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## Prevalence and Persistence of Uremic Symptoms in Incident Dialysis Patients

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### Abstract

**Background**—Uremic symptoms are major contributors to the poor quality of life among patients on dialysis, but whether their prevalence or intensity has changed over time is unknown.

**Methods**—We examined responses to validated questionnaires in two incident dialysis cohort studies, the Choices for Health Outcomes in Caring for ESRD (CHOICE) study ( $N=926$ , 1995–1998) and the Longitudinal United States/Canada Incident Dialysis (LUCID) study ( $N=428$ , 2011–2017). We determined the prevalence and severity of uremic symptoms—*anorexia, nausea/vomiting, pruritus, sleepiness, difficulty concentrating, fatigue, and pain*—in both cohorts.

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#### Author Contributions

E. Rhee, M. Tonelli, S. Moe, J. Himmelfarb, R. Thadhani, N. Powe, and T. Shafi conceptualized the study; E. Rhee and T. Shafi wrote the original draft of the manuscript; E. Rhee, E. Guallar, and T. Shafi provided supervision; E. Guallar, S. Hwang, N. Kim, and T. Shafi provided formal analysis; M. Tonelli, S. Moe, J. Himmelfarb, and R. Thadhani were responsible for funding acquisition; M. Tonelli, S. Moe, J. Himmelfarb, R. Thadhani, and N. Powe were responsible for project administration; and all authors reviewed and edited the manuscript.

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#### Supplemental Material

This article contains the following supplemental material online at <http://kidney360.asnjournals.org/lookup/suppl/doi:10.34067/KID.0000072019/-/DCSupplemental>.

**Results**—In CHOICE and LUCID, respectively, mean age of the participants was 58 and 60 years, 53% and 60% were male, and 28% and 32% were black. In both cohorts, 54% of the participants had diabetes. Median time from dialysis initiation to the symptoms questionnaires was 45 days for CHOICE and 77 days for LUCID. Uremic symptom prevalence in CHOICE did not change from baseline to 1-year follow-up and was similar across CHOICE and LUCID. Baseline symptom prevalence in CHOICE and LUCID was as follows: anorexia (44%, 44%, respectively), nausea/vomiting (36%, 43%), pruritus (72%, 63%), sleepiness (86%, 68%), difficulty concentrating (55%, 57%), fatigue (89%, 77%), and pain (82%, 79%). In both cohorts, >80% of patients had three or more symptoms and >50% had five or more symptoms. The correlation between individual symptoms was low ( $\rho < 0.5$  for all comparisons). In CHOICE, no clinical or laboratory parameter was strongly associated with multiple symptoms.

**Conclusions**—The burden of uremic symptoms among patients on dialysis is substantial and has not changed in the past 15 years. Improving quality of life will require identification of the factors that underlie the pathogenesis of uremic symptoms and better ways of removing the toxins that are responsible.

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## Introduction

Over 1 million people will start dialysis for ESKD in the next decade (1). Although dialysis prevents death from kidney failure over the short term, many patients continue to suffer from uremic symptoms including anorexia, nausea, pruritus, fatigue, excessive daytime sleepiness, difficulty concentrating, and pain (2). Uremic symptoms are a major contributor to the poor health-related quality of life experienced by patients on dialysis, which is often a greater concern than survival for these patients. Indeed, when asked about the possibility of improvement in quality of life or survival by switching to intensive hemodialysis, 94% would consider it for improving energy, 57% for improving sleep, but only 19% would consider it for improving survival at 3 years (3). Further, “the best ways to manage symptoms in people receiving or nearing dialysis, including poor energy and nausea” was identified as a top research priority in a survey of patients on dialysis and the providers caring for them (4,5).

Despite this significant interest from both patients and providers, relatively few studies have rigorously examined uremic symptoms in large, longitudinal ESKD cohorts, leaving several notable gaps in the existing literature. First, prevalence studies have often focused on individual symptoms rather than a broad range of symptoms (6). Second, how uremic symptoms change over time after dialysis initiation has not been examined. Third, no studies have addressed whether the burden of uremic symptoms experienced by patients on dialysis has changed over the past two decades, as might be expected given the numerous changes in clinical practice over that time.

