



# Temporal Trends in Incident Hospitalization for Diabetes-Related Foot Ulcer in Type 2 Diabetes: The Fremantle Diabetes Study

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*Diabetes Care* 2021;44:722–730 | <https://doi.org/10.2337/dc20-1743>

## OBJECTIVE

To determine whether, reflecting trends in other chronic complications, incident hospitalization for diabetes-related foot ulcer (DFU) has declined over recent decades in type 2 diabetes.

## RESEARCH DESIGN AND METHODS

Participants with type 2 diabetes from the community-based Fremantle Diabetes Study phases I (FDS1; 1,296 participants, mean age 64.0 years, 48.6% males, recruited 1993–1996) and II (FDS2; 1,509 participants, mean age 65.4 years, 51.8% males, recruited 2008–2011) were followed from entry to first hospitalization for/with DFU, death, or 5 years (whichever came first). Incident rate ratios (IRRs) and incident rate differences (IRDs) were calculated for FDS2 versus FDS1 overall and in 10-year age-groups. Cox proportional hazards modeling determined independent predictors of first DFU hospitalization in the combined cohort.

## RESULTS

Incident DFU hospitalization (95% CI) was 1.9 (0.9–3.3)/1,000 person-years in FDS1 during 5,879 person-years of follow-up and 4.5 (3.0–6.4)/1,000 person-years in FDS2 during 6,915 person-years of follow-up. The crude IRR (95% CI) was 2.40 (1.17–5.28) ( $P = 0.013$ ) and IRD 2.6 (0.7–4.5)/1,000 person-years ( $P = 0.010$ ). The highest IR for any age-group was 23.6/1,000 person-years in FDS2 participants aged 31–40 years. Age at diabetes diagnosis (inverse), HbA<sub>1c</sub>, insulin use, height, ln(urinary albumin/creatinine), absence of any foot pulse, previous peripheral revascularization, and peripheral sensory neuropathy (PSN) were independent predictors of incident hospitalization for/with DFU.

## CONCLUSIONS

Incident DFU hospitalizations complicating type 2 diabetes increased between FDS phases, especially in younger participants, and were more likely in those with PSN, peripheral arterial disease, and suboptimal glycemic control at baseline.

Diabetes-related foot ulcer (DFU) is a common and costly complication of diabetes that is associated with infection, amputation, and premature death (1). The 5-year mortality and direct costs of care of DFU appear comparable to those of all-cause cancer (2), and ~85% of nontraumatic lower-extremity amputations (LEA) are preceded by foot ulceration (3). While there is evidence that the incidence of

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Received 12 July 2020 and accepted 14 December 2020

This article contains supplementary material online at <https://doi.org/10.2337/figshare.13377134>.

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LEA in people with diabetes has recently been increasing in the U.S., epidemiologic data from many other countries suggest that the incidence has decreased over the last few decades, a change driven mainly by fewer major amputations since the incidence of minor and recurrent amputations has remained stable or increased (4–10). This may reflect increased awareness and improved multidisciplinary management of DFU as well as changes in surgical management. It is unclear if the reduction in LEA in most countries is also a consequence of a contemporaneous reduction in DFUs.

The reported prevalence of DFU in developed countries has varied widely from 1.5% to 10% (11), but data relating to temporal trends are sparse. We have previously reported a relatively low baseline prevalence of DFU of 1.2% in a representative, community-based sample of people with type 2 diabetes assessed at baseline in the Fremantle Diabetes Study phase I (FDS1), which was largely unchanged 15 years later at 1.5% in FDS phase II (FDS2) conducted in the same geographic area (12). The reported incidence of DFU also varies considerably, from 0.6%/year to 7.2%/year (1,11,13–15), but there are few data describing temporal changes in incidence.

People with DFU can be managed across a diverse range of clinical settings, with varying risk factors, comorbidities, and stage of disease at first presentation. These factors, as well as a lack of consistency in definitions and methodology, complicate ascertainment and contribute to the marked variations in reporting of local prevalence and incidence of DFU (11,16,17). Hospitalization for/with DFU captures those patients with predominantly moderate to severe acute presentations of DFU and provides a relatively reliable metric for incident DFU in this situation. The aims of the current study were, therefore, to determine if there was a change in 5-year DFU hospitalization incident rates (IRs) in people with type 2 diabetes and no prior DFU over the 15-year period separating FDS1 and FDS2 and, if there was a significant change, to characterize the underlying contributing factors.

