Foot Ulcer and Risk of Lower Limb Amputation or Death in People With Diabetes: A National Population-Based Retrospective Cohort Study

Rosemary C. Chamberlain,[1] Kelly Fleetwood,[2] Sarah H. Wild,[3] Helen M. Colhoun,[4] Robert S. Lindsay,[5] John R. Petrie,[6] Rory J. McCrimmon,[7] Fraser Gibb,[8] Sam Philip,[9] Naveed Sattar,[10] Brian Kennon,[11] and Graham P. Leese[12]

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OBJECTIVE

To describe incidence of foot ulceration and amputation-free survival associated with foot ulceration status in a national population-based cohort study of people with diabetes.

RESEARCH DESIGN AND METHODS

The study population included 233,459 people with diabetes who were alive in Scotland on 1 January 2012 identified from the national population-based register (national prevalence 4.9%). Characteristics of patients identified from linked hospital and mortality records during follow-up to the end of November 2017 were compared by outcome. Cox regression was used to assess the association between history of foot ulcer and amputation-free survival.

RESULTS

The population included 23,395 people with type 1 diabetes and 210,064 people with type 2 diabetes. In total there were 13,093 (5.6%) people who had a previous foot ulceration, 9,023 people who developed a first ulcer, 48,995 who died, and 2,866 who underwent minor or major amputation during follow-up. Overall incidence of first-time foot ulcers was 7.8 per 1,000 person-years (95% CI7.6–7.9) and 11.2 (11.0–11.4) for any ulcer. Risk factors for reduced amputation-free survival included social deprivation, mental illness, and being underweight in addition to conventional cardiovascular risk factors. Adjusted hazard ratios (95% CI) were 2.09 (1.89–2.31) for type 1 diabetes and 1.65 (1.60–1.70) for type 2 diabetes.

CONCLUSIONS

The overall incidence of foot ulceration in a population-based study of people with diabetes was 11.2 per 1,000 person-years. Foot ulceration is associated with lower amputation-free survival rate, a potential measure of effectiveness of care among people with diabetes. Mental illness and social deprivation are also highlighted as risk factors.

Almost half of all lower limb amputations in the U.K. are associated with diabetes (1). In people with diabetes, lower limb amputations are preceded by foot ulcers in

[1]Department of Diabetes and Endocrinology, Ninewells Hospital, Dundee, U.K.
[2]Usher Institute, University of Edinburgh, Edinburgh, U.K.
[3]Usher Institute, University of Edinburgh, Edinburgh, U.K.
[4]Institute of Genetics and Cancer, University of Edinburgh, Edinburgh, U.K.
[5]Institute of Cardiovascular and Medical Sciences, University of Glasgow, Glasgow, U.K.
[6]Institute of Cardiovascular and Medical Sciences, BHF Glasgow Cardiovascular Research Centre, University of Glasgow, Glasgow, U.K.
[7]School of Medicine, University of Dundee, Dundee, U.K.
[8]Edinburgh Centre for Endocrinology and Diabetes, Royal Infirmary of Edinburgh, Edinburgh, U.K.
[9]Diabetes Centre, Aberdeen Royal Infirmary, Aberdeen, U.K.
[10]Institute of Cardiovascular and Medical Sciences, University of Glasgow, Glasgow, U.K.
[11]Diabetes Centre, New Victoria Hospital, Glasgow, U.K.
[12]Department of Diabetes and Endocrinology, Ninewells Hospital, Dundee, U.K.

Corresponding author: Graham P. Leese, graham.leese2@nhs.scot

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~85% of cases (2). Care for people who have foot ulcers and amputations requires the input of complex multidisciplinary teams, and diabetes-related amputations are the most costly complication of diabetes (3). It is thus important to understand the epidemiology of diabetes-related foot ulceration and amputations to enable accurate planning and appropriate resource allocation.

The annual incidence of any lower limb amputation was previously reported to be between 1 and 4.5 per 1,000 people with diabetes (1,4–8). The ratio of minor to major amputation has increased from 1 (4) to >2 (7,8) with time, which may reflect declining rates of major amputation. The incidence of major amputation declined in Finland from 0.9 to 0.5 (9), Belgium from 0.4 to 0.3 (7), Germany from 0.8 to 0.6 (8), and Scotland from 1.9 to 1.1 (4), with all amputations declining in the U.S. from 11.2 to 3.9, per 1,000 person-years (5). However, although decreasing rates of amputation may reflect improved care, they may also reflect delayed presentation and early death in patients with foot ulceration or ischemia (1,2). Thus "amputation-free survival" for patients with foot ulcers has been suggested as a useful outcome measure.