To address these gaps, we analyzed data from two prospective cohort studies of patients who had recently initiated dialysis, the Choices for Health Outcomes in Caring for ESRD (CHOICE) study, which enrolled patients from 1995 to 1998, and the Longitudinal United States/Canada Incident Dialysis (LUCID) study, which enrolled patients from 2011 to 2017. We compared symptom burden both at study entry and at 1 year after enrollment in

CHOICE, as well as symptom burden at study entry across both cohorts, which span >20 years of ESKD care. Longitudinal follow-up in CHOICE further enabled an exploratory assessment of the association between symptom burden and longitudinal outcomes. Taken together, our study outlines the prevalence and persistence of uremic symptoms among patients on dialysis and emphasizes the urgent need for an improved understanding of underlying mechanisms (7).

## Materials and Methods

We analyzed data from two prospective, incident dialysis cohort studies, the CHOICE study (1995–1998) and the LUCID (2011–2017) study.

### CHOICE Study

From October 1995 to June 1998, 1041 participants (767 on hemodialysis and 274 on peritoneal dialysis) were enrolled from 19 states in the United States, a median of 45 days after initiation of dialysis (95% within 3.5 months). Eligibility criteria were initiation of maintenance dialysis therapy in the preceding 3 months, ability to provide informed consent, age >18 years, and ability to speak English or Spanish. Participants were followed for all-cause mortality through December 31, 2008 and for cardiovascular mortality through December 31, 2004. The subset of 926 individuals who filled out the CHOICE Health Experience Questionnaire at study entry was included in this analysis. The Johns Hopkins Medicine Institutional Review Board (Baltimore, MD) and the Dialysis Clinic, Inc. (DCI) Institutional Review Board approved the study, which adhered to the Declaration of Helsinki, and participants provided written informed consent.

### LUCID Study

From May 2011 to December 2017, 823 participants (808 on hemodialysis, 15 on peritoneal dialysis) were enrolled in three centers (New England, Washington, Indiana) a median of 77 days after initiation of dialysis (95% within 6.0 months); although the original intent was to include participants from both the United States and Canada in a single cohort, Canadian participants were ultimately enrolled in a separate study. Eligibility criteria were initiation of maintenance dialysis, ability to provide informed consent, and age >18 years. The subset of 428 individuals who filled out a Kidney Disease Quality of Life (KDQOL) survey at study entry was included in this analysis. The Massachusetts General Hospital Institutional Review Board (Boston, MA) approved the study, which adhered to the Declaration of Helsinki, and participants provided written informed consent.

### Uremic Symptoms (CHOICE and LUCID)

Symptom prevalence and intensity were assessed by patient responses to self-administered questionnaires conducted at study entry. The CHOICE Health Experience Questionnaire (8) and KDQOL instrument (9) were used in CHOICE and LUCID, respectively. Both studies use similar questions to assess uremic responses, assessing symptoms during the 4 weeks preceding the survey. The responses to seven questions (Supplemental Table 1) were used to assess anorexia, nausea, pruritus, sleepiness, difficulty concentrating, fatigue, and pain. These responses were recorded on a Likert scale and scored in a standardized manner (10).

The generated numeric scores have a range of 0–100, with a higher score representing better health (lower severity of symptoms). For exploratory analyses in CHOICE, an overall uremic symptom score was calculated for each study participant as an average of scores for all seven uremic symptoms weighted equally (U-score).

### Longitudinal Outcomes (CHOICE)

As an exploratory analysis in CHOICE, we also considered secondary outcomes of all-cause mortality, cardiovascular mortality, and first cardiovascular event. Mortality was adjudicated using information from clinic report, hospital records, the National Death Index, Centers for Medicare and Medicaid Services death notification forms, and Social Security records, as previously described (11). We defined first atherosclerotic cardiovascular event (fatal or nonfatal) as an event due to myocardial infarction, cardiac revascularization procedure, stroke, carotid endarterectomy, extremity gangrene or peripheral revascularization procedure, limb amputation, or abdominal aortic aneurysm repair that occurred after enrollment in the study (11).

