Trends of Nontraumatic Lower-Extremity Amputation in End-Stage Renal Disease and Diabetes: United States, 2000–2015

Jessica L. Harding, Meda E. Pavkov, Edward W. Gregg, and Nilka R. Burrows

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OBJECTIVE

Nontraumatic lower-extremity amputation (NLEA) is a complication of end-stage renal disease (ESRD) and diabetes. Although recent data show that NLEA rates in the U.S. ESRD population are declining overall, trends in diabetes and diabetes subgroups remain unclear.

RESEARCH DESIGN AND METHODS

We estimated annual rates of NLEA hospitalizations during 2000–2015 among >2 million adults (≥18 years) with ESRD from the U.S. Renal Data System. Age, sex, and race-adjusted NLEA rates were stratified by diabetes status, age, sex, race, and level of amputation (toe, foot, below the knee, and above the knee). Time trends were assessed using Joinpoint regression with annual percent changes (APC) reported.

RESULTS

Among adults with diabetes, NLEA rates declined 43.8% between 2000 and 2013 (from 7.5 to 4.2 per 100 person-years; APC −4.9, $P < 0.001$) and then stabilized. Among adults without diabetes, rates of total NLEAs declined 25.5% between 2000 and 2013 (from 1.6 to 1.1; APC −3.0, $P < 0.001$) and then stabilized. These trends appear to be driven by a slowing or stagnation in declines of minor NLEAs (toe and foot) in more recent years, while major NLEAs (above the knee) continue to decline.

CONCLUSIONS

Despite an initial period of decline, this analysis documents a stall in progress in NLEA trends in recent years in a high-risk population with both ESRD and diabetes. Increased attention to preventive foot care in the ESRD population should be considered, particularly for those with diabetes.

In 2016, 124,675 people in the U.S. began treatment for end-stage renal disease (ESRD) (i.e., kidney failure requiring dialysis or transplantation). The incidence of ESRD increased in the 1980s and 1990s and has remained stable since 2000 (1). Diabetes is the most common cause of kidney failure, accounting for 46% of all new ESRD cases in 2016 (1). The progression of diabetes to ESRD is associated with neuropathy and peripheral vascular disease (2), which, in turn, is associated with an increased risk for nontraumatic lower-extremity amputation (NLEA). Both ESRD and NLEA are serious complications of diabetes, leading to a decrease in quality of life and an increased risk for premature mortality (3).

Division of Diabetes Translation, Centers for Disease Control and Prevention, Atlanta, GA

Corresponding author: Jessica L. Harding, jharding@cdc.gov

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The findings and conclusions in this report are those of the authors and do not necessarily represent the official position of the Centers for Disease Control and Prevention.

Table 1—Descriptive characteristics of the ESRD population, with and without diabetes, at time of ESRD treatment initiation

	Diabetes	No diabetes	*P* value[1]
Demographics			
N	934,472	1,123,166	
Sex (women)	46.8	42.3	<0.001
Age (years)	63.1 (12.9)	63.2 (16.9)	0.01
Race			
White	65.9	66.3	<0.001
Black	26.7	28.7	
Other	7.4	5.0	
Hispanic	18.4	9.7	<0.001
Employment			
Full-time	20.8	20.9	<0.001
Part-time	13.1	16.3	
Unemployed	64.0	60.6	
Retired	2.1	2.2	
Current smoker	4.9	6.7	<0.001
Renal transplant (yes)	8.8	15.8	<0.001
Clinical measurements			
BMI (kg/m^2)	29.9 (7.9)	27.1 (7.3)	<0.001
Serum creatinine (mg/dL)[2]	6.0 (2.3)	6.5 (2.6)	<0.001
LDL (mg/dL)	89.1 (59.1)	90.8 (57.1)	<0.001
Hemoglobin (g/dL)	10.1 (15.1)	10.2 (12.3)	0.01
Serum albumin (g/dL)	2.7 (3.4)	2.9 (3.1)	<0.001
Comorbidities			
Ischemic heart disease	15.7	11.2	<0.001
Myocardial infarction	5.3	4.1	<0.001
Congestive heart failure	38.1	26.9	<0.001
Atherosclerosis	13.6	9.9	<0.001
Cerebrovascular disease	10.6	8.2	<0.001
Peripheral vascular disease	17.7	10.2	<0.001
Hypertension	85.2	82.5	<0.001
COPD	8.0	9.1	<0.001
Cancer	4.1	8.9	<0.001
Disability[3]	8.2	7.0	<0.001

Data are % for categorical variables and mean (SD) for continuous variables. Data on clinical measurements and comorbidities were complete for >80% of the population and demographic data were complete. [1]*P* value for difference between populations with and without diabetes. [2]Due to outliers, we defined the mean (SD) of serum creatinine among the central 0.95 of the population, with creatinine defined as ≥0.6 and ≤13.7. [3]Disability defined as needing assistance in activities of daily living.