It is difficult to collect high-quality epidemiological data on unbiased populations with diabetic foot ulcers. This is because the management of diabetes-related foot ulcers can take place in a large number of different community and hospital locations. To collect data from all these settings can be challenging, but to recruit from only a few of these may result in bias.

Both ulcer-specific and person-level factors influence outcomes for patients with a diabetes-related foot ulcer. In a recent review by the International Working Group on the Diabetic Foot, the main ulcer and foot-related criteria that predict poor healing of diabetes-related foot ulcers included ulcers that are large in area, deep, multiple, infected, or located at the mid-foot or heel, in addition to loss of protective foot sensation (10). The main patient-level predictors of poor healing were reported as age, diabetes duration, male sex, renal failure, peripheral vascular disease (PVD), and prior history of ulcer/amputation (10–14). More recently, social deprivation (15,16) and depression (17) have been identified as risk factors for poor outcomes in people with diabetes and foot disease.

Using population-based data, with identification of people with diabetes and foot ulcers treated in community and hospital settings, we previously reported outcomes of people in Scotland at high risk of foot ulceration over a 2-year follow-up (18). In this analysis we describe foot ulcer incidence and the association of foot ulcer history and a wide variety of person-level variables with lower limb amputation or death over a longer period of follow-up.

RESEARCH DESIGN AND METHODS

Data Sources

In this study we used data from the Scottish Care information – Diabetes (SCI-Diabetes) data that were extracted in 2017. SCI-Diabetes is a disease-specific electronic patient record covering >99% of all people with a diagnosis of diabetes in Scotland (19). It integrates demographic, clinical, biochemical, and prescription data from primary and secondary care health care information systems, downloaded daily. This data set was linked to Scottish data regarding hospital admissions (SMR01, general/acute inpatient and day case, and SMR04, mental health inpatient and day case), death records, and the Scottish Renal Registry. SMR01 and SMR04 data cover hospital discharges from 1981 onward. ICD-9 codes were used to define diagnoses for discharges up to March 1996 and ICD-10 from April 1996 to present. Office of Population Censuses and Survey (OPCS) Classification of Interventions and Procedures version 3 (OPCS-3) codes were used to record operations with discharges up to 1988 and OPCS-4 (version 4) from 1989 to present. All ICD/OPCS codes used in this study can be found in Supplementary Table 1. Data were linked with use of the unique patient identifier used for all health records in Scotland by the electronic Data Research and Innovation Service (eDRIS) of Public Health Scotland. Approval for creation and analysis of the linked data set was obtained from the Scotland A multicenter research ethics committee and the Public Benefit and Privacy Panel of National Health Service Scotland.

Cohort Derivation

Patients were eligible for inclusion in this study if they were recorded as being diagnosed with type 1 or 2 diabetes before 1 January 2012, alive on this date, and resident in Scotland; if their records had no known data-linkage errors; and if they had data available on all covariates of interest. The study population comprised 233,459 people, who were followed up to 30 November 2017, the most recent date for which linked data were available (Supplementary Fig. 1).

Covariate Definitions

Diabetes type was assigned through an algorithm that combines clinician recording and insulin/sulfonylurea prescription data, as described previously (20). Area-based socioeconomic status was assigned with use of the 2012 Scottish Index of Multiple Deprivation (SIMD) at the residential address. The SIMD is an area-level index combining indicators of income, education, employment, health, access to services, housing, and crime.

History of ischemic heart disease (IHD), stroke, PVD, and end-stage renal disease were identified with hospital records of diagnoses and relevant operations. (See Supplementary Table 1.) A dialysis record in the Scottish Renal Registry was also used as an indicator of history of end-stage renal disease. A history of mental illness was defined as having a mental health inpatient or day case admission before 1 January 2012 or a minimum of 90 days' prescription of drugs in British National Formulary (BNF) sections 4.2 (drugs for psychosis) or 4.3 (antidepressants), with restriction of section 4.3.1 (tricyclic antidepressants) prescriptions to those at a daily dose >50 mg because lower doses are more usually used for neuropathy than for depression.

