Trends of non-traumatic lower extremity amputation in end-stage renal disease and diabetes, United States, 2000-2015

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

Division of Diabetes Translation, Centers for Disease Control and Prevention (CDC), Atlanta, United Sates

Corresponding author: Dr Jessica L Harding, Centers for Disease Control, 4770 Buford Hwy NE MS F75, Atlanta, GA 30341 USA

Phone: +1 404 498 5458

Email: jharding@cdc.gov

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Abstract

Objective

Non-traumatic lower extremity amputation (NLEA) is a complication of end-stage renal disease (ESRD) and diabetes. While recent data show that NLEA rates in the overall 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, gender and race-adjusted NLEA rates were stratified by diabetes status, age, gender, race, and level of amputation (toe, foot, below the knee, 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 1.12; 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.

Introduction

In 2016, 124,675 persons in the United States (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 1980 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, are associated with an increased risk for non-traumatic 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).

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 to those having either condition alone [4]. In the United States, 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 gender, 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. did not explore NLEA rates among people with and without diabetes by key demographic subgroups such as age, gender 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, gender, and race), and examining multiple trends within the 16-year time period.

Methods

Study design and population

The US 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 and 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 first 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, gender or race; if first ESRD treatment was a transplant; renal transplant or death event occurred prior to January 1st 2000; 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.

Non-traumatic lower extremity amputation (NLEA) hospitalizations

NLEA hospitalizations were ascertained from CMS data from 1 January 2000 through 31 December 2015. The year 2000 was chosen as the first 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 International Classification of Diseases, Ninth Revision, Clinical Modification (ICD-9-CM) procedure codes from January 2000 through September 2015, and ICD-10-CM from October-December 2015, excluding disease codes for

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traumatic amputation, **eTable 1**. To prevent overestimation of NLEA rates due to planned multi-step 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 ankle (BKA), above the ankle (AKA) and minor and major, **eTable 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 healthcare 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's χ^2 test for proportions, and Student's t-test for means from approximately normal distributions and Wilcoxon's rank sum test for skewed data.

Annual NLEA hospitalization rates, per 100 person-years, were estimated using Stata version 14.1 (StataCorp, College Station, Texas, USA). 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 standard errors estimated using the Delta method. All models were adjusted for age, gender, 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 analyse 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, ≥75 years of age), gender, race (White, Black, other (Native American, Asian, other/multi-racial), and level of amputation (toe, foot, below (BKA), above the knee (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 body mass index (BMI), lower serum creatinine, lower low-density lipoproteins (LDL), lower haemoglobin 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. C**ompared 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 body mass index (BMI) and serum albumin, lower serum creatinine, and more likely to have 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, 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.

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 and 2013 and then increased non-significantly between 2013-2015 (APC: 8.9 (-2.1, 21.1), p=0.11); and 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 (APC: 3.8 (2.4, 5.1), p<0.001), no change was seen in those aged 45-64, and declines were observed in those aged 65-74 and 75+ between 2000 and 2013, followed by no change. By gender, 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.

Discussion

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 gender and among white adults with and without diabetes. . Third, though

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 sub-groups within the diabetes and non-diabetes 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 reported a 43% reduction in NLEA rates between 2000 and 2009 (from 5.4 to 3.1 per 1,000 persons, 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 persons, 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 general diabetes and non-diabetes populations, 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 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 co-morbidities among the ESRD population, poor survival rates following NLEA have been reported in several studies (4, 16-19). In a study of U.S. Medicare ESRD beneficiaries, cumulative survival at one-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 United States are unclear, though several hypotheses exist. First, a flattening of hospitalization rates of minor NLEA may suggest changes in clinical practice that favour 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, **eTable 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 NLEAs. However, when we compared characteristics of those initiating ESRD in 2000 vs 2010 findings were mixed. While 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, while 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 foot wear 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 sub-groups such as younger adults without diabetes and Whites.

Although we use a large, national database of individuals with ESRD linked to hospitalization records, some limitations should be considered. We use 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 use 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 three 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 observe 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 United States. 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.

