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Citation

Symptom Burden before and after Dialysis Initiation in Older Patients

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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, & measurements The European Quality (EQUAL) study is an ongoing, prospective, multicenter study in patients ≥65 years with an incident eGFR ≤20 ml/min per 1.73 m². Using the dialysis symptom index (DSI), 30 symptoms were assessed every 3–6 months between 2012 and 2021. Scores for symptom number range from zero to 30 and, for burden, from zero to 150, with higher scores indicating more severity. Using mixed effects models, we studied symptoms during the year preceding and the year after dialysis initiation.

Results We included 456 incident patients on dialysis who filled out at least one DSI during the year before or after dialysis. At dialysis initiation, mean (SD) participant age was 76 (6) years, 75% were men, mean (SD) eGFR was 8 (3) ml/min per 1.73 m², 44% had diabetes, and 46% had cardiovascular disease. In the year before dialysis initiation, symptom number increased +3.6 (95% confidence interval [95% CI], +2.5 to +4.6) and symptom burden increased +13.3 (95% CI, +9.5 to +17.0). In the year after, symptom number changed −0.9 (95% CI, −3.4 to +1.5) and burden decreased −5.9 (95% CI, −14.9 to −3.0). At dialysis initiation, "fatigue," "decreased interest in sex," and "difficulty becoming sexually aroused" had the highest prevalence of 81%, 69%, and 68%, respectively, 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). CKD-related symptom burden increases considerably as kidney function declines and is more pronounced in the elderly (3–6). Because older patients with kidney failure are frequently ineligible for kidney transplantation due to comorbidity, dialysis is the most common 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 Kidney Disease Outcomes Quality Initiative 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 itself can 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 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, although dialysis may affect individual kidney failure–related symptoms differently in this population. 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.

Materials and 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 eGFR drop to or below 20 ml/min per 1.73 m^2 in the last 6 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 3–6 months until kidney transplantation, death, refusal for further participation, transfer to a nonparticipating center, loss to follow-up, or end of follow-up, whichever came first. For the 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 in December 2021, when the data were extracted.

Data Collection
In the EQUAL study, patients were followed while receiving routine medical care as provided by their nephrology clinic. Data were collected every 3–6 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 <10 ml/min per 1.73 m^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

equation (19). Primary kidney disease was classified by the treating nephrologist according to the codes of the European Renal Association (ERA) (20).

Kidney failure–related symptoms were assessed every 3–6 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 five-point Likert scale, ranging from one for "not at all" to five for "very much" burdensome. Absent symptoms were assigned a score of zero, resulting in an overall symptom burden score ranging from zero to 150, with higher scores indicating larger burden.

Statistical Analyses
For this study, baseline was defined as the date of the first dialysis treatment. Baseline characteristics are presented as mean±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 after 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 nonlinear around dialysis initiation. Therefore, we modeled time in a three-knot restricted cubic spline function with 95% confidence intervals (95% CIs) to allow for more flexibility (22). The knots were chosen at dialysis initiation, 0.5 year before dialysis initiation, 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 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 1 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 at dialysis initiation, 0.5 year before dialysis initiation, 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 Tables 2–5.

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. Because 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 3 years before dialysis initiation. This extended inclusion was made because, in our main analyses, we only included patients with at least one symptom number or burden score available in the 1 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 the 1 year before or after dialysis initiation and were thus included (Supplemental Figure 1). No relevant baseline differences were observed between included and excluded patients (Supplemental Table 6). For included patients at dialysis initiation, mean±SD age was 76±6 years, 75% were men, 96% were White, 44% had diabetes, 9% were current smokers, 46% had a history of cardiovascular disease, the mean±SD eGFR was 8±3 ml/min per 1.73 m^2, and mean±SD hemoglobin was 10.3±1.5 g/dl (Table 1). Mean±SD symptom number and burden was 16±7 and 49±24, respectively. During 1 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 (interquartile range) 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 7.