People with diabetes have an elevated risk for developing ESRD, and people with both ESRD and diabetes are at much higher risk for NLEA compared with those having either condition alone (4). In the U.S., between 1991 and 1994, the rate of NLEA in ESRD patients with diabetes was approximately six times higher than the rate of NLEA in the ESRD population without diabetes (4). In addition to diabetes, risk factors for NLEA among people with ESRD include older age, male sex, black race, and Native American heritage (4).

The epidemiology of NLEA in people with diabetes has been explored in several reviews (3,5,6). Overall, significant reductions in NLEA incidence over time have been shown as well as reductions in the excess risk between people with and without diabetes (3,5,6). Few studies, however, have explored contemporary trends in NLEA rates among the ESRD population with and without diabetes. In the U.S. ESRD population, a relative decline in NLEA rates of 52.8% and 48.0% between 2000 and 2014 has been observed for people with and without diabetes, respectively (7). However, Franz et al. (7) did not explore NLEA rates among people with and without diabetes by key demographic subgroups such as age, sex, and race or by amputation type. In addition, this study assumed a linear trend in NLEA rates over time, which fails to identify multiple time points in which trends may change significantly in either direction or magnitude within a 15-year period.

Therefore, we analyzed trends in annual NLEA rates among the U.S. ESRD population, adding one more year of data (2015), by demographic subgroups (age, sex, and race), and examining multiple trends within the 16-year time period.

RESEARCH DESIGN AND METHODS

Study Design and Population

The U.S. Renal Data System (USRDS) is a national registry of people with ESRD drawn from clinical and claims data reports submitted to the Centers for Medicare & Medicaid Services (CMS) (1). All adults aged ≥18 years initiating dialysis treatment and registered on the USRDS between 1996 and 2015 were included in this study. The year 1996 was chosen as the 1st year of study inclusion, as the CMS2728 form used to ascertain comorbid conditions was not required until 1995. We excluded patients for the following reasons: <18 years of age; missing CMS data; missing data on age, sex, or race; if first ESRD treatment was a transplant; renal transplant or death event occurred prior to 1 January 2000; and USRDS registration occurred on or after 31 December 2015. The final sample size was 2,060,638, made up of 16 cross-sectional populations of adults with prevalent ESRD per year between 2000 and 2015.

NLEA Hospitalizations

NLEA hospitalizations were ascertained from CMS data from 1 January 2000 through 31 December 2015. The year 2000 was chosen as the 1st year of analysis due to the accrual of prevalent patients from 1996 onwards, allowing a large enough sample size to estimate NLEA rates in the ESRD population with and without diabetes. NLEA hospitalizations were defined using the ICD-9 Clinical Modification (ICD-9-CM) procedure codes from January 2000 through September 2015 and ICD-10-CM from October to December 2015, excluding disease codes for traumatic amputation (Supplementary Table 1). To prevent overestimation of NLEA rates due to planned multistep procedures that may occur across weeks or months, as well as recurrent amputations that may simply reflect a failure of healing of the initial amputation, we included only the highest-level amputation per patient per calendar year. NLEAs were categorized as toe, foot, below the knee (BKA), above the knee (AKA), and minor and major (Supplementary Table 1). Data are

presented as annual rates of NLEAs between 2000 and 2015.

Covariates

Information on covariates was collected from CMS data. Besides demographic information, USRDS data include the date patients were first treated for ESRD with dialysis, primary cause of ESRD, some clinical measurements, and comorbidities obtained from CMS that health care providers are required by law to complete for each new patient with ESRD. In this study, diabetes was defined based on clinician-assigned primary cause of ESRD.

Statistical Analysis

Differences in characteristics between adults with and without diabetes at time of dialysis initiation, and between adults initiating dialysis in 2000, 2005, or 2010, were assessed using Pearson χ^2 test for proportions and Student *t* test for means from approximately normal distributions and Wilcoxon rank sum test for skewed data.