SCI-Diabetes data were used to determine smoking status, BMI, systolic blood pressure, glycated hemoglobin (HbA_{1c}), and cholesterol. Data from the time point closest to 1 January 2012 were used, with a 2-year maximum interval imposed for all apart from smoking status, for which no maximum interval was defined. "Never smokers" were reclassified as "ex-smokers" if >15% of prior recordings were "current" or "ex-smoker." BMI was classified as follows: underweight, <18.5 kg/m^2; normal weight, ≥18.5 and <25 kg/m^2; overweight, ≥25

and <30 kg/m^2; and obese, ≥30 kg/m^2. HbA_{1c} was categorized into three groups: <7.5% (58 mmol/mol), 7.5–9.0% (58–75 mmol/mol), and >9.0% (75 mmol/mol), reflecting national audit data categories. Prescribing data were also used to identify prescribing of antihypertensives in BNF section 2.5.5 (ACE inhibitors, angiotensin receptor blocker blockers, and renin inhibitors), lipid-lowering therapies from BNF section 2.12, and insulin from BNF sections 6.1.1.1 and 6.1.1.2. Only prescriptions for ≥90 days were included. In the analyses, high blood pressure was defined as systolic blood pressure ≥140 mmHg or antihypertensive prescription and high cholesterol as total cholesterol >5 mmol/L or prescription of lipid-lowering drugs.

Incidence of Foot Ulcers

Diabetes-related foot ulcers were identified with use of both hospital admission (SMR01) and SCI-Diabetes data. Annual foot examinations are recorded in SCI-Diabetes, including records of foot ulcer status (active, previous, or none). A history of diabetes-related foot ulcer at baseline was defined as any record of active or previous diabetes-related foot ulcer in SCI-Diabetes from 1 January 2004 (start of national SCI-Diabetes coverage) to 31 December 2011 inclusive or any hospital admission with a diagnosis indicating diabetes-related foot ulcer up to 31 December 2011. A new foot ulcer after baseline was defined as a new record between 1 January 2012 and 30 November 2017 inclusive. These dates were chosen to allow sufficient time for follow-up alongside a reasonable length of time prior to baseline to reliably identify people with previous ulcers.

Lower Limb Amputation and Death

History of prior amputation at baseline was identified with use of SCI-Diabetes and hospital admission records. Amputations during the follow-up period were identified on the basis of hospital admissions only, as more data were available on the level of amputation from hospital records than from SCI-Diabetes. Amputation below the ankle was defined as minor and above the ankle was defined as major. Where minor and major amputations were recorded within a single hospital admission, only the major amputation was counted. Traumatic amputation and amputations prior to diagnosis of diabetes were excluded. Deaths and date of death were identified from linked Scottish death records.

Analysis Methods

Descriptive Tables

We compared the distribution of baseline variables between people in the study population who underwent amputation or died during follow-up and those who survived to the end of follow-up without having an amputation using χ^2 tests.

Time-to-Event Analysis

The outcomes of interest were incidence of ulcers during follow-up and lower limb amputation (major or minor) and death. Kaplan-Meier curves were plotted to show the probability of amputation-free survival across the follow-up period in the groups with and without history of foot ulcer at baseline.

Cox regression models were used to compare the hazards of amputation/death between the groups by foot ulcer status. Time to event was defined as the time from 1 January 2012 to the earliest date of first amputation (major or minor) in the follow-up period, or date of death, with censoring at the end of the study period (30 November 2017). A univariable model for history of foot ulcer was fitted first, followed by multivariable models to adjust incrementally for further variables. The first multivariable model included adjustment for demographic data such as age, sex, socioeconomic deprivation (as measured by quintiles of SIMD 2012), and diabetes duration (as categorized in Table 2). The second included further adjustment for prebaseline amputation history and the

Table 1—Numbers of ulcers, lower limb amputations, and deaths among study population with diabetes in Scotland by foot ulcer history at 1 January 2012 and type of diabetes