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). Modeling 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 Figures 3 and 4).

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 (Table 2, Supplemental Figure 5). 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 symptoms during the year before and after dialysis initiation ($n=456$). We present symptoms grouped in nine symptom systems according to the review of systems (Supplemental Table 2) (25). "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%, respectively, 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 neurologic symptoms also increased in the year before dialysis initiation, but afterward 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 by −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 1 year to 3 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 older incident patients on dialysis, we found a considerable increase in symptom burden before dialysis initiation that stabilized 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 the 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 patients not on dialysis or patients on dialysis (27,28). Patients with CKD stage 4–5 have a high
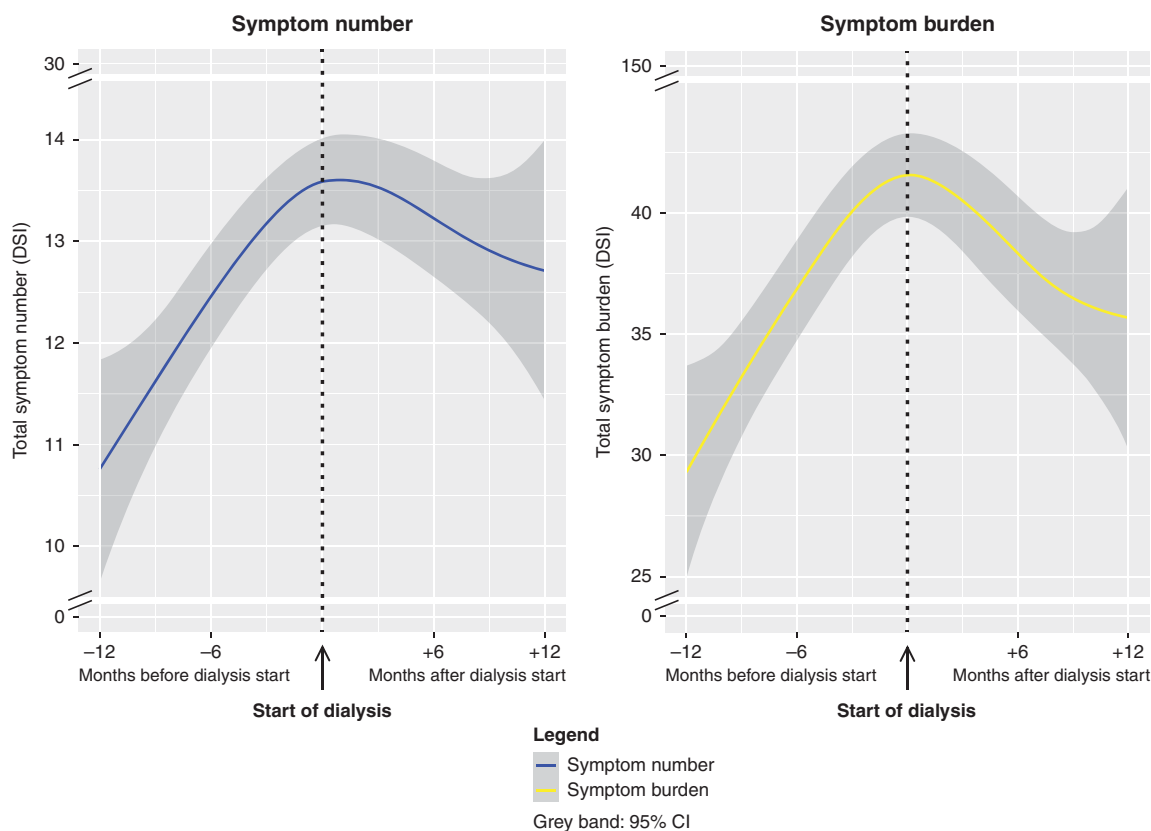
Figure 1. | Symptom number and symptom burden worsened considerably in the year before and stabilized in the year after start of dialysis in 456 older patients. These results represent the change in total symptom number and burden during the year preceding and after dialysis initiation. To obtain these results, linear mixed models were used in which time (days before or after start of dialysis) was modeled in a three-knot restricted cubic spline function with 95% confidence intervals (95% CIs) to allow for more flexibility. The knots were chosen at the start of dialysis initiation, 6 months before dialysis initiation, 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. DSI, dialysis symptom index.

