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Symptom burden before and after dialysis initiation in older patients

Running head: Symptoms in older patients with kidney failure

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Abstract

Background and objectives. For older patients with kidney failure, lowering symptom burden may be more important than prolonging life. Dialysis initiation may affect individual kidney failure-related symptoms differently, but the change in symptoms before and after start of dialysis has not been studied. Therefore, we investigated the course of total and individual symptom number and burden before and after starting dialysis in older patients.

Design, setting, participants, and measurements. The European Quality (EQUAL) study is an ongoing prospective multicenter study in patients ≥ 65 years with an incident $eGFR \leq 20$ mL/min/1.73m². Using the dialysis symptom index (DSI), 30 symptoms were assessed every 3-6 months between 2012 and 2021. Scores for symptom number range from 0-30 and for burden from 0-150, with higher scores indicating more severity. Using mixed-effects models we studied symptoms during the year preceding and the year following dialysis initiation.

Results. We included 456 incident dialysis patients who filled out at least one DSI during the year before or after dialysis. At dialysis initiation, mean(SD) age was 77(6) years, 75% were men, $eGFR$ was 8(3) ml/min/1.73m², 44% had diabetes and 46% had cardiovascular disease. In the year before dialysis initiation, symptom number increased +3.6 (95%CI: +2.5;+4.6) and symptom burden +13.3 (95%CI: +9.5;+17.0). In the year after, symptom number changed -0.9 (95%CI: -3.4;+1.5) and burden decreased -5.9 (95%CI: -14.9;-3.0). At dialysis initiation, "fatigue", "decreased interest in sex" and "difficulty becoming sexually aroused" had the highest prevalence of 81%, 69% and 68%, with a burden of 2.7, 2.4 and 2.3, respectively. "Fatigue" somewhat improved after dialysis initiation, whereas the prevalence and burden of sexual symptoms further increased.

Conclusions. Symptom burden worsened considerably before and stabilized after dialysis initiation. "Fatigue", "decreased interest in sex" and "difficulty becoming sexually aroused"

were considered most burdensome, of which only “fatigue” somewhat improved after dialysis initiation.

Introduction

Globally the number of older (≥ 65 years) patients with kidney failure doubled over the past three decades, mainly driven by the increasing prevalence of diabetes and hypertension.[1,2] Chronic kidney disease (CKD)-related symptom burden increases considerably as kidney function declines and is more pronounced in elderly.[3-6] Since older patients with kidney failure are frequently ineligible for kidney transplantation due to comorbidity, dialysis is the most common kidney replacement therapy (KRT).[7] Given the limited life expectancy and treatment options in older patients with kidney failure, the goal of dialysis initiation can be to improve quality of life by lowering symptom burden, rather than primarily the prolongation of life.[8-10]

The 2019 KDOQI Clinical Practice Guideline identified “To what extent do uremic symptoms change after initiation of dialysis?” as a knowledge gap.[11] Indeed, uremic toxins may cause kidney failure-related symptom burden and adversely affect health-related quality of life (HRQOL).[12,13] Dialysis treatment, however, does not effectively remove uremic toxins bound to proteins.[14,15] Furthermore, both uremic and non-uremic kidney failure-related symptoms often have a multifactorial origin and dialysis will not treat all causes.[16] Finally, dialysis treatment can in itself lead to the development of symptoms.

We recently showed that older patients experienced a clinically relevant decline of both mental and physical HRQOL before dialysis initiation, which stabilized thereafter.[17] A better understanding of the effect of dialysis initiation on individual kidney failure-related symptoms is essential for targeting interventions and addressing those symptoms that contribute most to overall symptom burden in order to improve HRQOL.[12] Furthermore,

knowledge on the evolution of symptoms before and after dialysis initiation could aid both nephrologists and patients who decided to start dialysis. This is especially relevant for older patients with kidney failure, considering their limited life expectancy and treatment options. To our knowledge, the change in symptom burden before and after the initiation of dialysis has not been studied before in older patients, even though dialysis may affect individual kidney failure-related symptoms differently. Therefore, our aim is to investigate the evolution of total symptom number and burden and individual symptoms in the year before and after starting dialysis in older patients with kidney failure.