## RESEARCH DESIGN AND METHODS

### Study Site, Participants, and Approvals

The FDS is an observational, longitudinal study of known diabetes conducted in a zip code-defined geographical area surrounding

the port city of Fremantle in the state of Western Australia (WA) (18,19). There were ~120,000 people residing in the catchment area at the start of FDS1 in 1993 and 157,000 when FDS2 recruitment began in 2008. Socioeconomic data from this area at the time of FDS2 recruitment showed an average Index of Relative Socio-Economic Advantage and Disadvantage (20) of 1,033 with a range by zip code of 977–1,113, figures comparable to the Australian national mean  $\pm$  SD of  $1,000 \pm 100$ .

The recruitment period for FDS1 was between 1993 and 1996, with follow-up of diabetes complications and mortality data in the present substudy to end-2013. The FDS2 used the same design as FDS1 (19), with recruitment between 2008 and 2011 and follow-up to end-2016. Participants in both phases were identified from hospital, clinic, and primary care patient lists, widespread advertising through local media, pharmacies, optometrists, networks of health care professionals, and, in the case of FDS2, third-party mailouts to registrants of the Australian National Diabetes Services Scheme and the National Diabetes Register (19). Details of recruitment, sample characteristics including classification of diabetes types, and nonrecruited individuals with diabetes in the catchment area (who were of similar age, sex, and diabetes type to those who were recruited) have been published (18,19). The FDS1 was approved by the Fremantle Hospital Human Rights Committee (Perth, Western Australia, Australia) and the FDS2 by the Human Research Ethics Committee of the Southern Metropolitan Area Health Service (East Perth, WA, Australia). All participants gave written informed consent. In FDS1, 2,258 people with diabetes were identified from a population of ~120,000, 1,426 (63%) were recruited, and 1,296 (91%) had clinically defined type 2 diabetes. In FDS2, 4,639 people with diabetes were identified from a population of ~157,000, 1,668 (36%) were recruited, and 1,509 (90%) had clinically defined type 2 diabetes.

### Baseline and Follow-up Assessments

In both FDS phases, assessment at entry and at each annual (FDS1) or second yearly (FDS2) face-to-face review included a comprehensive questionnaire, physical examination, and fasting biochemical tests performed in a single nationally accredited

laboratory (18). In addition to details of all medical conditions, demographic, socioeconomic, and lifestyle data were collected. Patients were requested to bring all medications to each visit, and full details were recorded. In FDS2, comprehensive postal questionnaires were sent to participants in the years between face-to-face assessments.

Complications were identified using standard definitions (21), including albuminuria assessed by early morning spot urinary albumin-to-creatinine ratio (uACR) measurement and renal impairment from the estimated glomerular filtration rate (eGFR) (22). A general foot inspection was performed to detect the presence or absence of DFU located at or below the level of the malleoli, deformity, corns/callus, fissures, infections, and nail pathology. Peripheral sensory neuropathy (PSN) was defined using the clinical portion of the Michigan Neuropathy Screening Instrument (23). Patients were classified as having prevalent coronary heart disease if there was a history of myocardial infarction, angina, coronary artery bypass grafting, or angioplasty and as having prevalent cerebrovascular disease if there was a history of stroke and/or transient ischemic attack. Peripheral arterial disease (PAD) was defined as an ankle brachial index  $\leq 0.90$  or the presence of a diabetes-related LEA.