symptom burden and may suffer from six to 20 kidney failure–related symptoms (29). This symptom burden increases by 0.5–2.9 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 the 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 patients on dialysis 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, 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 patients on maintenance dialysis (34). Research on sexual dysfunction in CKD is scarce, but several studies showed various underlying factors, such as stress,

fatigue, antihypertensive 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," "diarrhea," 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 after 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 patients on dialysis (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

Table 1.   Characteristics and symptom number and burden of 456 participants in the European Quality study on treatment of older people with advanced CKD at start of dialysis

Characteristic	Value
Demographics	
Age (yr), mean (SD)	76 (6)
Men, n (%)	343 (75)
Country, n (%)	
Germany	77 (17)
Italy	91 (20)
The Netherlands	69 (15)
Poland	35 (8)
Sweden	93 (20)
United Kingdom	91 (20)
Marital status, n (%)	
Married	317 (71)
Divorced	27 (6)
Widowed	82 (19)
Never married	19 (4)
Education, n (%)	
Low	95 (25)
Intermediate	225 (54)
High	90 (21)
Clinical characteristics	
Primary kidney disease, n (%)	
Diabetes	110 (24)
Hypertension	124 (27)
Systemic/glomerular disease	116 (26)
Other/unknown	106 (23)
Dialysis modality, n (%)	
Hemodialysis	325 (77)
Peritoneal dialysis	99 (23)
Charlson comorbidity index, mean (SD)	6.9 (1.9)
History of diabetes, n (%)	199 (44)
History of cardiovascular disease, n (%)[a]	200 (46)
History of heart failure, n (%)	77 (18)
History of chronic lung disease, n (%)	53 (12)
History of malignancy, n (%)	95 (22)
Current smoking, n (%)	40 (9)
BMI (kg/m^2), mean (SD)[b]	28 (6)
Systolic BP (mm Hg), mean (SD)[b]	147 (22)
Diastolic BP (mm Hg), mean (SD)[b]	75 (11)
Blood chemistry[b]	
Hemoglobin (g/dl), mean (SD)[c]	10.3 (1.5)
Creatinine (mg/dl), mean (SD)[d]	6.6 (2.3)
eGFR (ml/min per 1.73 m^2), mean (SD)[e]	8 (3)
Urea nitrogen (mg/dl), mean (SD)[f]	92 (42)
Uric acid (mg/dl), mean (SD)[g]	7.4 (1.9)
Albumin (g/dl), mean (SD)[h]	3.5 (0.6)
Cholesterol (mg/dl), mean (SD)[i]	159 (54)
Parathyroid hormone (pg/ml), median (IQR)[j]	218 (141–396)
Dialysis symptom index, mean (SD)[b]	
Symptom number	16 (7)
Symptom burden	48 (24)

BMI, body mass index; IQR, interquartile range.

[a]Cardiovascular disease was defined as any history of a cerebral vascular accident, a myocardial infarction, or peripheral vascular disease.

[b]Measured at start of dialysis or within 30 days before start of dialysis.

[c]To convert the values for hemoglobin to millimoles per liter, divide by 1.61.

[d]To convert the values for creatinine to micromoles per liter, multiply by 88.40.

[e]eGFR was estimated on the basis of serum creatinine using the Chronic Kidney Disease Epidemiology Collaboration formula.

[f]To convert the values for urea nitrogen to milllimoles per liter, multiply by 0.3571.

[g]To convert the values for uric acid to micromoles per liter, multiply by 59.48.

[h]To convert the values for albumin to grams per liter, multiply by 10.