Methods

Study design and population

The European Quality (EQUAL) study on treatment in advanced CKD, starting April 2012, is an ongoing prospective multicenter follow-up study in six European countries: Germany, Italy, Poland, Sweden, The Netherlands and the United Kingdom. All patients gave informed consent, and all local medical ethics committees or corresponding institutional review boards (as appropriate) approved the study. A full description of the EQUAL study has been published elsewhere.[18] Briefly, patients ≥ 65 years with advanced CKD followed in a nephrology clinic were included with an incident estimated glomerular filtration rate (eGFR) drop to or below $20 \text{ mL/min/1.73m}^2$ in the last six months. Patients were excluded when the eGFR drop was the result of an acute event or when a history of KRT was present. Identified patients who met the eligibility criteria were consecutively approached. Patients were followed every 3 to 6 months until kidney transplantation, death, refusal for further participation, transfer to a non-participating center, loss to follow-up or end of follow-up, whichever came first. For the present analyses, we included all patients who started dialysis (hemodialysis or peritoneal dialysis) and filled out at least one symptom questionnaire during the year before or after dialysis initiation. End of follow-up was at December 2021, when the data were extracted.

Data collection

In the EQUAL study, patients are followed while receiving routine medical care as provided by their nephrology clinic. Data were collected every 3 to 6 months and entered into a web-based clinical record form that was developed for this specific purpose. Extra follow-up visits were conducted at dialysis initiation and after the eGFR dropped below $10 \text{ mL/min/1.73m}^2$

for the first time. The collected information included patients' demographics, ethnicity, primary kidney disease, comorbid conditions, physical examination and laboratory data. All laboratory investigations and physical examinations were performed through standard protocols and procedures according to routine care at the local participating centers. Subsequently, all data were recalculated into one uniform unit of choice. The eGFR was calculated according to the Chronic Kidney Disease Epidemiology Collaboration (CKD-EPI) equation.[19] Primary kidney disease was classified by the treating nephrologist according to the codes of the European Renal Association.[20]

Kidney failure-related symptoms were assessed every 3 to 6 months using the Dialysis Symptom Index (DSI, Supplemental Table 1), a previously validated questionnaire.[21] Through this questionnaire, patients indicated the presence of 30 symptoms in the past month, resulting in a total sum score for symptom number ranging from 0 to 30.

Additionally, for each symptom present, patients rated symptom burden on a 5-point Likert scale ranging from 1 'not at all' to 5 'very much' burdensome. Absent symptoms were assigned a score of zero, resulting in an overall symptom burden score ranging from 0 to 150, with higher scores indicating larger burden.

Statistical analysis

For the present study, baseline was defined as the date of the first dialysis treatment. Baseline characteristics are presented as mean \pm SD, median (interquartile range), or number (proportion) where appropriate.

First, we used linear mixed models to explore the evolution of the total symptom number and burden during the year preceding and following dialysis initiation. A random intercept and slope for time were used to account for repeated measurements, allowing the trajectory over time to vary between individuals. We assumed the relation between symptoms and time to be non-linear around dialysis initiation. Therefore, we modelled time in a three-knot restricted cubic spline function with 95% confidence intervals (95% CI) to allow for more flexibility.[22] The knots were chosen at dialysis initiation, 0.5 year before and 0.5 year after dialysis initiation. We repeated this analysis with additional knots at 1 or 3 months before and after dialysis initiation. Finally, we repeated this model with adjustments for age, sex, diabetes and cardiovascular disease, in order to correct for symptom data missing at random.[23]

Second, we compared linear change in total symptom number and burden during the year before with the linear change after dialysis initiation. In these linear mixed models, we used three fixed variables to allow for a discontinuous change at dialysis initiation: 1) time; 2) indicator whether dialysis was already started (yes or no); and 3) interaction between time and the indicator.

Third, for individual symptoms, we assessed the prevalence and burden at dialysis initiation. For this analysis we included all participants (n=278) who completed a questionnaire during the 30 days before or after dialysis initiation. If a symptom was scored as present but the accompanying burden score was missing, the latter was indicated as “score missing”.

Fourth, for individual symptoms, we studied the evolution of prevalence and burden during one year before and after dialysis initiation. For symptom prevalence, we used logistic mixed effects models.[24] For symptom burden, we used linear mixed effects models. Follow-up time was added as a restricted cubic spline, with knots dialysis initiation, 0.5 year before and 0.5 year after dialysis initiation.

Fifth, we studied the linear change of symptom burden before and after dialysis initiation in various subgroups. The methods and results of these analyses are described in Supplemental Table 4-7.

Finally, we conducted two sensitivity analyses. First, we restricted follow-up time to 6 months after dialysis initiation. Patients who died in the year after dialysis initiation were no longer able to fill out questionnaires. Since these patients may have experienced a worse symptom burden than those who survived, informative dropout due to death should be considered. Second, we extended the inclusion and follow-up time to three years before dialysis initiation. This, since in our main analyses, we only included patients with at least one symptom number or burden score available in the one year before or after dialysis. All analyses were performed using R version 4.0.3 (R Core Team, Vienna, Austria).