### Ascertainment of 5-Year Incident DFU Hospitalization

Participants in both phases were followed to the first recorded hospitalization for/with DFU, death, or 5 years, whichever came first. The Hospital Morbidity Data Collection (HMDC) contains information regarding all public/private hospitalizations in WA since 1970, and the Death Register contains information on all deaths in WA (24). Both FDS phases have been linked through the WA Data Linkage System to these databases, as approved by the WA Department of Health Human Research Ethics Committee, to provide validated data on incident events to end-2017 for FDS1 and end-2016 for FDS2. Relevant ICD-9-CM (440.23 and 707.1 for lower-extremity ulcer) and ICD-10-AM diagnosis codes (L97 and I70.23 for lower-extremity ulcer and E10.73, E11.73, E13.73, and E14.73 for foot ulcer) were used to identify incident DFU hospitalization in the HMDC. Chart review was performed in

available cases (all of those in the public sector) with ICD-10-AM codes L97 and I70.23, and, since ICD-9-CM codes did not include a specific diagnosis code for DFU, those with codes 440.23 and 707.1 also had confirmation of the diagnosis via chart review. The HMDC was also used to supplement data obtained through FDS assessments relating to prevalent/prior disease.

### Statistical Analysis

The computer packages SPSS Statistics 25 (IBM Corporation, Armonk, NY) and StataSE 15 (StataCorp LP, College Station, TX) were used for statistical analysis. Data are presented as proportions, mean  $\pm$  SD, geometric mean (SD range), or, in the case of variables that did not conform to a normal or log-normal distribution, median (interquartile range). Two-sample comparisons were by Fisher exact test for proportions, Student *t* test for normally distributed variables, and Mann-Whitney *U* test for other variables. Five-year IRs for incident DFU hospitalization were derived for each FDS phase. IR ratios (IRRs) and IR differences (IRDs) were then calculated for those in FDS2 versus FDS1. Ten-year age-specific IRs of incident DFU hospitalization from 31 to 90 years of age were compared for FDS2 versus FDS1 with IRRs and IRDs calculated.

For the pooled FDS1 and FDS2 type 2 diabetes cohorts, some variables of interest were missing for up to 2.4% of participants. Missing covariates were multiply imputed ( $\times 20$ ) (7). Cox proportional hazards modeling was used to determine independent predictors of incident DFU hospitalization during follow-up from clinically plausible baseline variables with  $P < 0.20$  in bivariable analyses. Fine and Gray modeling was also conducted to assess the influence of the competing risk of death (25). To assess the effect of FDS phase, participation in FDS2 versus FDS1 was then added to the most parsimonious Cox and Fine and Gray models. Results for the pooled FDS1 and FDS2 cohorts only are reported for imputed data. The proportional hazards assumption was checked for each model using Schoenfeld global tests both overall and separately for each covariate.

## RESULTS

### Participant Characteristics

The baseline characteristics of participants in the two FDS phases categorized

by 5-year incident hospitalization for/with DFU in those without a prior history of, or prevalent, DFU at entry are summarized in Table 1. Compared with the equivalent group in FDS1, FDS2 participants who experienced incident hospitalization for/with DFU during the 5-year follow-up had a younger age at diabetes diagnosis, higher alcohol consumption, a more extensive smoking history, worse glycemic control, and higher rates of PSN and PAD, and they were more likely to be Indigenous.

### Incident DFU Hospitalization by FDS Phase

The FDS1 cohort comprised 1,296 participants with type 2 diabetes whose mean  $\pm$  SD age was 64.0  $\pm$  11.3 years at study entry, 48.6% were males, and median (interquartile range) diabetes duration was 4.0 (1.0–9.0) years. Excluding the 21 (1.6%) who had a DFU before or at study entry, during 5,879 person-years of follow-up (mean  $\pm$  SD 4.6  $\pm$  1.1 years) to incident DFU hospitalization or death or 5 years, whichever came first, 11 (0.9%) had an incident DFU hospitalization, an IR (95% CI) of 1.9 (0.9–3.3)/1,000 person-years. In the FDS2 cohort (mean age 65.4  $\pm$  11.7 years at study entry, 51.8% males, and median diabetes duration 8.0 [2.7–15.4] years) and after excluding the 43 (2.8%) who had a DFU before or at study entry, 31 (2.1%) had an incident DFU hospitalization during 6,915 person-years (4.7  $\pm$  0.9 years) of follow-up, an IR of 4.5 (3.0–6.4)/1,000 person-years.