Annual NLEA hospitalization rates, per 100 person-years, were estimated using Stata version 14.1 (StataCorp, College Station, TX). Individuals were followed from 1 January of the cohort year, or dialysis date if thereafter, to 31 December of cohort year, date of NLEA, date of renal transplant, or date of death—whichever occurred first. Annual NLEA rates were estimated using a log Poisson generalized linear model with robust SEs estimated using the delta method. All models were adjusted for age, sex, race, and ethnicity and included an offset term with log exposure time.

We used Joinpoint Trend Analysis Software version 4.5.0.1 (8) to analyze trends in annual NLEA hospitalization rates. This software uses permutation tests to identify points where linear trends change significantly in either direction or magnitude and calculates an annual percentage change (APC) for each time period identified. Statistical significance was established at $P < 0.05$. Trends were analyzed by diabetes, age-group (18–44, 45–64, 65–74, and ≥75 years of age), sex, race (white, black, and other [Native American, Asian, and other/multiracial]), and level of amputation (toe, foot, BKA, AKA, minor [below the ankle], and major [through or above the ankle]).

RESULTS

Characteristics of the ESRD population at time of ESRD treatment initiation are shown in Table 1. In brief, compared with adults without diabetes, adults with diabetes were more likely to be women, Hispanic, and unemployed; more likely to have higher mean BMI, lower serum creatinine, lower LDL, and lower hemoglobin and serum albumin; and more likely to have comorbidities, excluding cancer and chronic obstructive pulmonary disease (COPD).

Over time, there were differences in characteristics of those initiating ESRD dialysis treatment (Table 2). Compared with those initiating treatment in 2000 and 2005, those initiating ESRD treatment in 2010 were more likely to be men, older, unemployed, white, Hispanic, and current smokers. In 2010, patients were also more likely to have a higher mean BMI, higher serum albumin, lower serum creatinine, hypertension, and COPD.

Among adults with diabetes, NLEA hospitalization rates declined 43.8% between 2000 and 2013 (from 7.5 to 4.2 per 100 person-years; APC −4.9 [95% CI −5.5, −4.3], $P < 0.001$) and then stabilized (Table 3). Minor and major NLEAs declined between 2000 and 2012, and 2000 and 2013, respectively, and then no further declines were observed.

For all age-groups, excluding 18–44 years, and in men and women, NLEA rates declined in the first period and then no significant change occurred in the second period (Table 4). By race, significant declines in NLEA rates were observed for blacks and "other race" for the entire period, but among whites, declines occurred between 2000 and 2013 and then no further significant declines were observed.

Table 2—Descriptive characteristics of the ESRD population at time of ESRD treatment initiation in 2000 vs. 2005 vs. 2010

	Year of ESRD treatment initiation[1]		
	2000	2005	2010
Demographics			
n	92,866	105,289	114,506
Sex (women)	46.6	44.5	43.0
Age (mean, years)	62.8 (15.5)	63.3 (15.4)	63.5 (15.1)
Employment			
Full-time	19.1	20.3	21.4
Part-time	15.7	15.0	13.9
Unemployed	60.9	63.0	64.7
Retired	4.3	1.7	0.01
Race			
White	65.3	66.2	67.2
Black	28.2	28.0	27.1
Other	6.6	5.8	5.7
Hispanic	13.7	13.0	14.7
Current smoker	4.9	6.2	6.4
Renal transplant (yes)	14.8	14.5	11.9
Clinical measurements			
BMI	27.1 (7.1)	28.3 (7.7)	29.5 (8.0)
Serum creatinine (mg/dL)[2]	6.8 (2.5)	6.2 (2.4)	5.8 (2.4)
Hemoglobin (g/dL)	10.3 (9.0)	10.3 (4.4)	10.2 (15.1)
Serum albumin (g/dL)	2.3 (2.2)	2.8 (1.8)	3.2 (4.1)
Comorbidities			
Diabetes	45.6	45.0	45.1
Congestive heart failure	32.3	35.6	31.9
Cerebrovascular disease	9.2	10.3	9.4
Peripheral vascular disease	14.4	15.5	13.5
Hypertension	76.6	86.6	87.5
COPD	7.4	9.3	9.6
Cancer	5.6	9.7	7.7

Data are % for categorical variables and mean (SD) for continuous variables. Data on clinical measurements and comorbidities were available for >80% of the population and demographic data were complete. Only variables that were collected at each time point (2000, 2005, and 2010) were included. [1]All comparisons are $P < 0.05$. [2]Due to outliers, we defined the mean (SD) of serum creatinine among the central 0.95 of the population, with creatinine defined as ≥0.6 and ≤13.7.