	No history of ulcer	History of ulcer
Type 1 diabetes		
N	21,290	2,105
Foot ulcer during follow-up	998	826
Final outcomes* (% of all amputations and deaths)		
Amputation or death	1,736	770
Death	1,569 (90.4)	615 (79.9)
Amputation (any)	224 (12.9)	261(33.9)
Major amputation	110 (6.3)	145 (18.8)
Minor amputation	137 7.9)	156 (20.3)
Type 2 diabetes		
N	199,076	10,988
Foot ulcer during follow-up	8,025	3,669
Final outcomes* (% of all amputations and deaths)		
Amputation or death	42,478	5,712
Death	41,606 (97.9)	5,205 (91.1)
Amputation (any)	1,414 (3.3)	967 (16.9)
Major amputation	748 (1.8)	538 (9.4)
Minor amputation	831 (2.0)	579 (10.1)

$P < 0.001$ for all comparisons by ulcer history. *Some patients had minor and major amputations. Some patients had amputations and then died. Thus, the sum of the percentages is >100%.

Table 2—Characteristics of study population with diabetes in Scotland in 2012 by outcome of amputation or death during follow-up to 2017 and by type of diabetes

	Type 1 diabetes		Type 2 diabetes	
	Amputation-free survival (N = 20,889)	Amputation or death (N = 2,506)	Amputation-free survival (N = 161,874)	Amputation or death (N = 48,190)
Sex				
Female	9,241 (90.3)	994 (9.7)	71,629 (76.5)	21,992 (23.5)
Male	11,648 (88.5)	1,512 (11.5)	90,245 (77.5)	26,198 (22.5)
Age, years				
<55	16,237 (94.6)	919 (5.4)	38,701 (94.9)	2,071 (5.1)
≥55 and <65	2,905 (85.0)	513 (15.0)	46,772 (89.0)	5,793 (11.0)
≥65 and <75	1,317 (69.4)	580 (30.6)	48,209 (78.5)	13,202 (21.5)
≥75	430 (46.5)	494 (53.5)	28,192 (51.0)	27,124 (49.0)
Diabetes duration, years				
<5	3,133 (91.8)	280 (8.2)	69,394 (84.6)	12,663 (15.4)
≥5 and <10	3,212 (93.0)	240 (7.0)	50,460 (77.8)	14,389 (22.2)
≥10	14,544 (88.0)	1,986 (12.0)	42,020 (66.5)	21,138 (33.5)
SIMD 2012 quintile				
Quintile 1 (most deprived)	4,312 (86.4)	677 (13.6)	37,862 (75.3)	12,435 (24.7)
Quintile 2	4,264 (87.4)	613 (12.6)	36,993 (76.5)	11,390 (23.5)
Quintile 3	4,383 (89.8)	496 (10.2)	32,825 (77.5)	9,510 (22.5)
Quintile 4	4,011 (90.7)	413 (9.3)	29,436 (77.6)	8,498 (22.4)
Quintile 5	3,919 (92.7)	307 (7.3)	24,758 (79.6)	6,357 (20.4)
End-stage renal failure				
No	20,767 (89.8)	2,352 (10.2)	161,253 (77.3)	47,408 (22.7)
Yes	122 (44.2)	154 (55.8)	621 (44.3)	782 (55.7)
IHD history				
No	19,738 (91.8)	1,758 (8.2)	132,493 (81.2)	30,626 (18.8)
Yes	1,151 (60.6)	748 (39.4)	29,381 (62.6)	17,564 (37.4)
Stroke history				
No	20,638 (89.9)	2,331 (10.1)	157,048 (78.2)	43,877 (21.8)
Yes	251 (58.9)	175 (41.1)	4,826 (52.8)	4,313 (47.2)
PVD history				
No	20,573 (90.7)	2,119 (9.3)	158,203 (78.4)	43,696 (21.6)
Yes	316 (45.0)	387 (55.0)	3,671 (45.0)	4,494 (55.0)
History of foot ulcer at baseline				
No	19,554 (91.8)	1,736 (8.2)	156,598 (78.7)	42,478 (21.3)
Yes	1,335 (63.4)	770 (36.6)	5,276 (48.0)	5,712 (52.0)
Smoking status				
Never smoked	10,515 (93.7)	706 (6.3)	62,908 (81.8)	13,955 (18.2)
Ex-smoker	5,519 (84.7)	998 (15.3)	69,835 (73.6)	24,987 (26.4)
Current smoker	4,855 (85.8)	802 (14.2)	29,131 (75.9)	9,248 (24.1)
BMI category				
Underweight	436 (83.5)	86 (16.5)	361 (28.7)	895 (71.3)
Normal	7,452 (89.5)	873 (10.5)	16,300 (60.3)	10,719 (39.7)
Overweight	7,792 (90.7)	802 (9.3)	50,345 (75.5)	16,372 (24.5)
Obese	5,209 (87.5)	745 (12.5)	94,868 (82.4)	20,204 (17.6)
HbA_{1c}				
<7.5% (58 mmol/mol)	3,766 (88.5)	490 (11.5)	95,707 (76.0)	30,189 (24.0)
7.5–9.0% (58–75 mmol/mol)	8,839 (90.9)	881 (9.1)	41,764 (79.3)	10,886 (20.7)
>9.0% (75 mmol/mol)	8,284 (87.9)	1,135 (12.1)	24,403 (77.4)	7,115 (22.6)
High blood pressure				
No	11,352 (95.6)	522 (4.4)	40,375 (83.9)	7,742 (16.1)
Yes	9,537 (82.8)	1,984 (17.2)	121,499 (75.0)	40,448 (25.0)
High cholesterol				
No	11,301 (95.4)	544 (4.6)	30,423 (81.5)	6,920 (18.5)
Yes	9,588 (83.0)	1,962 (17.0)	131,451 (76.1)	41,270 (23.9)