### Other Covariates

In CHOICE, we collected data on participants' age, sex, race, residual kidney function (self-reported ability to produce more than one cup of urine daily) and body mass index (BMI). We adjudicated baseline comorbidities including prevalent cardiovascular disease by abstraction of dialysis unit records, hospital discharge summaries, medication lists, consultation notes, diagnostic imaging, and cardiac imaging reports and scoring of the Index of Coexistent Disease by two trained nurses. In CHOICE, we obtained routine laboratory data including serum albumin, creatinine,  $Kt/V_{\text{urea}}$ , and phosphate from medical records. In LUCID, we collected data on participants' age, sex, race, residual kidney function (self-reported ability to produce any urine), BMI, and comorbidities by patient interview and abstraction of dialysis unit records.

### Statistical Analyses

We described baseline characteristics of participants in CHOICE and LUCID using means and proportions, as appropriate. We determined the distribution of the uremic symptoms (present versus absent) for each symptom at baseline in both cohorts and compared correlation between symptom scores for individual symptoms using Spearman correlation coefficients. In CHOICE, we further examined the symptoms at year 1 for participants alive at that time point ( $N=585$ ) and with available data. We examined the cross-sectional association between baseline characteristics and individual symptom scores using univariate linear regression models. In exploratory analysis, we modeled the U-score as a continuous variable to examine associations with longitudinal outcomes. We used Cox proportional hazards regression to evaluate the association between U-score at baseline and outcomes (any-cause death, cardiac death, first cardiovascular event) during follow-up in the CHOICE study. We sequentially adjusted for potential confounders including demographics (age, sex, race), comorbidities (Index of Coexistent Disease severity score, cause of ESKD, BMI [categorized as  $<18$ ,  $18-25$ , and  $>25$   $\text{kg/m}^2$ ], residual kidney function (self-reported urine volume of more than one cup of urine daily), diabetes, dialysis modality), and predialysis laboratory tests (albumin, urea,  $Kt/V_{\text{urea}}$ , creatinine, calcium, phosphate, potassium, glucose,

and cholesterol). Statistical analyses were performed using SAS 9.4 (SAS Institute, Cary, NC). Statistical significance was defined as  $P < 0.05$  using two-tailed tests.

## Results

### Baseline Characteristics of the Study Sample

Baseline characteristics of study participants are shown in Table 1. The CHOICE and LUCID studies included 926 and 428 patients who had recently initiated dialysis who filled out symptom surveys, respectively, with similar distributions of age (mean, 58 years versus 60 years), race (28% black versus 32% black), gender (53% male versus 60% male), diabetes status (54% versus 54%), and self-reported residual kidney function (81% versus 89%). In CHOICE, 75% of participants were on hemodialysis and 25% were on peritoneal dialysis. By contrast, almost all participants in LUCID were on hemodialysis (97%). A comparison of individuals who did or did not fill out a symptom survey in CHOICE and LUCID are shown in Supplemental Tables 2 and 3, respectively. Individuals who did not fill out a survey were more likely to be male and be on peritoneal dialysis in CHOICE, and more likely to be black in LUCID. Questionnaires were completed at a median of 45 days from dialysis initiation (25th to 75th percentiles, 26–73 days) in CHOICE and 77 days from dialysis initiation (25th to 75th percentiles, 47–121 days) in LUCID.

### Prevalence and Severity of Uremic Symptoms in CHOICE and LUCID

Uremic symptom prevalence and severity in CHOICE was high and did not change substantially from baseline to year 1 follow-up (Table 2). Fatigue was the most common (89% at baseline and 89% at year 1) and nausea/vomiting was the least common symptom (36% at baseline and 40% at year 1). Participants on peritoneal dialysis (Supplemental Table 2) were more likely than those on hemodialysis to have nausea/vomiting (38% versus 31%,  $P = 0.05$ ) and less likely to have anorexia (42% versus 51%,  $P = 0.04$ ). No significant differences in symptom prevalence were observed for other symptoms between individuals on peritoneal dialysis versus hemodialysis (Supplemental Table 4).