Table 3—Hospitalization rates of total, minor, and major NLEA and APC among the ESRD population, by diabetes status, 2000–2015

	NLEA rate per 100 person-years (95% CI)					
	Diabetes			No diabetes		
	Total NLEA	Minor NLEA	Major NLEA	Total NLEA	Minor NLEA	Major NLEA
Year						
2000	7.5 (7.4–7.7)	2.8 (2.7–2.9)	5.2 (5.1–5.3)	1.6 (1.5–1.6)	0.6 (0.5–0.6)	1.1 (1.0–1.1)
2001	7.7 (7.5–7.8)	2.7 (2.6–2.8)	5.4 (5.2–5.5)	1.7 (1.6–1.8)	0.6 (0.5–0.6)	1.2 (1.1–1.3)
2002	7.4 (7.2–7.5)	2.6 (2.5–2.7)	5.1 (5.0–5.2)	1.7 (1.6–1.7)	0.5 (0.5–0.6)	1.2 (1.1–1.3)
2003	7.0 (6.8–7.1)	2.5 (2.4–2.6)	4.8 (4.6–4.9)	1.6 (1.5–1.7)	0.6 (0.5–0.6)	1.1 (1.1–1.2)
2004	6.9 (6.8–7.0)	2.5 (2.4–2.6)	4.7 (4.6–4.8)	1.6 (1.6–1.7)	0.6 (0.5–0.6)	1.1 (1.1–1.2)
2005	6.6 (6.3–6.6)	2.5 (2.4–2.6)	4.3 (4.2–4.4)	1.6 (1.5–1.6)	0.6 (0.6–0.6)	1.1 (1.0–1.1)
2006	6.0 (5.9–6.1)	2.4 (2.3–2.4)	3.9 (3.8–4.0)	1.4 (1.4–1.5)	0.6 (0.5–0.6)	1.0 (0.9–1.0)
2007	5.4 (5.2–5.5)	2.2 (2.1–2.2)	3.4 (3.4–3.5)	1.3 (1.3–1.4)	0.5 (0.5–0.5)	0.9 (0.8–0.9)
2008	5.3 (5.2–5.4)	2.2 (2.2–2.3)	3.3 (3.3–3.4)	1.4 (1.3–1.4)	0.5 (0.5–0.6)	0.9 (0.8–0.9)
2009	5.3 (5.2–5.4)	2.3 (2.2–2.4)	3.2 (3.1–3.3)	1.3 (1.3–1.4)	0.5 (0.5–0.6)	0.8 (0.8–0.9)
2010	5.0 (4.9–5.1)	2.2 (2.1–2.3)	3.0 (2.9–3.1)	1.3 (1.2–1.3)	0.5 (0.5–0.6)	0.8 (0.8–0.9)
2011	4.6 (4.5–4.6)	2.0 (2.0–2.1)	2.8 (2.7–2.8)	1.2 (1.2–1.3)	0.5 (0.5–0.6)	0.8 (0.7–0.8)
2012	4.2 (4.1–4.3)	1.9 (1.8–2.0)	2.5 (2.4–2.6)	1.2 (1.2–1.3)	0.5 (0.5–0.6)	0.7 (0.7–0.9)
2013	4.2 (4.2–4.3)	2.0 (1.9–2.1)	2.4 (2.4–2.5)	1.2 (1.1–1.2)	0.5 (0.5–0.5)	0.7 (0.7–0.7)
2014	4.4 (4.3–4.5)	2.1 (2.0–2.1)	2.5 (2.5–2.6)	1.2 (1.2–1.3)	0.6 (0.5–0.6)	0.7 (0.7–0.8)
2015	4.4 (4.3–4.5)	2.1 (2.1–2.2)	2.5 (2.4–2.5)	1.3 (1.2–1.3)	0.6 (0.5–0.6)	0.7 (0.7–0.8)
First trend						
Years	2000–2013	2000–2015	2000–2013	2000–2013	2000–2013	2000–2015
APC	−4.9 (−5.5, −4.3)	−2.8 (−3.4, −2.3)	−6.4 (−7.0, −5.7)	−3.0 (−3.6, −2.3)	−0.8 (−1.5, −0.2)	−3.8 (−4.4, −3.1)
P value	<0.001	<0.001	<0.001	<0.001	0.02	<0.001
Second trend						
Years	2013–2015	2012–2015	2013–2015	2013–2015	2013–2015	NA
APC	2.7 (−7.5, 14.2)	2.0 (−2.4, 6.6)	1.4 (−11.8, 16.5)	3.9 (−7.0, 16.0)	5.2 (−4.7, 16.2)	
P value	0.58	0.34	0.83	0.47	0.28	

All rates are adjusted for age, sex, race, and ethnicity. Major NLEA, through or above the ankle; minor NLEA, below the ankle; NA, second trend not identified.