Results

Baseline characteristics and follow-up

Of all EQUAL participants who started dialysis (n = 590), defined as baseline, 456 patients filled a DSI questionnaire during one year before or after dialysis initiation and were thus included.[Supplemental Figure 1] No relevant baseline differences were observed between in- and excluded patients.[Supplemental Table 2] For included patients at dialysis initiation, mean±SD age was 77±6 years, 75% were men, 96% were white, 44% had diabetes, 9% were current smokers, 46% had a history of cardiovascular disease, mean eGFR was 8±3 ml/min/1.73m² and mean hemoglobin was 10.3±1.5 g/dL.[Table 1] Mean symptom number and burden was 16±7 and 49±24, respectively. During one year after dialysis initiation, 74 (16%) patients died, of whom 24 and 41 within 3 and 6 months of follow-up, respectively. Of the patients who died, 64% completed at least one DSI after dialysis initiation.

Questionnaires

In total, 1497 DSI questionnaires were available during the year before and after dialysis initiation, with an average of 3.3 questionnaires per patient.[Supplemental Figure 2] On average, questionnaires were missing in 18% and 35% of all follow-up visits in the year before or after dialysis initiation, respectively. Of all included patients, 320 (70%) completed a DSI both before and after dialysis initiation, with a median (IQR) of 135 (90-184) days between questionnaires. Of the remaining 137 (30%) patients, 121 only filled DSI questionnaires before and 16 only after dialysis initiation. Missing follow-up visits and questionnaires are shown in Supplemental Table 3.

Evolution of symptom burden and individual symptoms

We observed a clear increase in symptom number and burden during the year before dialysis initiation, which stabilized thereafter. [Figure 1] Modelling time with knots closer to dialysis initiation, at -3 and +3 or -1 and +1 months before and after dialysis, or adjustments for age, sex, diabetes and cardiovascular disease showed similar results.[Supplemental Figure 2 and 3]

During the year preceding dialysis, mean symptom number and burden increased +3.6 (95%CI: +2.5 to +4.6) and +13.3 (95%CI: +9.5 to +17.0), respectively. In the year after dialysis initiation, mean symptom number changed -0.9 (95%CI: -3.4 to +1.5) and burden decreased -5.9 (95%CI: -14.9 to -3.0), respectively.[Table 2, Supplemental Figure 5]

The prevalence and burden of the 30 individual symptoms at dialysis initiation (n=278) is shown in Figure 2. Figure 3 and Supplemental Table 8 demonstrate the change of prevalence and burden for all 30 individual symptom during the year before and after dialysis initiation (n=456). We present symptoms grouped in 9 symptom systems according to the review of systems.[25, Supplemental Table 4] “Fatigue”, “decreased interest in sex” and “difficulty becoming sexually aroused” had the highest prevalence and burden during the year before and after dialysis, which peaked at dialysis initiation with a prevalence of 81%, 69% and 68% and a mean burden of 2.7, 2.4 and 2.3, respectively. Overall, the prevalence and burden of cardiopulmonary symptoms, emotional symptoms, sleep disorders and “fatigue” mostly increased during the year before and stabilized or decreased after dialysis initiation. The prevalence and burden of gastrointestinal and neurological symptoms also increased in the year before dialysis initiation but afterwards only decreased

in half of the symptoms concerned, the other half increased further. The prevalence and burden of sexual, integumentary and musculoskeletal symptoms also increased further after dialysis initiation or did not change at all.[Figure 3, Supplemental Table 8]

Sensitivity analyses

After restriction of follow-up to 6 months after dialysis initiation, mean (95%CI) symptom number and burden declined with -3.6 (95%CI: -7.7 to +0.5) and -19.9 (95%CI: -35.2 to -4.5). [Table 2, Supplemental Figure 6] By extending inclusion and follow-up time from one year to three years before dialysis initiation, we included 40 extra patients and found that mean (95%CI) symptom number and burden increased by +3.2 (95%CI: +2.2 to +4.3) and +12.9 (95%CI: +9.1 to +16.8).[Table 2] This increase was mainly driven by changes in the year before dialysis initiation.[Supplemental Figure 7] Thus, the results of these sensitivity analyses are in line with the main results.

Discussion

In this large European multicenter cohort of 456 incident older dialysis patients, we found a considerable increase in symptom burden before dialysis initiation that stabilised thereafter. In the year before dialysis symptom number and burden increased +3.6 and +13.3, and stabilized or decreased with changes of -0.9 and -5.9 in the year after dialysis initiation. At start of dialysis the most common symptoms with the highest burden were: “fatigue” (81%, burden 2.7), “decreased interest in sex” (69%, burden 2.4) and “difficulty becoming sexually aroused” (68%, burden 2.3).