The crude IRR (95% CI) for incident DFU hospitalization in FDS2 versus FDS1 was 2.40 (1.17–5.28) ( $P = 0.013$ ) and the crude IRD 2.6 (0.7–4.5)/1,000 person-years ( $P = 0.010$ ). The 10-year age-specific and overall IRs, IRRs, and IRDs for the FDS2 versus FDS1 type 2 diabetes cohorts for incident DFU hospitalization from 31 to 90 years of age are shown in Fig. 1. There was no incident DFU hospitalization in any FDS1 participant aged  $<61$  years compared with 11 (35.5%) in FDS2 ( $P = 0.041$ ), with the highest IR (23.6 [2.9–85.1]/1,000 person-years) in the 31–40-year-old age-group. In FDS1, 1 person (9.1%) with incident DFU hospitalization was aged  $<50$  years at diabetes diagnosis compared with 19 (61.3%) in FDS2 ( $P = 0.004$ ).

In the pooled FDS1 and FDS2 type 2 diabetes cohorts (mean  $\pm$  SD age 64.8  $\pm$

11.5 years, 50.3% males, and 64 [2.3%] with a prior history of or current DFU at study entry), the significant bivariable associates of incident DFU hospitalization in those without a history of, or prevalent, DFU included demographic and anthropometric factors (male sex, Australian Aboriginal background, and height), lifestyle choices (alcohol consumption and smoking), diabetes-specific variables (younger age at diagnosis, longer duration, and more intensive blood glucose-lowering treatment but worse glycemic control, including more frequent hypoglycemia), hypertension and its treatment, and a range of complications and comorbidities (albuminuria and lower eGFR, heart failure, cerebrovascular disease and PAD, LEA, atrial fibrillation, and PSN) (Table 2).

The most parsimonious Cox model of time to incident DFU hospitalization comprised age at diabetes diagnosis (inverse), HbA<sub>1c</sub>, insulin use, height, ln(uACR), absence of any foot pulse, PSN, and a history of peripheral revascularization/bypass (Table 3). FDS phase was added to this model, and the effect of participation in FDS2 versus FDS1 on risk of incident DFU hospitalization was of borderline statistical significance (HR [95% CI] 2.15 [0.98–4.70];  $P = 0.056$ ) (Table 3). The age at incident DFU hospitalization was not significantly different by phase (68.5 [54.7–77.3] years in FDS2 vs. 71.5 [68.8–79.5] years in FDS1;  $P = 0.16$ ), but the age range was greater in FDS2 than FDS1 (31–85 years old in FDS2 vs. 64–84 years in FDS1). Schoenfeld global tests showed that the proportional hazards assumption was met for these Cox regression models ( $P > 0.20$ ). The most parsimonious Fine and Gray model of independent predictors of hospital admission for/with DFU with age as the timeline had the same variables, except HbA<sub>1c</sub> was no longer significant (Supplementary Table 1).

## CONCLUSIONS

The current study shows that incident hospitalization for/with DFU has increased in the 15 years between FDS phases conducted in a representative Australian urban setting. Multivariable analysis suggests that this increase has been driven largely by changes in established DFU risk factors, including glycemic control, PSN, PAD, and diabetic nephropathy. In addition, there was a strong inverse association with age at diagnosis of diabetes and incident DFU

**Table 1—Characteristics of participants with type 2 diabetes from the two FDS phases separately categorized by 5-year incident hospitalization for/with first DFU**

