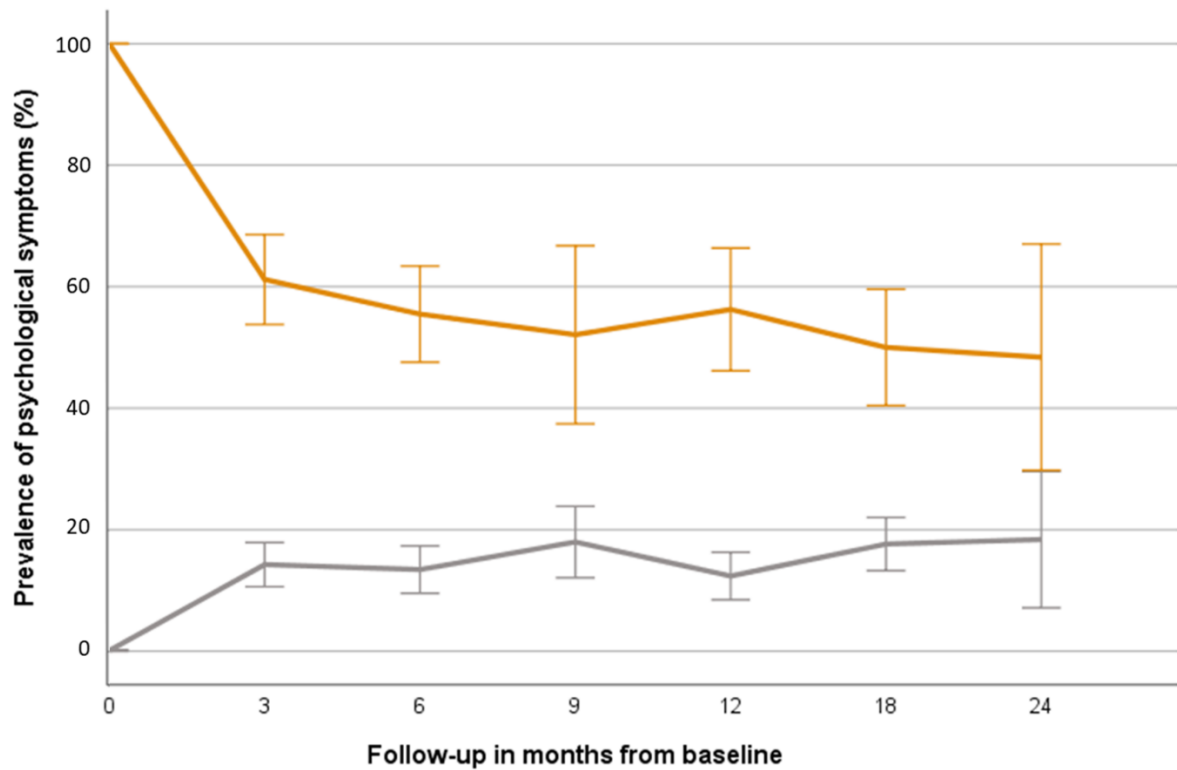


Figure S2a. Persistence of psychological symptoms during follow-up in patients with psychological symptoms (orange) and patients without psychological symptoms (grey) at baseline.

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

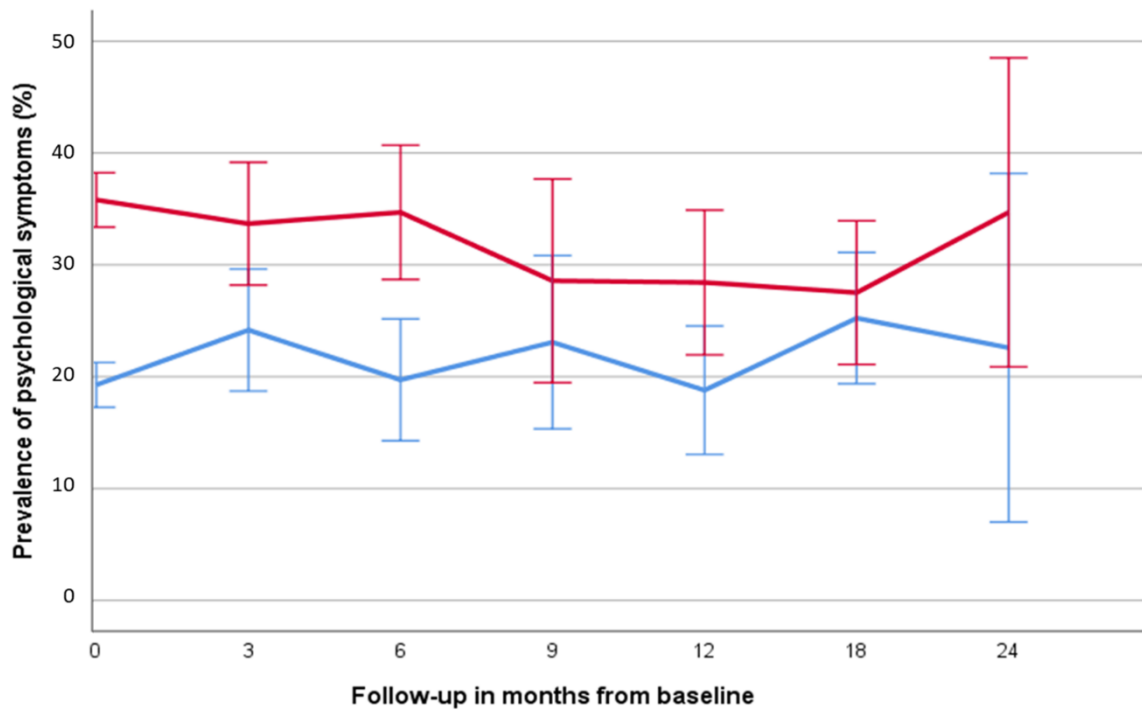


Figure S2b. Persistence of psychological symptoms during follow-up in patients with itching (red) and patients without itching (blue) at baseline.

Solid lines (bars) show the percentages (95% Confidence Intervals [CI]) in which psychological symptoms are present during follow-up, stratified for patients with itching (red) and without itching (blue) 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

1. 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.

2. 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.

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.

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 patients 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.).

3. 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.).

4. 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.

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.

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.).