Most previous studies assessing symptom burden in patients with advanced CKD did so cross-sectionally.[26] Studies investigating longitudinal symptom evolution were often limited to either non-dialysis or dialysis patients.[27,28] Patients with CKD stage 4-5 have a high symptom burden and may suffer from 6 to 20 kidney failure-related symptoms.[29] This symptom burden increases by 0.5 to 2.9 symptoms as kidney function declines.[27,30,31] An increase in symptom burden may negatively affect HRQOL and is associated with a combined poor health outcome of starting dialysis, receiving a kidney transplant or death.[5,31] We are first to study symptom burden longitudinally before and after dialysis initiation in older patients.

“Fatigue”, “decreased interest in sex” and “difficulty becoming sexually aroused” were the most prevalent and burdensome symptoms during the year before and after dialysis initiation. These results are in line with a recent study among 512 dialysis patients showing that “fatigue” was the most common and “difficulty becoming sexually aroused” the most bothersome symptom.[32] The high burden of “fatigue” in older patients starting dialysis is

often multifactorial, among others including older age, low residual kidney function or uremic toxins, heart failure, anemia, high ultrafiltration volume, anxiety, depression and poor sleep quality.[12,13,33] The prevalence and burden of “decreased interest in sex” and “difficulty becoming sexually aroused” did not improve after dialysis initiation, which is in line with a study investigating the evolution of sexual dysfunction in 43 maintenance dialysis patients.[34] Research on sexual dysfunction in CKD is scarce but several studies showed various underlying factors, such as stress, fatigue, anti-hypertensive use, presence of dialysis access device and dysregulation of the hypothalamic-pituitary-gonadal axis.[35,36] Furthermore, aging is associated with physiologic changes in sexual function. However, chronic diseases, such as diabetes and cardiovascular disease, may accelerate progression of sexual dysfunction. [37,38]

We found different patterns of evolution in the year before and after dialysis initiation among the 30-kidney failure-related symptoms that we studied. Although some of these 30 symptoms improved, almost half (e.g. “cough”, “itch”, “tingling in feet”, “diarrhoea” and sexual symptoms) only stabilized or further worsened after dialysis initiation. The change in burden may differ depending on the effect of dialysis initiation and the origin of the experienced symptoms. First, cardiopulmonary symptoms such as “leg swelling” and “shortness of breath” clearly improved after dialysis initiation, as could be expected following a better control of fluid overload due to dialysis treatment. Second, in contrast, the burden of “itch”, a classic uremic symptom, did not improve after dialysis initiation. This is in line with previous studies that also found a high burden of itching in dialysis patients.[39,40] This may be partly explained by the fact that dialytic clearance of uremic toxins is limited to the unbound fraction that can diffuse across the dialysis

membrane.[14,15] Protein-bound uremic toxins are cleared via tubular secretion for which residual kidney function is essential.[15] Indeed, previous research suggests that patients with residual kidney function experience less uremic symptoms.[41]

Third, dialysis treatment itself can induce symptoms, such as pain from vascular access cannulation and muscle cramps or headache from excess volume removal and electrolyte fluctuations.[12,42] We found no change in muscle cramps and headache after dialysis initiation, although these symptoms did not alter in the year preceding dialysis initiation either. The increase in burden of all emotional symptoms observed in the year prior to dialysis might partly be explained by fear of dialysis treatment, and the burden of these symptoms, in particular “worrying”, indeed somewhat improved after dialysis initiation.[43] Finally, symptoms can be multifactorial, and, especially in elderly, also be driven by comorbidities or medication use.[12,44]

Our results emphasize the importance of identifying and discussing kidney failure-related symptoms in routine clinical care and considering their differing patterns of evolution before and after dialysis initiation.[12] Indeed, increased physician awareness may lead to better symptom control and improve total symptom burden.[45] Furthermore, inquiring about sexual symptoms may help patients to address these sensitive but burdensome symptoms. As patient-reported outcome measures (PROMs), such as symptom questionnaires, are becoming more frequently incorporated in routine nephrology clinical care, individual symptom burden can now be measured in a standardized manner.[46] Routine use of symptom questionnaires might help clinicians in addressing symptoms important to the individual patient. However, considering multifactorial causes or limited

effective treatment options, adequate management of identified symptoms may remain a challenge.

Two phenomena need to be considered for an appropriate interpretation of our results.