By level of amputation, declines in NLEAs of the toe and BKA were observed between 2000 and 2012, with no further declines thereafter. NLEAs of the foot declined from 2000 to 2013 and then increased nonsignificantly between 2013 and 2015 (APC 8.9 [−2.1, 21.1], $P = 0.11$). NLEAs for AKA decreased from 2002 onwards (Table 4).

Among people without diabetes, rates of first NLEA declined 25.5% between 2000 and 2013 (from 1.6 to 1.2; APC −3.0 [−3.6, −2.3], $P < 0.001$) and then remained stable (Table 3). By age, significant increases were observed in those aged 18–44 years (APC 3.8 [2.4, 5.1], $P < 0.001$), no change was seen in those aged 45–64 years, and declines were observed in those aged 65–74 and 75+ years between 2000 and 2013, followed by no change. By sex, race, and level of amputation, patterns were similar in people with and without diabetes (Table 4), but the absolute magnitude of risk remained much higher in people with diabetes across all subgroups.

CONCLUSIONS

In this analysis, we note several patterns in rates of NLEA in adults with ESRD. First, initial declines in NLEA rates have been followed by a recent stagnation. This trend appears to be driven by a slowing or stagnation in declines of minor NLEAs (toe and foot) in more recent years while major NLEAs (above the knee) continue to decline. Second, a lack of decline in NLEAs in more recent years was seen across most subgroups of age and sex and among white adults with and without diabetes. Third, although trend patterns are similar in the ESRD population with and without diabetes, the absolute magnitude in NLEA risk remains substantially higher in people with diabetes.

The current study adds important complementary data to what is already known about NLEA rates in the U.S. ESRD population (7). Here, we address the concerning lack of decline in NLEA rates in recent years and highlight important subgroups within the population that may benefit most from preventive care and treatment. Trends observed in the current study are similar to those shown in a nationally representative study of people with diabetes in the general U.S. population (9). Geiss et al. (9) reported a 43% reduction in NLEA rates between 2000 and 2009 (from 5.4 to 3.1 per 1,000 people, $P < 0.001$) and then a 41% increase between 2009 and 2014 (from 3.1 to 4.3, $P < 0.002$). This was similarly driven by increasing rates of minor NLEAs and disproportionally affected younger and middle-aged adults. In contrast, among the general U.S. population without diabetes, NLEA rates declined 28% between 2000 and 2014 (from 0.24 to 0.17 per 1,000 people, $P < 0.001$) (9). As of 2014, people with ESRD and diabetes in the current study still had a 6- and 150-fold increased rate of NLEA, as compared with the general population with and without diabetes, respectively, as reported in the study by Geiss et al. (9).

The extremely high risk for NLEA among people with ESRD and diabetes can be attributed, in part, to more severe neuropathy and peripheral vascular

Table 4—Hospitalization rates for any NLEA in people with ESRD, by diabetes status, and APC, by age, sex, race, and level of amputation