	FDS1			FDS2		
	No incident hospitalization for/with DFU	Incident hospitalization for/with DFU	<i>P</i> value	No incident hospitalization for/with DFU	Incident hospitalization for/with DFU	<i>P</i> value
Number (%)	1,264 (99.1)	11 (0.9)		1,435 (97.9)	31 (2.1)	
Time from start of phase to participant entry (years)	1.2 ± 0.8	0.8 ± 0.9	0.122	1.6 ± 0.9	1.9 ± 0.9	0.025
Age at FDS entry (years)	64.0 ± 11.3	70.4 ± 5.7	0.004	65.6 ± 11.5	61.7 ± 15.4	0.097
Sex (% male)	48.4	63.6	0.374	51.4	74.2	0.017
Ethnic background (%)			0.336			0.009
Anglo-Celt	61.6	45.5		52.8	54.8	
Southern European	17.6	36.4		13.0	0	
Other European	8.2	18.2		7.4	6.5	
Asian	3.5	0		4.3	6.5	
Indigenous Australian	1.4	0		6.3	19.4	
Mixed/other	7.7	0		16.1	9.7	
Not fluent in English (%)	15.1	36.4	0.073	10.9	3.2	0.243
Education beyond primary level (%)	74.0	81.8	0.738	86.8	89.7	>0.999
Currently married/de facto (%)	66.0	54.5	0.525	63.6	51.6	0.189
Alcohol (standard drinks [equivalent to 10 units]/day)	0 [0–0.7]	0 [0–1.5]	0.996	0.1 [0–1.2]	0.8 [0–1.9]	0.006
Smoking status (%)			0.706			0.004
Never	45.1	36.4		45.9	22.6	
Ex	39.9	54.5		44.0	51.6	
Current	15.0	9.1		10.2	25.8	
Age at diagnosis (years)	57.9 ± 11.7	59.2 ± 7.7	0.698	55.9 ± 12.1	43.8 ± 15.7	<0.001
Duration of diabetes (years)	4.0 [1.0–9.0]	10.0 [3.0–19.0]	0.025	8.0 [2.3–15.2]	16.8 [10.0–25.0]	<0.001
Diabetes treatment (%):			0.006			<0.001
Diet	32.6	9.1		25.6	3.2	
Oral agents	55.8	45.5		54.1	32.3	
Insulin with or without oral agents	11.6	45.5		20.3	64.5	
Fasting serum glucose [mmol/L]	8.0 [6.5–10.2]	9.1 [5.7–11.8]	0.499	7.2 [6.2–8.8]	8.7 [6.2–12.5]	0.013
HbA <sub>1c</sub> [%]	7.2 [6.2–8.5]	7.3 [6.7–12.1]	0.420	6.8 [6.2–7.7]	7.9 [6.7–10.3]	<0.001
HbA <sub>1c</sub> [mmol/mol]	55 [44–69]	56 [50–109]	0.420	51 [44–61]	63 [50–89]	<0.001
Self-reported hypoglycemia in the previous year (%)	23.0	18.2	>0.999	33.0	54.8	0.019
Height (m)	1.65 ± 0.10	1.66 ± 0.10	0.591	1.66 ± 0.10	1.68 ± 0.11	0.181
BMI (kg/m <sup>2</sup> )	29.6 ± 5.4	30.3 ± 5.2	0.647	31.3 ± 6.2	31.2 ± 5.2	0.973
Pulse rate (bpm)	70 ± 12	72 ± 12	0.498	70 ± 12	77 ± 16	0.003
Systolic blood pressure (mmHg)	151 ± 24	160 ± 24	0.202	145 ± 22	154 ± 34	0.090
Diastolic blood pressure (mmHg)	80 ± 11	81 ± 15	0.756	80 ± 12	83 ± 16	0.257
Antihypertensive medication (%)	50.2	72.7	0.225	73.0	80.6	0.417
Serum total cholesterol (mmol/L)	5.5 ± 1.1	5.5 ± 1.4	0.922	4.3 ± 1.1	4.6 ± 1.6	0.293
Serum HDL-cholesterol (mmol/L)	1.06 ± 0.32	0.96 ± 0.40	0.279	1.24 ± 0.34	1.21 ± 0.33	0.605
Serum triglycerides (mmol/L)	2.2 (1.2–3.9)	2.3 (1.4–3.9)	0.710	1.5 (0.9–2.5)	1.8 (1.0–3.3)	0.041
Lipid-modifying medication (%)	10.8	0	0.619	68.0	67.7	>0.999
Aspirin use (%)	21.8	27.3	0.713	37.1	32.3	0.708
uACR (mg/mmol)	5.1 (1.5–17.4)	24.3 (6.2–95.5)	<0.001	3.1 (0.8–11.7)	12.5 (1.8–89.2)	<0.001