First, patients starting dialysis are partly selected on their relatively high or increased symptom burden shortly before dialysis initiation, since symptoms are one of the reasons for dialysis initiation.[11] Because of this selection, regression to the mean may, to some extent, explain a decrease in symptom burden after dialysis initiation.[47] Second, response shift might also contribute to the stabilization of symptom burden after dialysis initiation. Response shift is a change in the meaning of one's evaluation of a self-reported outcome over time.[48] Since dialysis initiation is an event with a large impact on daily life, a dialysis patient's frame of reference might differ from that before dialysis initiation. Through this, response shift could have a beneficial effect on the experienced symptom burden after dialysis initiation.

There are several strengths to our study. First, we used a validated questionnaire to assess the presence of a broad spectrum of kidney failure-related symptoms and their burden longitudinally, both before and after dialysis initiation in a large cohort of older patients. This allowed us, for the first time, to describe the evolution of this important patient-reported outcome before and after dialysis initiation. Second, we included older patients from six European countries, whereas previous studies were often restricted to a single nation or centre. Since the origin and perception of symptom burden and treatment strategies can vary across country and nationality, our broad patient sample will increase the generalizability of our results.[49]

Our study also has some limitations. First, we could not include all EQUAL dialysis patients in the present analysis since DSI questionnaires were only available in 77% of all dialysis patients during the year before and after dialysis initiation. However, clinical characteristics at dialysis initiation did not differ between in- and excluded EQUAL dialysis patients. Second, in 32% of all study visits during follow-up a DSI was missing. By using linear mixed effects models, we could take into account symptom data missing completely at random (e.g. a study coordinator forgot to send out a DSI) and missing at random (e.g. women are more likely to complete questionnaires), but not data missing not at random (e.g. a DSI not completed because a patient feels too sick and did not report this).[23] The latter may have resulted in an underestimation of symptom scores. However, adjusting for age, sex, diabetes and cardiovascular disease to partly explain data missing not at random showed similar results. Third, 16% of the older dialysis patients in our study died in the year after dialysis initiation. This one-year mortality rate is comparable to the rate of 15% established in 65 to 75 year old European dialysis patients and somewhat lower than the value of 24% of European dialysis patients >75 years old.[50] After restriction of follow-up time to 6 months after starting dialysis, symptom number and burden declined even more. This may imply that the informative dropout due to death did not result in a large overestimation of the symptom burden that we calculated one year after dialysis initiation. Fourth, the effect of frailty on symptoms could not be assessed since frailty was not formally measured. Fifth, we only assessed patients starting dialysis and could not investigate symptom burden in patients not starting dialysis, e.g. those treated with conservative care or those who died before initiating dialysis. Therefore, our results can only inform kidney failure patients who already decided to start dialysis and will survive up to dialysis initiation. As conservative care

is becoming increasingly considered as an alternative to dialysis initiation in frail or older patients, assessing its effect on symptom burden would be important.

In conclusion, our results indicate that, on average, symptom number and burden worsened considerably during the year preceding dialysis, but stabilized after dialysis initiation. During the year before and after dialysis initiation, “fatigue”, “decreased interest in sex” and “difficulty becoming sexually aroused” were the most burdensome symptoms. The pattern of symptom burden evolution varied among individual symptoms, possibly because of their different causes. These results could help informing older patients with kidney failure who decided to start dialysis on what to expect regarding the development of their symptom burden.

Authors' Contributions

Research idea and study design: ENMdR, EKH, YM, FWD; data acquisition: FWD, KJJ, NCC, ME, FJC, CT, MS, CD, CW, EKH; data analysis/interpretation: ENMdR, EKH, YM, FWD, JWdF; statistical analysis: ENMdR, EKH, SLC, FWD; supervision or mentorship: EKH, YM, FWD, JWdF, SLC, FWD, KJJ, NCC, ME, AAP, FJC, CT, GP, MS, CD, CW. Each author contributed important intellectual content during manuscript drafting or revision and accepts accountability for the overall work by ensuring that questions pertaining to the accuracy or integrity of any portion of the work are appropriately investigated and resolved.

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Disclosure

The authors have no conflicts of interest to declare in relation to this manuscript. No support or funding was received for this work.

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Figure Legends

Figure 1:

Title:

Figure 1. Evolution of symptom number (blue) and burden (yellow) with 95% confidence interval (grey band) in the year before and after start of dialysis in 456 older patients.

Legend under figure:

DSI: Dialysis symptom index

These results represent the change in total symptom number and burden during the year preceding and following dialysis initiation. To obtain these results, linear mixed models were used in which time (days before or after start of dialysis) was modelled in a three-knot restricted cubic spline function with 95% confidence intervals (95% CI) to allow for more flexibility. The knots were chosen at start of dialysis initiation, 6 months before and 6 months after start of dialysis initiation. A random intercept and slope for time were used to account for repeated measurements, allowing the trajectory before and after the discontinuity to vary between individuals.