Contribution Statement

JLH conducted the analyses, interpretation the results and wrote the manuscript. MEP and EWG contributed to interpretation and reviewed the manuscript. NRB conceptualised the manuscript and contributed to interpretation and reviewed the manuscript.

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Table 1 Descriptive characteristics of the end-stage renal disease (ESRD) population, with and without diabetes, at time of ESRD treatment initiation

	Diabetes	No Diabetes	P-value*
Demographics			
N	934,472	1,123,166	
Gender (women)	46.8	42.3	<0.001
Age (mean, 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			
Fulltime	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			
Body mass index (kg/m^2)	29.9 (7.9)	27.1 (7.3)	<0.001
Serum creatinine (mg/dL)[1]	6.0 (2.3)	6.5 (2.6)	<0.001
Low-density lipoprotein (mg/dL)	89.1 (59.1)	90.8 (57.1)	<0.001
Haemoglobin (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
Chronic obstructive pulmonary disease	8.0	9.1	<0.001
Cancer	4.1	8.9	<0.001
Disability[2]	8.2	7.0	<0.001

Data are % for categorical variables and mean (standard deviation) for continuous variables. Data on clinical measurements and comorbidities were complete for more than 80% of the population and demographic data was 100% complete.

[1]Due to outliers, we defined the mean (SD) of serum creatinine among the central 0.95 of the population, creatinine defined as >=0.6 and <=13.7 ; [2]Disability defined as needing assistance in activities of daily living

*p-value for difference between diabetes and non-diabetes populations

Table 2 Descriptive characteristics of the end-stage renal disease (ESRD) population at time of ESRD treatment initiation*

	Year of ESRD treatment initiation		
	2000	**2005**	**2010**
Demographics			
N	92,866	105,289	114,506
Gender (women)	46.6	44.5	43.0
Age (mean, years)	62.8 (15.5)	63.3 (15.4)	63.5 (15.1)
Employment			
Fulltime	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			
Body mass index	27.1 (7.1)	28.3 (7.7)	29.5 (8.0)
Serum creatinine (mg/dL)[1]	6.8 (2.5)	6.2 (2.4)	5.8 (2.4)
Haemoglobin (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
Chronic obstruction pulmonary disease	7.4	9.3	9.6
Cancer	5.6	9.7	7.7

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

Table 3 Hospitalization rates of total, minor and major non-traumatic lower extremity amputation (NLEA) and annual percent change (APC) among the end-stage renal disease (ESRD) population, by diabetes status, 2000-2015

	NLEA rate (per 100 person-years) (95%CI)					
	Diabetes			No Diabetes		
Year	Total NLEA	Minor NLEA	Major NLEA	Total NLEA	Minor NLEA	Major NLEA
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						
Year	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						
Year	2013-2015	2012-2015	2013-2015	2013-2015	2013-2015	n/a
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; n/a: second trend not identified

Table 4 Hospitalization rates for *any* non-traumatic lower extremity amputation (NLEA) in people with end-stage renal disease (ESRD), by diabetes status, and annual percent change (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								
18-44	5.0 (4.4-5.5)	4.2 (3.9-4.5)	2000-2015	-1.8 (-2.4, -1.3)	<0.001	n/a		
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	n/a		
Other	5.4 (5.0-5.9)	2.8 (2.6-3.1)	2000-2015	-5.3 (-5.9, -4.7)	<0.001	n/a		
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
Below knee	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
Above knee	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								
18-44	0.2 (0.1-0.3)	0.4 (0.3-0.4)	2000-2015	3.8 (2.4, 5.1)	<0.001	n/a		
45-64	1.0 (0.9-1.1)	1.2 (1.1-1.2)	2000-2015	0.0 (-0.5, 0.6)	0.994	n/a		
65-74	2.4 (2.2-2.6)	1.8 (1.7-1.9)	2000-2015	-2.8 (-3.4, -2.1)	<0.001	n/a		
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	n/a		
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	n/a		
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	n/a		
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
Below knee	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
Above knee	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; n/a: no second trend identified