	NLEA rate per 100 person-years (95% CI)		First trend			Second trend		
	2000	2015	Year	APC (95% CI)	*P* value	Year	APC (95% CI)	*P* value
Diabetes								
Age-group (years)								
18–44	5.0 (4.4–5.5)	4.2 (3.9–4.5)	2000–2015	−1.8 (−2.4, −1.3)	<0.001	NA		
45–64	7.1 (6.9–7.4)	4.7 (4.5–4.8)	2000–2012	−4.3 (−4.9, −3.7)	<0.001	2012–2015	0.9 (−3.8, 5.8)	0.68
65–74	8.7 (8.4–9.0)	4.6 (4.5–4.8)	2000–2013	−5.3 (−6.0, −4.7)	<0.001	2013–2015	2.2 (−9.9, 15.9)	0.71
75+	7.8 (7.4–8.2)	3.6 (3.4–3.8)	2000–2013	−6.7 (−7.5, −5.8)	<0.001	2013–2015	1.4 (−13.5, 18.8)	0.86
Sex								
Men	8.3 (8.0–8.6)	5.2 (5.0–5.3)	2000–2012	−4.3 (−5.0, −3.6)	<0.001	2012–2015	0.2 (−5.0, 5.7)	0.94
Women	6.7 (6.4–6.9)	3.6 (3.4–3.7)	2000–2013	−5.8 (−6.5, −5.2)	<0.001	2013–2015	2.9 (−9.4, 16.7)	0.63
Total	7.5 (7.4–7.7)	4.4 (4.3–4.5)	2000–2013	−4.9 (−5.5, −4.3)	<0.001	2013–2015	2.7 (−7.5, 14.2)	0.58
Race								
White	7.9 (7.7–8.1)	4.4 (4.3–4.5)	2000–2013	−5.2 (−5.8, −4.7)	<0.001	2013–2015	4.0 (−6.0, 15.0)	0.42
Black	7.3 (7.0–7.6)	4.7 (4.6–4.9)	2000–2015	−3.7 (−4.2, −3.2)	<0.001	NA		
Other	5.4 (5.0–5.9)	2.8 (2.6–3.1)	2000–2015	−5.3 (−5.9, −4.7)	<0.001	NA		
Level of amputation								
Toe	2.0 (1.9–2.1)	1.5 (1.4–1.5)	2000–2012	−2.8 (−3.5, −2.2)	<0.001	2012–2015	1.4 (−3.4, 6.4)	0.55
Foot	1.0 (0.9–1.1)	0.8 (0.8–0.8)	2000–2013	−2.6 (−3.3, −2.0)	<0.001	2013–2015	8.9 (−2.1, 21.1)	0.11
BKA	3.4 (3.3–3.5)	1.6 (1.6–1.7)	2000–2012	−6.5 (−7.2, −5.9)	<0.001	2012–2015	0.1 (−5.5, 6.1)	0.97
AKA	1.9 (1.8–2.0)	0.9 (0.9–0.9)	2000–2002	2.9 (−12.9, 21.5)	0.713	2002–2015	−6.7 (−7.5, −5.9)	<0.001
No diabetes								
Age-group (years)								
18–44	0.2 (0.1–0.3)	0.4 (0.3–0.4)	2000–2015	3.8 (2.4, 5.1)	<0.001	NA		
45–64	1.0 (0.9–1.1)	1.2 (1.1–1.2)	2000–2015	0.0 (−0.5, 0.6)	0.994	NA		
65–74	2.4 (2.2–2.6)	1.8 (1.7–1.9)	2000–2015	−2.8 (−3.4, −2.1)	<0.001	NA		
75+	2.5 (2.3–2.6)	1.5 (1.4–1.5)	2000–2013	−5.4 (−6.2, −4.6)	<0.001	2013–2015	3.4 (−11.4, 20.7)	0.64
Sex								
Men	1.6 (1.5–1.7)	1.5 (1.4–1.5)	2000–2013	−2.1 (−2.7, −1.6)	<0.001	2013–2015	4.8 (−4.4, 15.0)	0.29
Women	1.5 (1.4–1.6)	1.0 (0.9–1.0)	2000–2015	−3.9 (−4.6, −3.2)	<0.001	NA		
Total	1.6 (1.5–1.6)	1.3 (1.2–1.3)	2000–2013	−3.0 (−3.6, −2.3)	<0.001	2013–2015	3.9 (−7.0, 16.0)	0.47
Race								
White	1.6 (1.5–1.7)	1.2 (1.1–1.2)	2000–2012	−3.9 (−4.7, −3.0)	<0.001	2012–2015	2.4 (−4.0, 9.3)	0.44
Black	1.6 (1.5–1.7)	1.5 (1.4–1.6)	2000–2002	6.3 (−9.6, 25.0)	0.424	2002–2015	−2.1 (−2.7, −1.5)	<0.001
Other	0.7 (0.5–0.9)	0.6 (0.4–0.7)	2000–2015	−2.3 (−3.5, −1.1)	<0.01	NA		
Level of amputation								
Toe	0.4 (0.4–0.4)	0.4 (0.4–0.4)	2000–2015	−0.4 (−1.0, 0.1)	0.098	NA		
Foot	0.2 (0.2–0.2)	0.2 (0.2–0.2)	2000–2013	−0.6 (−1.9, 0.6)	0.288	2013–2015	10.3 (−7.9, 32.2)	0.26
BKA	0.6 (0.5–0.6)	0.4 (0.4–0.4)	2000–2011	−4.0 (−4.9, −3.2)	<0.001	2011–2015	1.5 (−2.1, 5.3)	0.38
AKA	0.5 (0.5–0.6)	0.3 (0.3–0.4)	2000–2002	7.6 (−11.2, 30.5)	0.419	2002–2015	−5.3 (−6.1, −4.4)	<0.001