Continued on p. 87

Table 2—Continued

	Type 1 diabetes		Type 2 diabetes	
	Amputation-free survival (N = 20,889)	Amputation or death (N = 2,506)	Amputation-free survival (N = 161,874)	Amputation or death (N = 48,190)
Insulin prescription				
No	n/a	n/a	146,131 (78.4)	40,228 (21.6)
Yes	n/a	n/a	15,743 (66.4)	7,962 (33.6)
Mental illness				
No	16,150 (91.0)	1,602 (9.0)	121,634 (77.6)	35,113 (22.4)
Yes	4,739 (84.0)	904 (16.0)	40,240 (75.5)	13,077 (24.5)
Previous amputation				
No	20,737 (90.1)	2,279 (9.9)	161,192 (77.4)	46,933 (22.6)
Yes	152 (40.1)	227 (59.9)	682 (35.2)	1,257 (64.8)

Data are *n* (%). Differences in criteria were all statistically significant ($P < 0.0001$) between those who survived without amputation and those who did not for both type 1 and type 2 diabetes. n/a, not applicable.

third included further adjustment for history of preexisting conditions, namely, stroke, IHD, PVD, end-stage renal failure, and mental illness, while the fourth included further adjustment for metabolic risk factors, namely, BMI, HbA_{1c}, insulin prescription (type 2 diabetes only), smoking, high blood pressure, and high cholesterol. In the fifth model we additionally included adjustment for the time-varying ulcer status during follow-up by allowing patients who were in the "no ulcer history" group at baseline to move into the ulcer history group at the time point at which their first ulcer was recorded. We assessed the proportional hazards assumption using plots of log(−log (amputation-free survival probability)) against time (Supplementary Fig. 2) and found no evidence of violation of the assumption.

All results were stratified by diabetes type because there was a statistically significant interaction between type of diabetes and history of foot ulcer in the fully adjusted multivariable model.

All analyses were conducted in R, version 3.6.0.

RESULTS

The study population of 233,459 people reflects 89.4% of 261,215 potentially eligible individuals after exclusion of 27,756 people with missing data for one or more covariate (Supplementary Fig. 1). During follow-up to 30 November 2017, 9,023 (4.1%) people with no foot ulcer at baseline developed new ulcers. Of people who had a foot ulcer prior to baseline, 4,495 (34.3%) developed a further foot ulcer during follow-up. The incidence of first-time foot ulcers was 7.8 per 1,000 person-years of follow-up (95% CI 7.6–7.9) and the rate of recurrent ulceration was 97 per 1,000 person-years (95% CI 94–99). For all patients there was an incidence of a new or recurrent ulcer of 11.2 per 1,000 person-years (95% CI 11.0–11.4).

The numbers of people with outcomes of interest by type of diabetes and foot ulcer history are shown in Table 1. In total, 50,696 people had 51,861 events. Overall, 21.7% of the cohort had an amputation or died during follow-up, with a higher proportion among people with a previous history of foot ulcer compared with those with no history of foot ulcer. For type 1 diabetes there were 2,506 (10.7% of the population) events, with 9.3% of patients dying and 2.1% undergoing an amputation. For type 2 diabetes there were 48,190 (22.9% of the population) events, with 22.3% dying and 1.1% undergoing an amputation (some died after an amputation).