The average symptom prevalence was similar between LUCID and CHOICE despite the approximately 15–20 year difference in study enrollments (Table 2). Baseline values in CHOICE and LUCID were fatigue (89% and 77%, respectively), anorexia (44% and 44%), pruritus (72% and 63%), sleepiness (86% and 68%), nausea/vomiting (36% and 43%), difficulty concentrating (55% and 57%), and pain (82% and 79%). In both cohorts, >80% of patients had three or more uremic symptoms and >50% had five or more uremic symptoms (Figure 1).

### Characteristics Associated with Uremic Symptom Burden in CHOICE

The correlation between individual symptoms was low in CHOICE (correlation coefficient  $< 0.4$  for all comparisons) (Table 3). Similar findings were observed in LUCID (Supplemental Table 5). In CHOICE, increased age was associated with lower symptom scores for anorexia, sleepiness, nausea/vomiting, and pain; male sex was associated with lower symptom scores for anorexia, nausea/vomiting, difficulty concentrating, and pain (Table 4). Several clinical characteristics and laboratory parameters had nominally

significant associations with symptoms, although several were likely indicative of reverse causation (*e.g.*, less anorexia associated with higher BUN, albumin, phosphate, and potassium). Considering the multiple comparisons, only a handful of associations were significant at a more stringent  $P < 0.001$  threshold: increased age with less sleepiness and nausea/vomiting, male sex with less nausea/vomiting, and higher BUN with less anorexia. No association with any uremic symptom score was observed for diabetes status, BMI  $< 25$  versus  $\geq 25$  kg/m<sup>2</sup>, ESKD cause (diabetes versus other), creatinine, calcium, or glucose.

### Association of Uremic Symptoms and Longitudinal Outcomes

In CHOICE, there were 580 deaths (282 cardiac deaths) and 516 cardiovascular events during follow-up. Baseline characteristics of individuals alive or dead at 1-year follow-up are shown in Supplemental Table 6, demonstrating higher baseline BMI among survivors. In exploratory analysis, a higher baseline U-score was associated with any-cause death, cardiac death, and first cardiovascular event in age-, sex-, and race-adjusted models (Supplemental Table 7). In fully adjusted models, each ten-point-lower U-score (more symptoms) was associated with a 5% higher risk of death (hazard ratio [HR], 1.05; 95% CI, 1.01 to 1.10), 6% higher risk of cardiac death (HR, 1.06; 95% CI, 0.99 to 1.12), and 5% higher risk of first cardiovascular event (HR, 1.05; 95% CI, 1.00 to 1.10).

### Discussion

Our study has two principal findings. First, uremic symptoms are very common among patients with ESKD who have recently initiated dialysis. Very few ( $< 3\%$ ) of the patients had no symptoms and  $> 80\%$  of the patients experienced three or more uremic symptoms. Second, the prevalence of uremic symptoms at or close to initiation of dialysis has been remarkably consistent over the past 15 or more years, despite many other changes in patient demographics and/or care processes during this time.

In a systematic review of the literature, Murtagh *et al.* (6) compiled 60 distinct studies of ESKD that reported on symptom prevalence. Most of these prior studies examined one or two symptoms at a time, and the few studies that looked more broadly across multiple symptoms were relatively small (12-16). A recent exception used both focus groups and surveys to demonstrate high symptom prevalence in 119 individuals with ESKD (17). In our study, we simultaneously assessed the prevalence of key uremic symptoms—fatigue, anorexia, pruritus, sleepiness, nausea, difficulty concentrating, and pain—in a total of 1354 patients, representing the largest sample examined to date. The simultaneous assessment of numerous symptoms is valuable, because it most effectively demonstrates the truly grim burden of symptoms experienced by patients on dialysis. We found that all symptoms were common in CHOICE and LUCID, with individual frequencies of 36%–89%; these values are consistent with the mean prevalence values summarized by Murtagh *et al.* (6). Further, the majority of patients experienced three or more symptoms, and more than a half of patients experienced five or more symptoms. However, the correlation between individual symptoms was relatively low, suggesting that underlying mechanisms may differ, further reinforcing the value of examining multiple symptoms simultaneously.