Figure 2:

Title:

Figure 2. Mean symptom prevalence (x-axis) and burden according to the 5-point Likert scale (legend) of 30 kidney failure-related symptoms in 278 older patients during the *30 days before and after start of dialysis.

Figure 3:

Title:

Figure 3. Prevalence (dotted line, right y-axis) and burden (solid line, left y-axis) of 30 kidney disease-related symptoms in the year before and after start of dialysis in 456 older patients, ordered by their 9 corresponding symptom systems.

Tables and Figures

Table 1. Characteristics and symptom number and burden of 456 participants in the European Quality (EQUAL) study on treatment of older people with advanced chronic kidney disease at start of dialysis.

Demographics	
Age (yr)	76 (6)
Men, <i>n</i> (%)	343 (75)
Country, <i>n</i> (%)	
Germany	77 (17)
Italy	91 (20)
The Netherlands	69 (15)
Poland	35 (8)
Sweden	93 (20)
United Kingdom	91 (20)
Marital status, <i>n</i> (%)	
Married	317 (71)
Divorced	27 (6)
Widowed	82 (19)
Never married	19 (4)
Education, <i>n</i> (%)	
Low	95 (25)
Intermediate	225 (54)
High	90 (21)
Clinical characteristics	
Primary kidney disease, <i>n</i> (%)	
Diabetes	110 (24)
Hypertension	124 (27)
Systemic / glomerular disease	116 (26)
Other / unknown	106 (23)
Dialysis modality, <i>n</i> (%)	
Hemodialysis	325 (77)
Peritoneal dialysis	99 (23)
Charlson comorbidity index	6.9 (1.9)
History of diabetes, <i>n</i> (%)	199 (44)
History of cardiovascular disease, <i>n</i> (%) ^a	200 (46)
History of heart failure, <i>n</i> (%)	77 (18)
History of chronic lung disease, <i>n</i> (%)	53 (12)
History of malignancy, <i>n</i> (%)	95 (22)
Current smoking, <i>n</i> (%)	40 (9)
BMI (kg/m ²) ^b	28 (6)
Systolic BP (mmHg) ^b	147 (22)
Diastolic BP (mmHg) ^b	75 (11)
Blood chemistry^b	
Hemoglobin (g/dL) ^c	10.3 (1.5)
Creatinine (mg/dL) ^d	6.6 (2.3)

eGFR (ml/min/1.73m ²) ^e	8 (3)
Urea nitrogen (mg/dL) ^f	92 (42)
Uric acid (mg/dL) ^g	7.4 (1.9)
Albumin (g/dL)	3.5 (0.6)
Cholesterol (mg/dL) ^h	159 (54)
Parathyroid hormone (pg/mL) ⁱ	218 (141-396)
Dialysis symptom index^b	
Symptom number	16 (7)
Symptom burden	48 (24)

Data are expressed as number (%), mean (\pm standard deviation), or median (IQR).

^aCardiovascular disease was defined as any history of a cerebral vascular accident, a myocardial infarction or peripheral vascular disease

^bMeasured at start of dialysis or within 30 days before start of dialysis

^cTo convert the values for hemoglobin to millimoles per liter, divide by 1.61

^dTo convert the values for creatinine to micromoles per liter, multiply by 88.40

^eeGFR, was estimated based on serum creatinin using the CKD-EPI formula

^fTo convert the values for urea nitrogen to millimoles per liter, multiply by 0.3571

^gTo convert the values for uric acid to micromoles per liter, multiply by 59.48

^hTo convert the values for cholesterol to millimoles per liter, multiply by 0.02586