For people without a history of foot ulcers, there were 44,214 (20.1% of the population) events, with 43,175 deaths (19.6%) and 1,638 amputations (0.7%). For people with a history of an ulcer, there were 6,482 events (49.5% of the population), with 5,820 deaths (44.5%) and 1,228 amputations (9.4%).

Among people with type 1 diabetes who reached an end point (amputation or death), 12.9% and 33.9% had an amputation for those with no history of an ulcer and those with a previous ulcer, respectively (Table 1). The proportions were similar between minor and major amputations. Proportions for type 2 diabetes were much lower, at 3.3% and 16.9% for those without and with previous foot ulcers. There was a similar equal split between minor and major amputations.

The characteristics of patients with type 1 and type 2 diabetes who had an amputation or died are compared with the characteristics of those with amputation-free survival in Table 2. The following baseline characteristics were associated with increased risk of death or amputation: male sex (type 1 diabetes only), increasing age, increasing duration of diabetes, end-stage renal failure, history of IHD, PVD, stroke, previous foot ulcer, history of amputation, and cardiovascular risk factors such as current/ex-smoker, hypertension, and high cholesterol. Differences in distributions of all of the above characteristics were statistically significant by outcome status ($P < 0.0001$). Social deprivation and mental illness were also associated with increased risk of death or amputation ($P < 0.0001$), especially in type 1 diabetes. For social deprivation the crude risks were 1.9-fold higher in the most compared with least deprived quintiles in type 1 diabetes and 1.2-fold higher in type 2 diabetes. The crude risk of death or amputation was 1.7-fold and 1.1-fold higher for those with mental illness and type 1 and type 2 diabetes respectively, compared with those without mental illness.

In the case of both type 1 and type 2 diabetes, low BMI was associated with death or amputation (Table 2). For both diabetes types there was an apparent

U-shaped association for HbA_{1c} and outcome.

Kaplan-Meier curves show the reduced probability of amputation-free survival among patients with a history of foot ulcer (Fig. 1) compared with people without a history of foot ulcer at baseline. Cox regression hazard ratios (HRs) for history of foot ulcer from univariable and multivariable models were higher for type 1 than type 2 diabetes and were attenuated by increasing adjustments but remained statistically significant (Table 3). Results stratified by sex did not show substantial differences from the overall findings (not shown).

CONCLUSIONS

During a potential duration of 6 years' follow-up, 21.7% of the whole study population died or had an amputation. Death was a more common outcome than amputation, both for people with and for people without a history of foot ulcer at baseline. Amputation or death occurred for approximately one in two of those with a prior foot ulcer and one in five with no previous foot ulcer. The univariable HR of amputation or death for those with a history of foot ulcer history at baseline was 5.43 (95% CI 4.98–5.91) for type 1 diabetes and 3.12 (95% CI 3.03–3.21) for type 2 diabetes. Overall, type 1 diabetes is a risk factor for adverse outcomes in people with a history of a foot ulcer. After adjustment for all variables such as diabetes duration, presence of macrovascular and microvascular disease, HbA_{1c}, and vascular risk factors, there remains a significant difference (Table 3). As expected, death and amputations were more common in those with existing vascular disease and end-stage kidney disease and also those with established cardiovascular risk factors, increased age, longer diabetes duration, and previous amputations. In addition, higher risk of death or amputation was associated with living in more socially deprived areas, mental illness, and being underweight (BMI <18.5 kg/m^2). Higher proportions of people with an HbA_{1c} $<7.5\%$ (58 mmol/mol) or $>9.0\%$ (75 mmol/mol) died or had an amputation compared with those in the mid-range (58–75 mmol/mol).

We previously reported 76% amputation-free survival after 2 years among people with diabetes who were at high risk of foot disease, defined as having multiple risk factors (e.g., neuropathy and vascular disease) or prior ulceration (18). In this analysis, for people with diabetes and a foot ulcer prior to baseline, 50% were free of amputation during a maximum of 5.9 years of follow-up (48% of those with type 2 diabetes and 63% of those with type 1 diabetes).