Whereas prior studies have examined symptom prevalence, ours is the first to assess whether symptom prevalence has improved in the modern era. In the interval between recruitment for the CHOICE (1995–1998) and LUCID (2011–2017) studies, several changes have occurred in hemodialysis care, including more widespread use of biocompatible and high-flux membranes, lowering of hemoglobin targets, the development of activated vitamin D analogues and calcimimetics, a focus on “fistula first” for dialysis access, and near universal attainment of  $Kt/V_{\text{urea}}$  targets. In parallel, numerous changes have occurred in the treatment of common comorbidities in patients on dialysis, including the management of hypertension, diabetes, and cardiovascular disease. Yet, we found only small differences in any individual symptom between CHOICE and LUCID. Because these analyses focused on baseline-symptom assessments among patients on incident dialysis, it is possible they did not reflect the full benefit of hemodialysis over a longer period of time on relieving uremic symptoms. However, we found that there was no difference in symptoms among participants in the CHOICE study from baseline to 1-year follow-up. This is consistent with a prior study that also showed no change in symptoms in a cohort of 97 patients surveyed twice over the course of 1 year (18). Taken together, these findings show that minimal progress has been made over the past 20 years in relieving symptom burden in ESKD, and that progress in this area is unlikely to be achieved by minor adjustments in current practice parameters.

The pathogenesis of uremic symptoms remains poorly characterized (19). Clearly, other factors such as anemia, depression, gastroparesis, and medications can contribute to symptom burden. Nevertheless, the observation that uremic symptoms improve markedly or resolve completely after kidney transplantation has led to the long-standing view that uremic symptoms are due, at least in part, to retained uremic toxins (20–24). Based on a given toxin’s physical properties (size, protein binding, volume of distribution, *etc.*) and origin (endogenous, diet, microbiome, *etc.*), one could theoretically design more specific treatment approaches, including both dialytic and nondialytic therapies (7). The traditional bench-to-bedside paradigm has involved demonstrating solute toxicity *in vitro* or in animal models followed by development of targeted assays and clinical validation. This approach, in conjunction with traditional analytical techniques, has identified approximately 150 uremic solutes over the last >40 years (25), but many are not toxic whereas others have shown mixed associations in clinical studies (26). Although the progress in identifying toxins responsible for uremic symptoms has been relatively slow, it is possible that emerging high-throughput approaches in well phenotyped dialysis cohorts may accelerate this process. As an example, Kurella Tamura *et al.* (27) recently used liquid chromatography, mass spectrometry–based metabolite profiling to identify 4-hydroxyphenylacetate, phenylacetylglutamine, hippurate, and prolyl-hydroxyproline as novel markers of cognitive impairment in participants of the Frequent Hemodialysis Network trial.

Our study has several strengths. We examined two multicenter ESKD cohorts, with >1300 patients in aggregate. CHOICE has longitudinal follow-up with extensive phenotyping, whereas LUCID is more reflective of contemporary practice in the United States. To assess symptoms, we used patient responses to similar questions on the Health Experience Questionnaire in CHOICE and the KDQOL in LUCID, respectively. Both instruments have been validated, and the KDQOL has emerged as the most widely used tool for health-related quality of life assessment in the nephrology literature. In fact, the KDQOL is administered

annually to patients on dialysis in the United States to meet the requirements of the Center for Medicare and Medicaid Services for incorporating assessment of health-related quality of life into ESKD care (28).