*Continued on p. 726*

Table 1—Continued

	FDS1			FDS2		
	No incident hospitalization for/with DFU	Incident hospitalization for/with DFU	P value	No incident hospitalization for/with DFU	Incident hospitalization for/with DFU	P value
eGFR categories (%)			0.004			<0.001
≥90 mL/min/1.73 m <sup>2</sup>	33.0	0		39.4	32.3	
60–89 mL/min/1.73 m <sup>2</sup>	49.6	45.5		45.2	29.0	
45–59 mL/min/1.73 m <sup>2</sup>	11.7	36.4		8.5	6.5	
<45 mL/min/1.73 m <sup>2</sup>	5.8	18.2		6.9	32.3	
Atrial fibrillation (%)	4.6	9.1	0.409	4.3	12.9	0.047
Hospitalization for/with heart failure (%)	8.0	18.2	0.221	5.8	19.4	0.009
Hospitalization for/with myocardial infarction (%)	8.7	0	0.613	7.6	19.4	0.030
Ischemic heart disease (%)	29.2	36.4	0.740	28.3	32.3	0.687
Hospitalization for/with stroke (%)	0.4	0	>0.999	2.8	3.2	0.589
Cerebrovascular disease (%)	9.7	36.4	0.017	10.5	19.4	0.134
Hospitalization for LEA (%)	0.9	9.1	0.099	0.2	6.5	0.004
PAD (%)	28.7	45.5	0.313	21.6	29.0	0.377
Intermittent claudication (%)	12.7	27.3	0.157	8.5	22.6	0.015
Any posterior tibial or popliteal pulse absent (%)	39.4	54.5	0.399	14.4	51.6	<0.001
PSN (%)	29.6	55.6	0.137	56.7	87.1	0.001
Peripheral revascularization (%)	0.9	9.1	0.107	1.8	19.4	<0.001
ApoE genotype (%)			0.005			0.447
22	0.7	10.0		0.4	0	
23	11.6	30.0		11.3	6.5	
24	2.4	0		2.5	3.2	
33	65.5	60.0		65.0	58.1	
34	18.7	0		19.0	29.0	
44	1.3	0		1.8	3.2	

Data are %, mean ± SD, median [interquartile range], or geometric mean (SD range).

hospitalization in the pooled multivariable analysis. This observation is consistent with emerging data suggesting that type 2 diabetes in young people is associated with a more severe phenotype and relatively high rates of chronic complications (10,26,27) and aligns with data from the U.S. reporting a recent resurgence in both minor and major LEA in middle-aged and younger adults with diabetes (10).

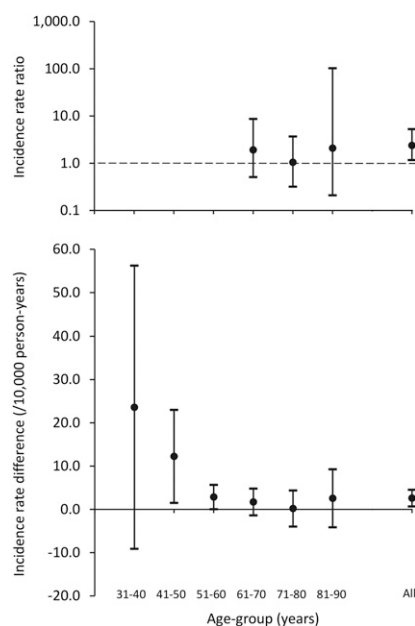
There are limited available data with which our findings can be compared. The published incidence of DFU varies widely from 0.6%/year to 7.2%/year (1,11,13–15,28), probably reflecting between-study differences in participant sources, definitions of DFU, and ascertainment. These reports include rates of 2.2%/year of any self-reported DFU in a community-based cohort of people with diabetes of any type from the U.K. (13) and 5.0%/year for screened or self-reported DFU in a cohort of largely male U.S. veterans with a history of diabetes

and no prior DFU (15). Since the DFU events in our study were first hospitalizations and thus likely at the more severe end of the spectrum, it is probably not surprising that rates in FDS1 (equivalent to 0.2%/year) and FDS2 (0.5%/year) were relatively low. Furthermore, those subjects with a prevalent DFU at their baseline FDS assessment were excluded from analysis.