[i]To convert the values for cholesterol to millimoles per liter, multiply by 0.02586.

[j]To 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

Period of Time	Symptom Number, Change (95% Confidence Interval)	Symptom Burden, Change (95% Confidence Interval)
Main analyses (n=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 (n=496)	+3.2 (+2.2 to +4.3)	+12.9 (+9.1 to +16.8)
Start of dialysis to +0.5 year after (n=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 (95% confidence interval, +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.

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 before 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 the elderly, can 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
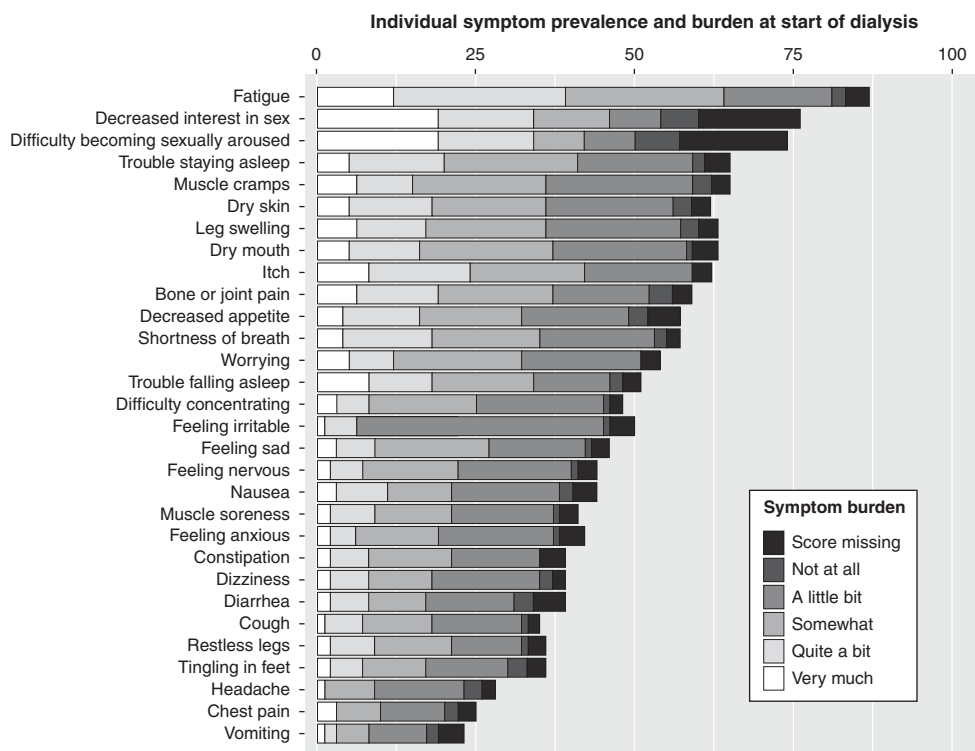