Several limitations also warrant mention. Although questionnaires permit accrual of large sample numbers and comparison across data sets, they may not be ideal for assessment of some symptoms. For example, compared to an extensive neurocognitive battery, the KDQOL has been shown to have limited sensitivity and specificity for identifying worse executive function and memory (29). In addition, we did not consider all potential uremic symptoms related to ESKD, *e.g.*, restless legs, or all questions that could be related to a given symptom. However, this is also a limitation of the symptom score generated from the KDQOL, which includes some but not all questions related to fatigue and lack of energy. To address this limitation of existing instruments, rigorous studies are needed to develop validated tools for specific uremic symptoms with gold-standard methods that objectively assess symptom severity. For example, severity of pruritus can be quantified using actigraphy (30,31), and fatigue can be assessed using the Borg rating of perceived exertion scale in response to a standardized, 5-minute slow-paced treadmill walk (0.67 m/second; 1.5 mph) at 0% grade, as was done in the Baltimore Longitudinal Study of Aging (32,33). Further, selection bias in those who chose to answer baseline symptom questionnaires, survival bias in those who were available to answer the year 1 questionnaire in CHOICE, and the vintage of CHOICE may all limit the generalizability of our findings. Finally, although symptoms are known manifestations of uremia, they are also known manifestations of other clinical conditions such as anemia, hyperphosphatemia, and depression, further complicating the exploratory examination of uremic symptoms and longitudinal outcomes.

In conclusion, uremic symptoms are common, persistent, and associated with poor outcomes, but their cause remains unknown. In addition, the identification of toxins responsible for uremic symptoms remains an important priority, with the goal to develop more specific treatment approaches and to improve quality of life, and perhaps long-term outcomes, in ESKD.

## Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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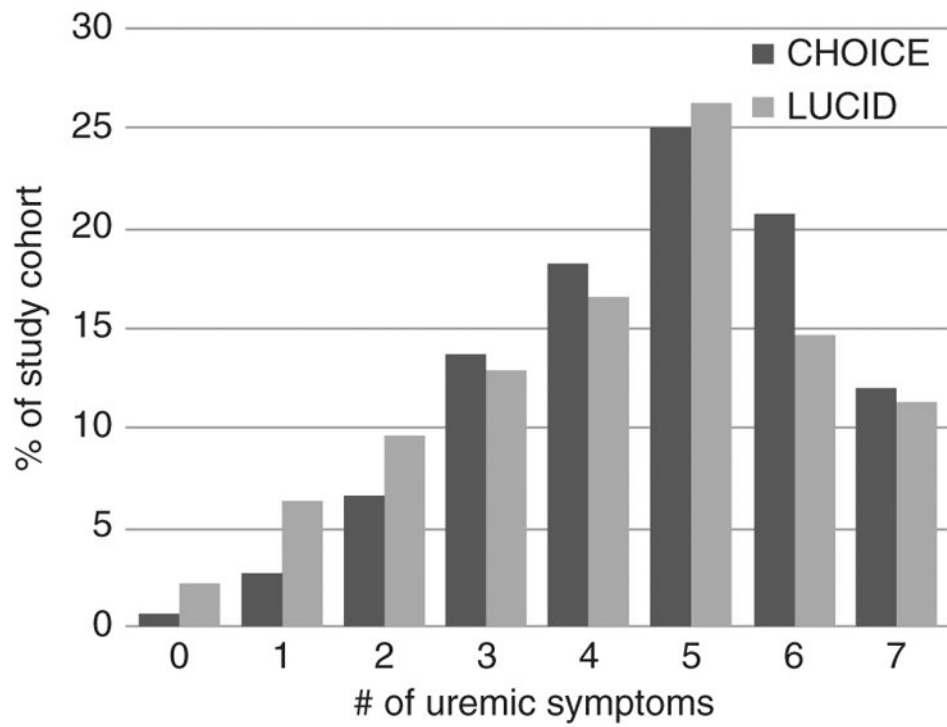
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**Figure 1. 1. Many individuals in CHOICE and LUCID have multiple uremic symptoms.** The y axis shows the percentage of each study cohort ( $N=926$  in CHOICE and  $N=428$  in LUCID) with the corresponding number (#) of uremic symptoms shown on the x axis. CHOICE, Choices for Health Outcomes in Caring for ESRD; LUCID, Longitudinal United States/Canada Incident Dialysis.