All rates are adjusted for age, sex, race, and ethnicity where appropriate. NA, no second trend identified.

disease, complicated by poor wound healing, foot ulcers, and gangrene (10–14). Further, an initial NLEA is associated with a higher risk of subsequent NLEA to the same or other limb. In a study of people with diabetes, among 435 patients who had an initial NLEA, 19.8% had a recurrent NLEA (15). In our population of adults with ESRD and a previous amputation, 42.6% and 35.0% with and without diabetes, respectively, had a recurrent amputation between 2001 and 2015. In addition to a high level of comorbidities among the ESRD population, poor survival rates after NLEA have been reported in several studies (4,16–19). In a study of U.S. Medicare ESRD beneficiaries, cumulative survival at 1-year post-NLEA was only 49.3% compared with 78.7% for ESRD patients who had not had an NLEA (4). Collectively, this highlights a group of patients with a disproportionately high risk for NLEA, morbidity, and mortality. As individuals with ESRD are in frequent contact with the health care system to obtain renal replacement therapy, there are numerous opportunities to reduce the rates of NLEA with preventive foot care and early detection of foot problems (4).

Reasons for the observed slowing in NLEA trends in the U.S. are unclear, although several hypotheses exist. First, a flattening of hospitalization rates of minor NLEA may suggest changes in clinical practice that favor earlier minor NLEAs to prevent major NLEAs in the future. This hypothesis is supported in our study with declines or stabilizations in recurrent major NLEAs (Supplementary Table 2). Second, it is possible that the incident ESRD population may be more "sick" as compared with previous years, leading to an increased risk for complications such as NLEA. However, when we compared characteristics of those initiating ESRD in 2000 vs. 2005 vs. 2010, findings were mixed. Although new ESRD patients in 2010 were more likely to have hypertension, COPD, a higher BMI, and be current smokers, they also had higher serum albumin, which is associated with a decreased risk for NLEA in people with ESRD (10). Further, although these differences

were statistically significant, the absolute differences between those initiating ESRD treatment in 2000 vs. 2010 were small. Third, it is possible that stagnating NLEA rates are due to shortcomings in early prevention practices (i.e., physician and patient self-management education, use of appropriate footwear, and identification of high-risk feet [20]), leading to an increase in the prevalence of foot problems (ulcers and infection) that are known to disproportionality affect dialysis patients with diabetes (21). It is also possible that delayed access to treatment has led to a greater severity of foot problems, leading to a greater need for amputation. Other alternative explanations include changes in coding practice for NLEA procedures and a possible increase in coding of diabetes on NLEA hospitalizations. However, it is unclear why these factors should have a greater impact on different subgroups such as younger adults without diabetes and whites.

Although we used a large national database of individuals with ESRD linked to hospitalization records, some limitations should be considered. We used clinician-assigned "primary cause" of ESRD to assign diabetes status, and so it is possible we have over- or underestimated the proportion of ESRD attributed to diabetes (1). We also used ICD-9-CM between January 2000 and September 2015 to identify NLEAs. ICD-9-CM is limited by its inability to distinguish between left and right legs and between toes. A shift to ICD-10-CM for the last 3 months of the study period may have affected our observed rates. However, observed changes in trends occurred before this period, and therefore, it is unlikely that this coding shift influenced the overall patterns that we observed in this study.

Despite an initial period of decline, this analysis documents a discouraging stall in progress in NLEA trends in recent years in a high-risk population with both ESRD and diabetes in the U.S. A better understanding of the factors driving these changes may help to reverse these recent trends and sustain positive future trends. In the meantime, continued efforts to improve access to and uptake of preventive foot care, improve diabetes self-management, and promote education might be a priority for ESRD patients, particularly among those with diabetes.