A large retrospective cohort study conducted between 2005 and 2010 from the U.S. found no temporal change in the incidence of DFU hospitalizations (29), but the ratio of diabetes-related versus nondiabetes-related DFU admissions increased significantly, and those related to infection increased in people with but not without diabetes (29). By contrast, a large-scale study in the Australian state of Queensland, also conducted between 2005 and 2010, found a decline in all hospitalizations for diabetes-related foot disease as well as both major and minor LEA (9). The relatively short-term (5-year)

duration of follow-up in these two studies makes their comparison with the FDS phases difficult since the period spanned by the present analyses represented a total of 24 years. Furthermore, the Queensland study was conducted during a coordinated statewide Diabetic Foot Innovation Project aimed at reducing hospitalizations and amputations as a result of diabetes-related foot complications, while there has been no similar initiative in WA.

When entered as a simple binary variable, FDS phase was of borderline statistical significance in both the Cox and Fine and Gray models. This raises the possibility that the increased risk of incident hospitalization with DFU in the 15 years between FDS phases could, in part, reflect temporal changes in DFU awareness and management. After the present FDS1 follow-up and before FDS2 began, there was a push to develop multidisciplinary high-risk foot care in Australia (30) based on contemporaneous national



**Figure 1**—Ten-year age-specific IRRs and 95% CIs (top panel) and IRDs and 95% CIs (bottom panel) for DFU in participants with type 2 diabetes from the FDS2 vs. those from FDS1. No IRRs are shown for age-groups  $\leq 60$  years, as there were no FDS1 participants between 31 and 60 years of age who had an incident DFU hospitalization.

management guidelines, which have been updated since (31). In addition, government-subsidized General Practice Management Plans and Team Care Arrangements were established in 1999 with the aim of improving the outcome of chronic diseases such as diabetes in primary care, including ready access to regular podiatry reviews (32). These developments may have led to early identification and referral of people with DFUs as well as improved initial management by hospital-based specialists in FDS2 versus FDS1, thus increasing DFU hospitalization rates and contributing to lower rates of LEA at the same time. A detailed comparison of indications for, and management during, hospital admission for DFU in the two FDS phases was beyond the scope of the current study.

Although the age at incident DFU hospitalization was not significantly different by FDS phase, the age range was greater in FDS2 (31–85 years) than FDS1 (64–84 years). In addition, there were no incident DFUs in FDS1 participants aged  $<61$  years compared with 11 (35.5%) in FDS2, and the FDS2 participants aged 31–40 years exhibited the highest IR of any age-group at

**Table 2**—Characteristics of pooled participants with type 2 diabetes from the two FDS phases categorized by 5-year incident hospitalization for first DFU