**Table 1.**

Baseline characteristics of CHOICE and LUCID participants

Characteristic	CHOICE	LUCID
Sample size	926	428
<b>Demographics</b>		
Age, yr	58±15	60±15
Male sex	491 (53%)	258 (60%)
Black race	257 (28%)	137 (32%)
<b>Clinical characteristics</b>		
Diabetes	498 (54%)	231 (54%)
ICED score	1.9±0.8	—
Residual kidney function	749 (81%)	379 (89%)
BMI, kg/m <sup>2</sup>	27.1±6.7	28.9±7.7
<b>Dialysis characteristics</b>		
Dialysis modality, hemodialysis	697 (75%)	413 (97%)
Cause of ESKD, diabetes	423 (46%)	155 (36%)
<b>Predialysis laboratory tests</b>		
BUN, mg/dl	56.9±16.3	—
Kt/V <sub>urea</sub>	1.3±0.4	—
Albumin, g/dl	3.6±0.4	—
Creatinine, mg/dl	7.3±2.5	—
Calcium, mg/dl	9.1±0.7	—
Phosphate, mg/dl	5.2±1.3	—
Potassium, mEq/L	4.5±0.6	—
Glucose, mg/dl	167±86	—
Cholesterol, mg/dl	190±48	—

Values for categorical variables are given as count (%); values for continuous variables, as mean±SD. CHOICE, Choices for Health Outcomes in Caring for ESRD; LUCID, Longitudinal United States/Canada Incident Dialysis; ICED, Index of Coexistent Disease; BMI, body mass index.

**Table 2.**

Prevalence of uremic symptoms in CHOICE and LUCID

Symptom	CHOICE		LUCID
	Baseline (%)(N=926)	Year 1 (%)(N=585)	Baseline (%)(N=428)
Fatigue	89	89	77
Anorexia	44	43	44
Pruritus	72	74	63
Sleepiness	86	87	68
Nausea/vomiting	36	40	43
Difficulty concentrating	55	60	57
Pain	82	85	79

CHOICE, Choices for Health Outcomes in Caring for ESRD; LUCID, Longitudinal United States/Canada Incident Dialysis.

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**Table 3.**

Spearman correlation between individual symptoms in CHOICE

Symptoms	Fatigue	Anorexia	Pruritus	Sleepiness	Nausea/ Vomiting	Difficulty Concentrating	Pain
Fatigue	1						
Anorexia	0.26 (<0.001)	1					
Pruritus	0.20 (<0.001)	0.20 (<0.001)	1				
Sleepiness	0.23 (<0.001)	0.24 (<0.001)	0.18 (<0.001)	1			
Nausea/vomiting	0.18 (<0.001)	0.38 (<0.001)	0.22 (<0.001)	0.14 (<0.001)	1		
Difficulty concentrating	0.31 (<0.001)	0.22 (<0.001)	0.23 (<0.001)	0.27 (<0.001)	0.18 (<0.001)	1	
Pain	0.29 (<0.001)	0.24 (<0.001)	0.21 (<0.001)	0.23 (<0.001)	0.26 (<0.001)	0.21 (<0.001)	1

CHOICE, Choices for Health Outcomes in Caring for ESRD. Values are Spearman correlation (*P* value).

Table 4.