Figure 2. | At dialysis initiation, "fatigue," "decreased interest in sex," and "difficulty becoming sexually aroused" had the highest mean symptom prevalence and burden (x axis) according to the five-point Likert scale (legend) of 30 kidney failure–related symptoms in 278 older patients during the 30 days before and after start of dialysis.
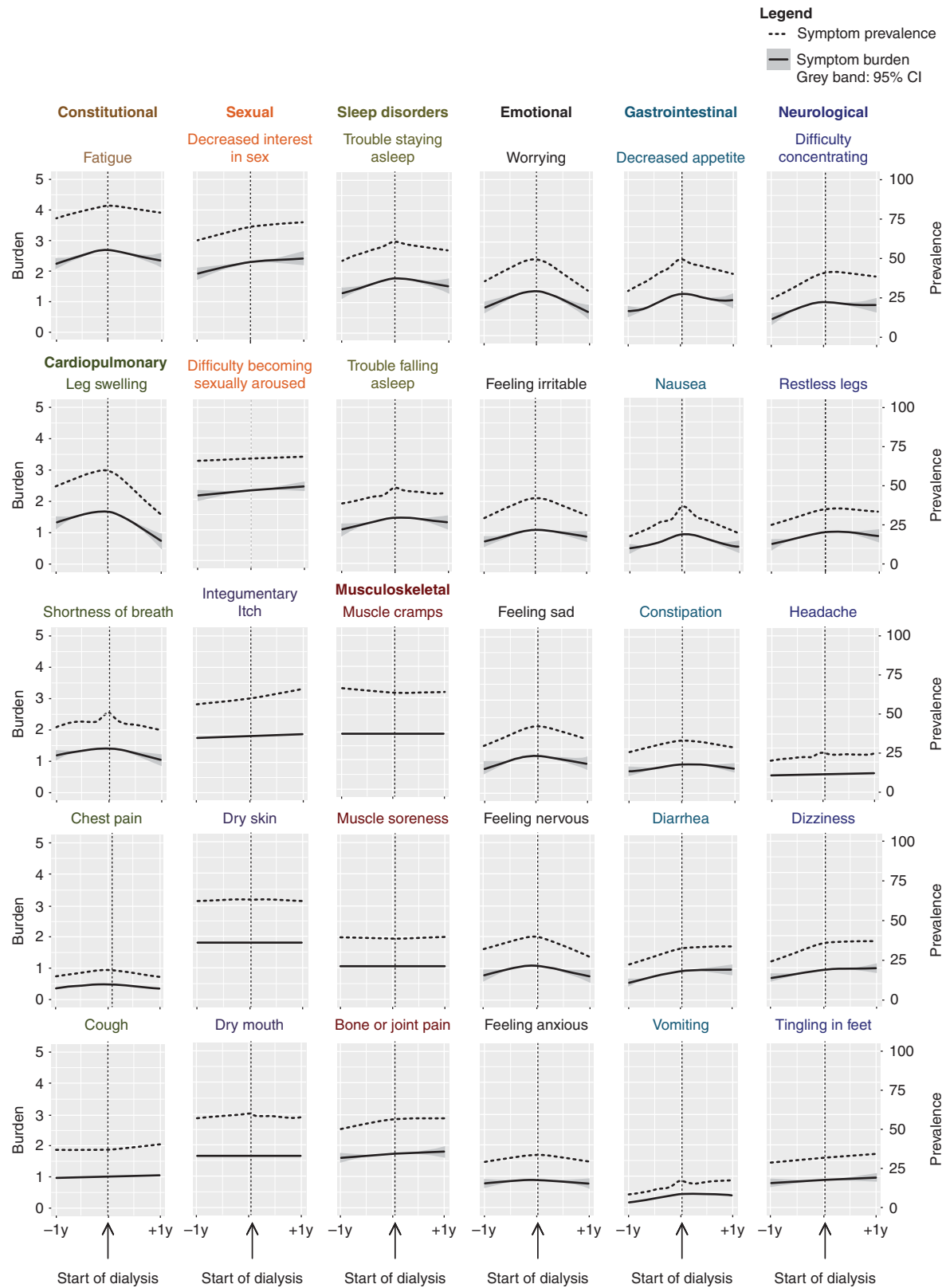
Figure 3. | "Fatigue," "decreased interest in sex," and "difficulty becoming sexually aroused" were the most prevalent and burdensome of all 30 kidney failure-related symptoms during the year before and after starting dialysis. Prevalence (dotted line, right *y* axis) and burden (solid line, left *y* axis) of 30 kidney failure–related symptoms in the year before and after start of dialysis in 456 older patients, ordered by their nine corresponding symptom systems.