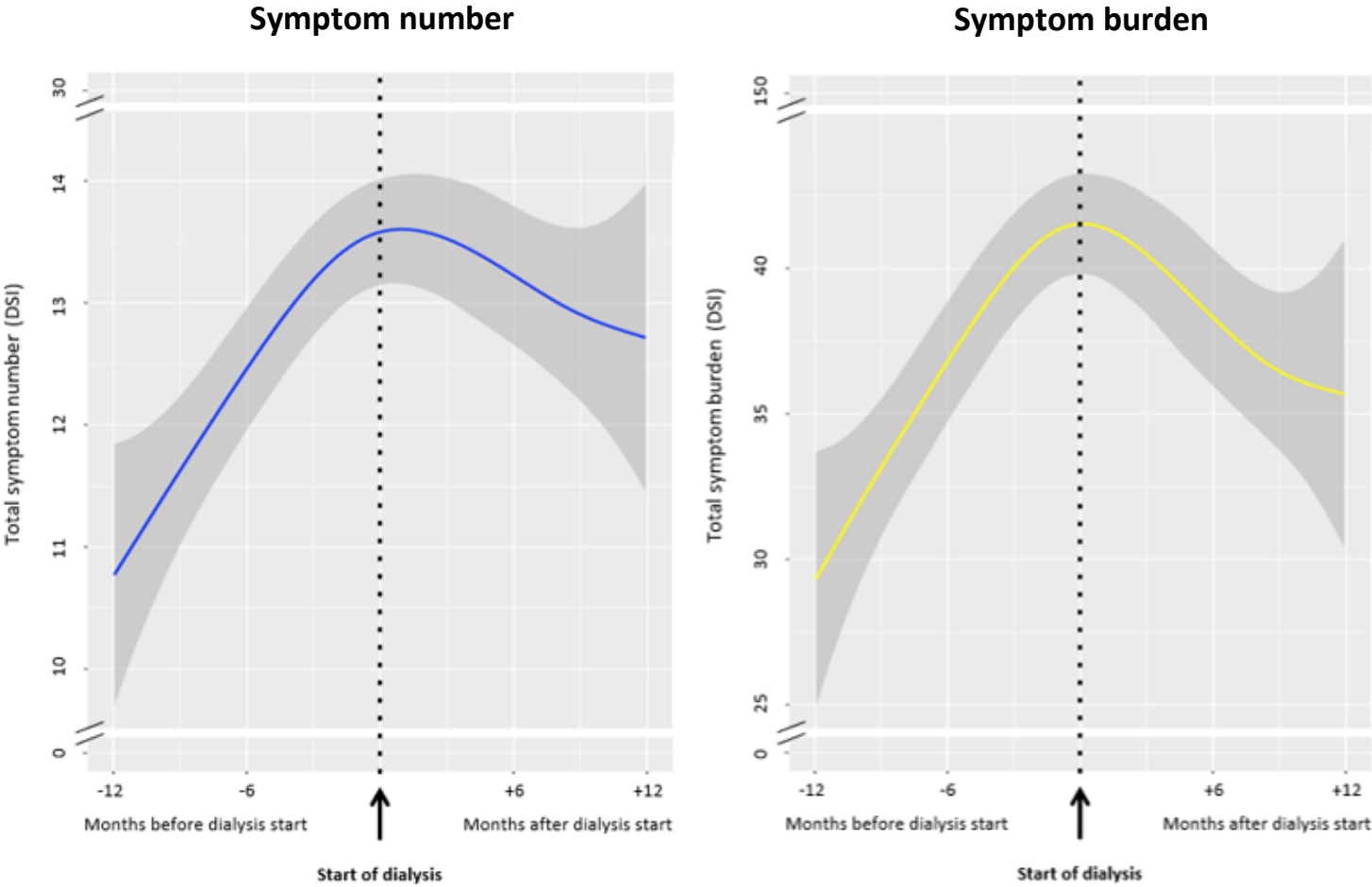
ⁱTo convert the values for parathyroid hormone to picomoles per liter, divide by 9.43

Table 2. Evolution of symptom number and burden before and after start of dialysis in older patients.

	Symptom number change (95% CI)	Symptom burden change (95% CI)
Main analyses (<i>n</i> =456)		
-1 year before to start of dialysis	+3.6 (+2.5 to +4.6)	+13.3 (+9.5 to +17.0)
Start of dialysis to +1 year after	-0.9 (-3.4 to +1.5)	-5.9 (-14.9 to -3.0)
Sensitivity analyses		
-3 years before to start of dialysis (<i>n</i> =496)	+3.2 (+2.2 to +4.3)	+12.9 (+9.1 to +16.8)
Start of dialysis to +0.5 year after (<i>n</i> =449)	-3.6 (-7.7 to +0.5)	-19.9 (-35.2 to -4.5)

These results represent linear changes in symptom number and burden during different time periods before or after dialysis initiation. For example, symptom number increased +3.2 (+2.2 to +4.3) in total during the 3 years before dialysis initiation. Linear changes were calculated with linear mixed models in which we used three fixed variables to allow for a discontinuous change at start of dialysis initiation: 1) time; 2) indicator whether dialysis was already started (yes or no); and 3) interaction between time and the indicator. In this model the interaction term estimates the difference in change before and after start dialysis. A random intercept and slope for time were used to account for repeated measurements, allowing the trajectory before and after the discontinuity to vary between individuals.

Figure 1. Evolution of symptom number (blue) and burden (yellow) with 95% confidence interval (grey band) in the year before and after start of dialysis in 456 older patients.