Predictors of uremic symptoms in the CHOICE study

Predictor	$\beta$ (SEM)							
	Fatigue	Anorexia	Pruritus	Sleepiness	Nausea/ Vomiting	Difficulty Concentrating	Pain	
Age, per 10 yr older	-0.77 (0.65)	-1.46 (0.64) <sup>a</sup>	-1.19 (0.75)	-3.51 (0.69) <sup>b</sup>	-3.20 (0.58) <sup>b</sup>	-1.08 (0.58)	-1.93 (0.63) <sup>c</sup>	
Sex, male versus female	-2.70 (1.94)	-5.55 (1.89) <sup>c</sup>	-4.05 (2.23)	-1.20 (2.09)	-6.32 (1.73) <sup>b</sup>	-5.44 (1.72) <sup>c</sup>	-3.70 (1.86) <sup>a</sup>	
Race, black versus nonblack	-1.86 (2.16)	4.25 (2.13) <sup>a</sup>	0.39 (2.51)	3.69 (2.34)	4.37 (1.95) <sup>a</sup>	2.18 (1.93)	2.29 (2.08)	
Diabetes, yes versus no	0.31 (1.94)	1.56 (1.90)	-1.77 (2.24)	-2.17 (2.09)	2.44 (1.75)	0.63 (1.73)	2.80 (1.87)	
ICED score, <3 versus 3	2.42 (2.12)	0.68 (2.09)	-0.25 (2.45)	-1.12 (2.30)	-0.21 (1.92)	-0.86 (1.90)	5.87 (2.04) <sup>c</sup>	
Residual kidney function, yes versus no	-4.31 (2.60)	-6.89 (2.55) <sup>c</sup>	-5.57 (3.01)	-0.68 (2.81)	-1.46 (2.34)	-4.49 (2.33)	-5.08 (2.51) <sup>a</sup>	
BMI, 25 versus <25 kg/m <sup>2</sup>	3.89 (2.02)	0.36 (1.98)	1.01 (2.31)	0.35 (2.19)	0.16 (1.81)	1.68 (1.79)	3.22 (1.94)	
Dialysis modality, HD versus PD	1.79 (2.23)	-3.88 (2.19)	2.15 (2.58)	0.61 (2.41)	3.67 (2.01)	-0.05 (1.99)	5.44 (2.15) <sup>a</sup>	
Cause of ESKD, diabetes versus other	0.30 (1.95)	0.97 (1.91)	-2.63 (2.24)	-2.24 (2.10)	3.21 (1.75)	1.23 (1.74)	1.84 (1.88)	
BUN, per 10 mg/dL	-1.75 (0.72) <sup>a</sup>	-2.41 (0.73) <sup>b</sup>	0.57 (0.85)	1.28 (0.81)	-0.14 (0.69)	0.78 (0.66)	0.17 (0.72)	
Kt/V <sub>urea</sub> , per 0.2 unit	-0.63 (0.57)	-0.32 (0.56)	0.10 (0.65)	-1.64 (0.62) <sup>c</sup>	-0.75 (0.53)	-0.53 (0.51)	-0.79 (0.56)	
Albumin, per 0.5 g/dL	-2.77 (1.29) <sup>a</sup>	-4.09 (1.27) <sup>c</sup>	-1.92 (1.51)	0.25 (1.40)	-1.74 (1.17)	0.22 (1.16)	-0.47 (1.25)	
Creatinine, per 1 mg/dL	-0.15 (0.38)	-0.54 (0.38)	-0.24 (0.45)	0.78 (0.41)	0.05 (0.35)	-0.14 (0.35)	-0.30 (0.37)	
Calcium, per 1 mg/dL	2.67 (1.36)	-0.36 (1.34)	1.28 (1.58)	1.27 (1.47)	0.70 (1.23)	1.02 (1.22)	1.80 (1.31)	
Phosphate, per 1 mg/dL	0.10 (0.73)	-2.09 (0.72) <sup>c</sup>	0.28 (0.85)	1.90 (0.79) <sup>a</sup>	0.92 (0.66)	1.12 (0.66)	1.56 (0.70) <sup>a</sup>	
Potassium, per 1 mEq/L	0.66 (1.64)	-4.40 (1.61) <sup>c</sup>	-0.75 (1.91)	0.42 (1.78)	-1.05 (1.48)	1.54 (1.48)	0.03 (1.59)	
Glucose, per 10 mg/dL	-0.02 (0.11)	0.12 (0.11)	0.09 (0.13)	0.05 (0.12)	0.11 (0.10)	0.09 (0.10)	0.13 (0.11)	
Cholesterol, per 10 mg/dL	0.23 (0.22)	0.18 (0.22)	-0.23 (0.26)	0.07 (0.24)	0.36 (0.21)	0.41 (0.20) <sup>a</sup>	0.08 (0.21)	

+ $\beta$  denotes increased symptoms and - $\beta$  denotes decreased symptoms per 1-unit increase in the predictor. CHOICE, Choices for Health Outcomes in Caring for ESRD; ICED, Index of Coexistent Disease; BMI, body mass index; HD, hemodialysis; PD, peritoneal dialysis.

<sup>a</sup>  $P < 0.05$ .

<sup>b</sup>  $P < 0.001$ .

$P < 0.001$

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