Overall survival during follow-up for those with a history of ulcer was at 56% (type 1 diabetes, 71%, and type 2 diabetes, 53%) in our cohort, which compares with 5-year survival at 56–78% in other studies (21–27). Higher proportions survived in studies that excluded people with prior ulcer or peripheral vascular disease (22) or first-time attenders at a foot clinic, which will exclude many people with recurrent ulcers (23).

People who have diabetes and a prior foot ulcer are reported to have a crude fourfold increased mortality at a median of 3.6 years' follow-up (28), a 2.5-fold increased risk at 5 years' follow-up (21), and a 1.5-fold increased risk at 10 years' follow-up (29) compared with patients with diabetes and no history of foot ulcer. Our findings of a crude 2.3-fold increased mortality rate during 5.9 years' follow-up for those with a prior foot ulcer compared with those without are consistent with previous estimates.

Our findings reaffirm that previous myocardial infarction, stroke, and PVD, in addition to chronic kidney disease, are associated with higher risks for death/amputation (10,21,24). In addition, we have demonstrated that social deprivation and mental illness are also associated with poor outcomes. This was particularly notable for type 1 diabetes. Social deprivation has been associated with the onset of foot ulceration (15,16,30). In one study of 1,147 people with type 2 diabetes, the risk of early mortality among those who developed foot ulceration increased by 14% per quintile of deprivation in univariable analysis (30). Factors mediating the effect of social deprivation may include reduced access to, and/or use of, health care resources, reduced health literacy, poorer nutrition, and housing. In other populations that are more racially diverse, race and racial inequality are also likely to contribute to adverse

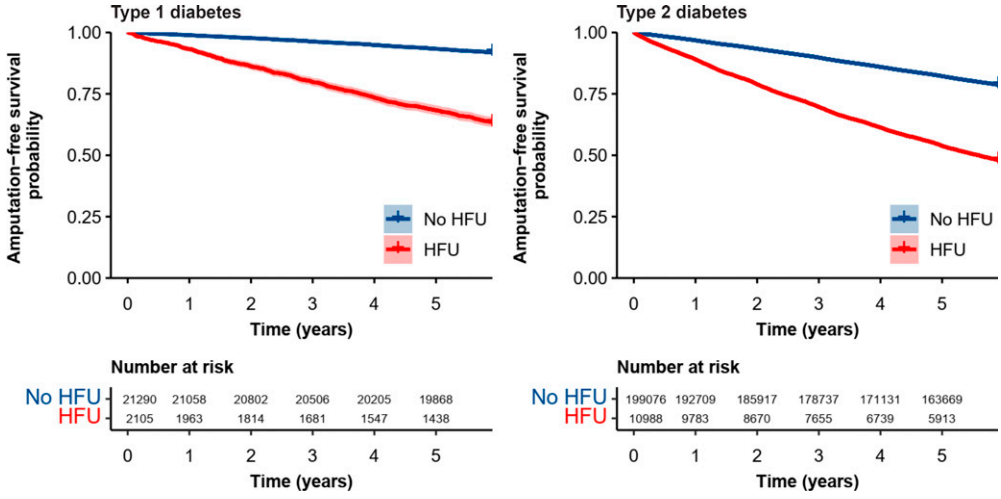

Figure 1—Kaplan-Meier curves for amputation-free survival by history of foot ulcer at baseline (HFU).

Table 3—Univariable and adjusted HRs (95% CI) for association of ulcer status with amputation or death by 2017 by diabetes type in study population with diabetes in Scotland in 2012

	Type 1 diabetes (n = 23,395)	Type 2 diabetes (n = 210,064)
Univariable	5.43 (4.98–5.91)	3.12 (3.03–3.21)
Multivariable model 1	3.06 (2.79–3.34)	2.13 (2.07–2.19)
Multivariable model 2	2.61 (2.36–2.88)	1.94 (1.88–2.00)
Multivariable model 3	2.19 (1.98–2.42)	1.71 (1.66–1.76)
Multivariable model 4	2.09 (1.89–2.31)	1.65 (1.60–1.70)
Multivariable model 5	3.39 (3.10–3.71)	2.42 (2.36–2.48)

Multivariable model 1, ulcer history, age, sex, social deprivation, diabetes duration (demographic data); multivariable model 2, previous amputation, in addition to model 2 covariates; multivariable model 3, history of stroke, IHD, PVD, end-stage renal failure, and mental illness, in addition to model 3 covariates (comorbidities); multivariable model 4, BMI, HbA_{1c}, smoking, high blood pressure, high cholesterol, and insulin use (type 2 diabetes only), in addition to model 4 covariates (clinical markers); multivariable model 5, time-varying ulcer status during follow-up in addition to model 4 covariates.

outcomes (31). A previous meta-analysis showed that depression was associated with a 1.7-fold increased risk of amputation (17) and increased risk of premature death after amputation in people with diabetes (32).