control and improve total symptom burden (45). Further-more, inquiring about sexual symptoms may help patients to address these sensitive but burdensome symptoms. As patient-reported outcome measures, 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, because 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). Because dialysis initiation is an event with a large effect on daily life, the frame of reference of a patient on dialysis 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 center. Because 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 patients on dialysis in this analysis because DSI questionnaires were only available in 77% of all patients on dialysis during the year before and after dialysis initiation. However, clinical characteristics at dialysis initiation did not differ between included and excluded EQUAL patients on dialysis. 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 showed similar results. Third, 16% of the older patients on dialysis in our study died in the year after dialysis initiation. This 1-year mortality rate is comparable to the rate of 15% established in 65- to 75-year-old European patients on dialysis and somewhat lower than the value of 24% of European patients on dialysis who are >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 informative dropout due to death did not result in a large overestimation of the symptom burden that we calculated 1 year after dialysis initiation. Fourth, the effect of frailty on symptoms could not be assessed because 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 patients with kidney failure who already decided to start dialysis and will survive up to dialysis initiation. Because conservative care is becoming increasingly considered as an alternative to dialysis initiation in patients who are frail or older, 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 inform older patients with kidney failure who decided to start dialysis on what to expect regarding the development of their symptom burden.

Author Contributions

J.W. de Fijter, F.W. Dekker, E.K. Hoogeveen, and Y. Meuleman provided supervision; F.W. Dekker, E.N.M. de Rooij, E.K. Hoogeveen, and Y. Meuleman conceptualized the study and were responsible for methodology; E.N.M. de Rooij was responsible for data curation, formal analysis, and investigation; E.N.M. de Rooij and E.K. Hoogeveen wrote the original draft and were responsible for visualization; and all authors reviewed and edited the manuscript.

Supplemental Material

This article contains supplemental material online at http://cjasn.asnjournals.org/lookup/suppl/doi:10.2215/CJN.09190822/-/DCSupplemental.

Supplemental Summary 1. Collaborator information.

Supplemental Table 1. Dialysis symptom index (DSI) symptom list.

Supplemental Table 2. The 30 symptoms from the dialysis symptom index (DSI) according to nine symptom systems.

Supplemental Table 3. Description of the methods and results of the conducted subgroup analyses.

Supplemental Table 4. Evolution of symptom number and burden in the year before and after start of dialysis within subgroups, adjusted for potential confounders.

Supplemental Table 5. Median (IQR) symptom number and burden scores at start of dialysis or within 30 days before start of dialysis per subgroup in those who filled a DSI at that time.

Supplemental Table 6. Characteristics of 590 patients in the European Quality (EQUAL) study on treatment of older people with advanced chronic kidney disease at start of dialysis.

Supplemental Table 7. The number (%) of patients who did or did not have a study visit of all included patients (n=456) within each follow-up interval.

Supplemental Table 8. Evolution of burden of 30 kidney disease-related symptoms in the year before and after start of dialysis in 456 older patients, ordered by their nine corresponding symptom systems.

Supplemental Figure 1. Flow diagram indicating the selection of EQUAL study participants.

Supplemental Figure 2. Histograms indicating the number of completed DSI questionnaires per dialysis patient in total (left) or during the year before or after start of dialysis (right).

Supplemental Figure 3. Evolution of symptom number (blue) and burden (yellow) with additional knots at 3 (left) and 1 (right) months before and after start of dialysis in 456 older patients.

Supplemental Figure 4. Evolution of symptom number (blue) and burden (yellow) in the year before and after start of dialysis in 456 older patients, with adjustments for age, sex, diabetes, and cardiovascular disease in order to correct for symptom data missing at random explained by these variables.

Supplemental Figure 5. Linear change of symptom number (blue) and burden (yellow) in the year before and after start of dialysis in 456 older patients, including a discontinuous change at start of dialysis.

Supplemental Figure 6. Evolution of symptom number (blue) and burden (yellow) with restriction of follow-up to 1 year before and 0.5 year after start of dialysis in 449 older patients.

Supplemental Figure 7. Evolution of symptom number (blue) and burden (yellow) with extension of follow-up to 3 years before and 1 year after start of dialysis in 496 older patients.

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