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References

1. United States Renal Data System. *USRDS Annual Data Report: Epidemiology of Kidney Disease in the United States*. Bethesda, MD, National Institutes of Health National Institute of Diabetes and Digestive and Kidney Diseases, 2018

2. Fernando DJ, Hutchison A, Veves A, Gokal R, Boulton AJ. Risk factors for non-ischaemic foot ulceration in diabetic nephropathy. Diabet Med 1991;8:223–225

3. Narres M, Kvitkina T, Claessen H, et al. Incidence of lower extremity amputations in the diabetic compared with the non-diabetic population: a systematic review. PLoS One 2017;12:e0182081

4. Eggers PW, Gohdes D, Pugh J. Nontraumatic lower extremity amputations in the Medicare end-stage renal disease population. Kidney Int 1999;56:1524–1533

5. Carinci F, Massi Benedetti M, Klazinga NS, Uccioli L. Lower extremity amputation rates in people with diabetes as an indicator of health systems performance. A critical appraisal of the data collection 2000-2011 by the Organization for Economic Cooperation and Development (OECD). Acta Diabetol 2016;53:825–832

6. Moxey PW, Gogalniceanu P, Hinchliffe RJ, et al. Lower extremity amputations–a review of global variability in incidence. Diabet Med 2011;28:1144–1153

7. Franz D, Zheng Y, Leeper NJ, Chandra V, Montez-Rath M, Chang TI. Trends in rates of lower extremity amputation among patients with end-stage renal disease who receive dialysis. JAMA Intern Med 2018;178:1025–1032

8. Division of Cancer Control & Population Sciences, National Cancer Institute. Joinpoint trend analysis software [Internet]. Available from https://surveillance.cancer.gov/joinpoint/. Accessed 12 February 2019

9. Geiss L, Li Y, Hora I, Albright A, Rolka D, Gregg EW. Resurgence of diabetes-related nontraumatic lower-extremity amputation in the young and middle-aged adult U.S. population. Diabetes Care 2019;42:50–54

10. Pecoraro RE, Reiber GE, Burgess EM. Pathways to diabetic limb amputation. Basis for prevention. Diabetes Care 1990;13:513–521

11. Boyko EJ, Monteiro-Soares M, Wheeler SGB. Peripheral arterial disease, foot ulcers, lower extremity amputations and diabetes. Chapter 20. In *Diabetes in America*. 3rd ed. Bethesda, MD, National Institutes of Health, 2017 (NIH publ. no. 17-1468)

12. Yue DK, McLennan S, Marsh M, et al. Effects of experimental diabetes, uremia, and malnutrition on wound healing. Diabetes 1987;36:295–299

13. Game FL, Chipchase SY, Hubbard R, Burden RP, Jeffcoate WJ. Temporal association between the incidence of foot ulceration and the start of dialysis in diabetes mellitus. Nephrol Dial Transplant 2006;21:3207–3210

14. Ndip A, Lavery LA, Lafontaine J, et al. High levels of foot ulceration and amputation risk in a multiracial cohort of diabetic patients on dialysis therapy. Diabetes Care 2010;33:878–880

15. Borkosky SL, Roukis TS. Incidence of re-amputation following partial first ray amputation associated with diabetes mellitus and peripheral sensory neuropathy: a systematic review. Diabet Foot Ankle 2012;3:1

16. Dossa CD, Shepard AD, Amos AM, et al. Results of lower extremity amputations in patients with end-stage renal disease. J Vasc Surg 1994;20:14–19

17. Fleming LW, Stewart CP, Henderson IS, Jain AS. Limb amputation on renal replacement therapy. Prosthet Orthot Int 2000;24:7–12

18. McGrath NM, Curran BA. Recent commencement of dialysis is a risk factor for lower-extremity amputation in a high-risk diabetic population. Diabetes Care 2000;23:432–433

19. Morbach S, Quante C, Ochs HR, Gaschler F, Pallast JM, Knevels U. Increased risk of lower-extremity amputation among Caucasian diabetic patients on dialysis. Diabetes Care 2001;24:1689–1690

20. Lavery LA, Hunt NA, Lafontaine J, Baxter CL, Ndip A, Boulton AJ. Diabetic foot prevention: a neglected opportunity in high-risk patients. Diabetes Care 2010;33:1460–1462

21. Lavery LA, Lavery DC, Hunt NA, La Fontaine J, Ndip A, Boulton AJ. Amputations and foot-related hospitalisations disproportionately affect dialysis patients. Int Wound J 2015;12:523–526