Legend
— Symptom number
— Symptom burden
 Grey band: 95% CI

DSI: Dialysis symptom index
 These results represent the change in total symptom number and burden during the year preceding and following dialysis initiation. To obtain these results, linear mixed models were used in which time (days before or after start of dialysis) was modelled in a three-knot restricted cubic spline function with 95% confidence intervals (95% CI) to allow for more flexibility. The knots were chosen at start of dialysis initiation, 6 months before and 6 months after start of dialysis initiation. A random intercept and slope for time were used to account for repeated measurements, allowing the trajectory before and after the discontinuity to vary between individuals.

Figure 2. Mean symptom prevalence (x-axis) and burden according to the 5-point Likert scale (legend) of 30 kidney failure-related symptoms in 278 older patients during the *30 days before and after start of dialysis.

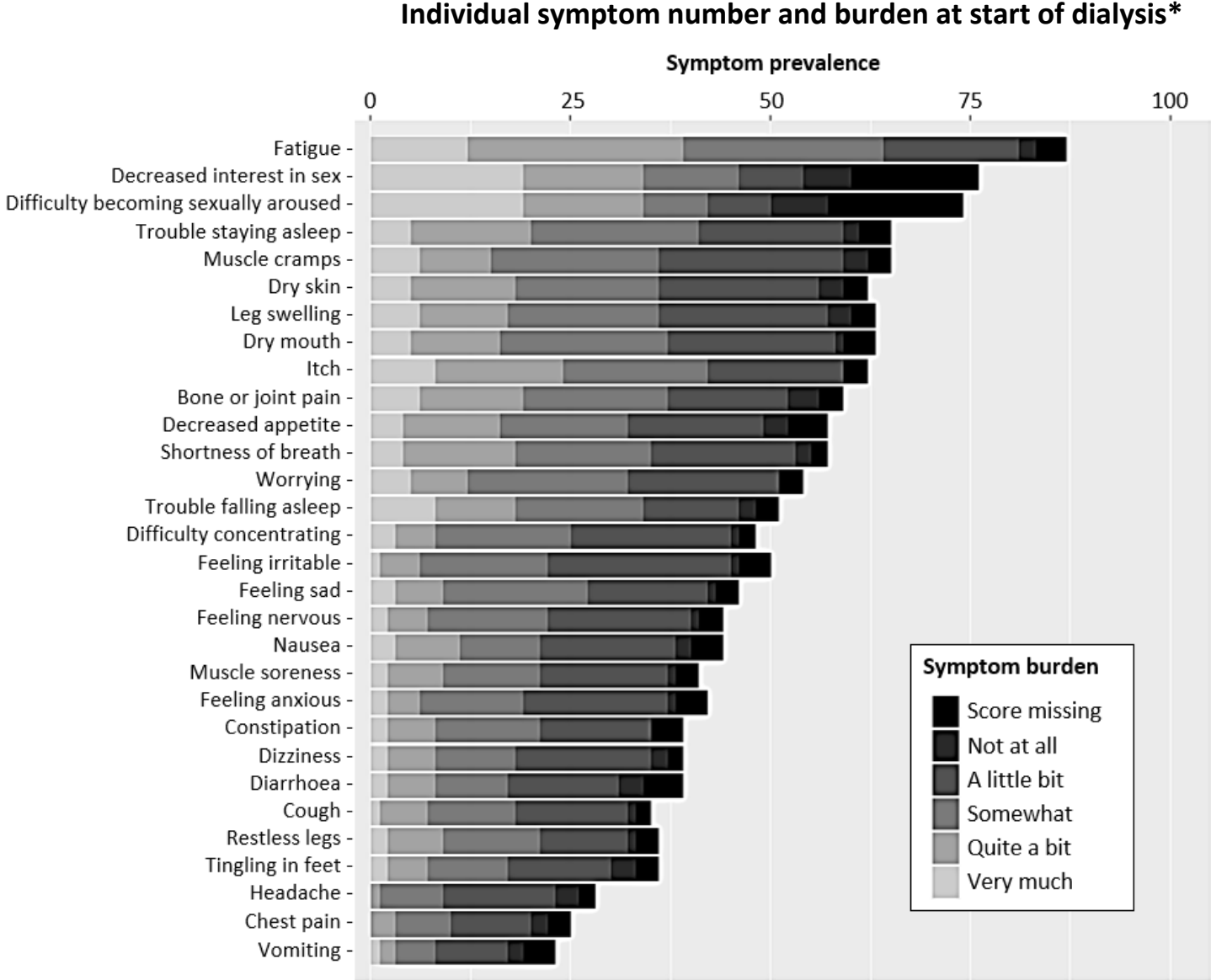


Figure 3. Prevalence (dotted line, right y-axis) and burden (solid line, left y-axis) of 30 kidney disease-related symptoms in the year before and after start of dialysis in 456 older patients, ordered by their 9 corresponding symptom systems.