We identified an association of death or amputation and low BMI that was particularly marked for people with type 2 diabetes. Those with BMI $<$18.5 kg/m^2 had twice the risk of amputation/death compared with those with a normal BMI. This has been noted in previous studies (33) and was independent of factors such as chronic kidney disease or cardiovascular disease. Low BMI may be due to known or undiagnosed malignancy, and there is likely to be residual confounding from inaccurate measurement of smoking. However, it is also likely to reflect undernutrition and sarcopenia, which is a known risk factor for death in those who have had an amputation (34) and is a likely cause of foot ulceration (35) due to loss of foot plantar fat pads and muscle wasting.

An additional intriguing factor is the association of low HbA_{1c} (in addition to high HbA_{1c}) and adverse outcomes, which has also been previously been reported (21). Although shown to be an additional independent risk factor, low HbA_{1c} may partly be attributed to poor nutrition, malignancy, and frailty. Poor nutrition and/or frailty or coexisting disease can be associated with lower HbA_{1c} and increased risk of death and amputation, giving a possible element of reverse causality. However, the increased risk of amputation/mortality associated with foot ulcer remained evident after adjustment for HbA_{1c} and BMI, indicating that they do not fully explain the association.

We report overall incidence of any new or recurrent foot ulcer between 2012 and 2017 of 11.2 per 1,000 person-years. This rate is lower than the range of 2–6% for combined incident and recurrent ulcers (11,12,36–38) reported in publications $>$5 years ago. First-time foot ulcer incidence of $<$1% was reported recently (30). The estimated incidence of any ulcer derived from a large community Dutch study was 1.1% when the study population was limited to people whose foot status was known for certain (39). These larger population-based studies seem to report a lower incidence of ulceration than that among smaller selected populations (11,12,36–38). An alternative explanation for the discrepancy between these studies is that the incidence of foot ulceration may have decreased in European populations in the last 15–20 years. Despite a decreasing incidence, the increasing prevalence of diabetes, as a consequence of increasing survival (40), can be expected to result in larger absolute numbers of people with foot ulcers and increasing costs of treatment. Lifetime incidence of foot ulcers has been estimated to be ≥15% or more with use of a predefined formula (38). Using the same formula for our data results in a marginally lower rate of 11.5% (one in eight people).

Limitations of this study include the possibility of underestimating the number of people with foot ulcers in the cohort. This is likely to have resulted in underestimating differences between those recorded with ulcers and those without, especially in terms of the outcome of death or amputation. This may also have resulted in an underestimate of the population incidence of foot ulceration. Recording of some of the events of associated conditions (e.g., in Table 2) depended on an inpatient episode, and thus outpatient episodes may have been missed such as for people with transient ischemic attack or angina. This may have resulted in underdiagnosis of stroke, PVD, and IHD, but this is unlikely to have differed between those with and without baseline foot ulceration. Further limitations include lack of data on foot ulcer characteristics, anemia, or other biochemical data and the use of a single baseline measure of covariates, some of which may have changed during follow up, likely resulting in bias toward the null. Approximately 10% of the study population had missing data for one or more variables, with the largest proportions of missing data for baseline BMI, deprivation, and HbA_{1c}. Proportions of people who received an amputation or who died were similar in the group excluded for having missing data to those among the study population. However, the national scale of the data set is a major strength.

In conclusion, these national data with almost 6 years of follow-up demonstrated a strong association between a history of foot ulcer and amputation or death. In addition to standard risk factors, several variables including social deprivation, mental illness, low BMI, and low HbA_{1c} were associated with poor outcomes. Factors including social

deprivation, mental illness, and vascular risk factors need to be addressed in order to reduce premature mortality and amputations for people with diabetes and foot ulcers.

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