	No DFU	DFU	P value
Number (%)	2,699 (98.5)	42 (1.5)	
FDS2 participants (%)	53.2	73.8	0.008
Time from start of phase to participant entry (years)	1.4 $\pm$ 0.9	1.2 $\pm$ 1.0	0.13
Age at FDS entry (years)	64.7 $\pm$ 11.5	65.0 $\pm$ 13.1	0.88
Sex (% male)	50.0	71.4	0.008
Ethnic background (%)			0.039
Anglo-Celt	56.9	52.4	
Southern European	15.2	9.5	
Other European	7.8	9.5	
Asian	3.9	7.1	
Indigenous Australian	4.0	14.3	
Mixed/other	12.2	7.1	
Not fluent in English (%)	12.9	11.9	$>0.99$
Education beyond primary level (%)	80.8	87.5	0.42
Currently married/de facto (%)	64.7	52.4	0.11
Alcohol (standard drinks [equivalent to 10 units]/day)	0.1 [0–0.8]	0.7 [0–1.6]	0.011
Smoking status (%)			0.022
Never	45.5	26.2	
Ex	42.0	52.4	
Current	12.4	21.4	
Age at diagnosis (years)	56.9 $\pm$ 11.9	48.2 $\pm$ 15.2	0.001
Duration of diabetes (years)	5.0 [1.6–12.1]	17.1 [10.0–22.8]	$<0.001$
Diabetes treatment (%)			$<0.001$
Diet	28.9	4.8	
Oral agents	54.9	35.7	
Insulin with or without oral agents	16.2	59.5	
Fasting serum glucose (mmol/L)	7.5 [6.2–9.5]	9.1 [7.0–12.9]	0.007
HbA <sub>1c</sub> (%)	7.0 [6.2–8.1]	7.9 [6.7–10.5]	0.001
HbA <sub>1c</sub> (mmol/mol)	53 [44–65]	63 [50–91]	0.001
Self-reported hypoglycemia in the previous year (%)	28.3	45.2	0.024
Height (m)	1.66 $\pm$ 0.10	1.70 $\pm$ 0.10	0.009
BMI (kg/m <sup>2</sup> )	30.5 $\pm$ 5.9	31.0 $\pm$ 5.6	0.56
Pulse rate (bpm)	70 $\pm$ 12	75 $\pm$ 16	0.053
Systolic blood pressure (mmHg)	148 $\pm$ 23	156 $\pm$ 28	0.024
Diastolic blood pressure (mmHg)	80 $\pm$ 12	83 $\pm$ 15	0.20
Antihypertensive medication (%)	62.3	78.6	0.036
Serum total cholesterol (mmol/L)	4.9 $\pm$ 1.2	4.9 $\pm$ 1.7	0.89
Serum HDL-cholesterol (mmol/L)	1.16 $\pm$ 0.34	1.14 $\pm$ 0.32	0.78
Serum triglycerides (mmol/L)	1.8 (1.0–3.2)	1.8 (1.0–3.1)	0.96
Lipid-modifying medication (%)	41.2	50.0	0.27
Aspirin use (%)	29.9	31.0	0.87
uACR (mg/mmol)	3.9 (1.1–14.1)	14.5 (2.2–97.5)	$<0.001$
eGFR categories (%)			$<0.001$
$\geq 90$ mL/min/1.73 m <sup>2</sup>	36.4	23.8	
60–89 mL/min/1.73 m <sup>2</sup>	47.2	33.3	
45–59 mL/min/1.73 m <sup>2</sup>	10.0	14.3	
30–44 mL/min/1.73 m <sup>2</sup>	4.3	14.3	
$<30$ mL/min/1.73 m <sup>2</sup>	2.0	14.3	
Atrial fibrillation (%)	4.4	11.9	0.040
Hospitalization for/with heart failure (%)	6.8	19.0	0.007
Hospitalization for/with myocardial infarction (%)	8.1	14.3	0.15
Ischemic heart disease (%)	28.7	33.3	0.50

Continued on p. 728

Table 2—Continued

	No DFU	DFU	P value
Hospitalization for/with stroke (%)	1.7	2.4	0.51
Cerebrovascular disease (%)	10.1	23.8	0.009
Hospitalization for LEA (%)	0.5	7.1	0.002
PAD (%)	24.9	33.3	0.21
Intermittent claudication (%)	10.5	23.8	0.011
Any posterior tibial or popliteal pulse absent (%)	26.3	53.7	<0.001
PSN (%)	44.3	80.0	<0.001
Foot ulcer present at baseline (%)	0	0	—
Prior hospitalization for foot ulcer (%)	0	0	—
Peripheral revascularization (%)	1.4	16.7	<0.001
ApoE genotype (%)			0.38
22	0.5	2.4	
23	11.4	12.2	
24	2.5	2.4	
33	65.2	58.5	
34	18.8	22.0	
44	1.5	2.4	

Data are %, mean  $\pm$  SD, median [interquartile range], or geometric mean (SD range).

23.6/1,000 person-years. This observation is consistent with evidence from other studies of adolescents and younger adults, suggesting that the relatively high rates of chronic complications in this group may be flattening the decline in people with type 2 diabetes as a whole (10).

Further indirect support for this observation of relevance to DFU comes from a clinic-based study of diabetes complications in adolescents, which found a similar rate of PSN, a major DFU risk factor, in type 1 (27%) versus type 2 diabetes (21%) but also that the median duration of diabetes was much shorter in the participants with type 2 diabetes (1.3 vs. 6.8 years in type 1 diabetes) (33). Furthermore, while there was an overall decrease in hospitalizations for diabetic foot disease and its complications, including LEA, in people from Queensland with diabetes studied

between 2005 and 2010, the only age-group to experience an increase in these outcomes was people aged <35 years (9). These and other relevant (10,26,27) findings, together with the present results, add weight to the suggestion that severe diabetes-related foot complications including DFU are increasing disproportionately in younger patients with type 2 diabetes. Possible reasons for this could include greater lifestyle-induced obesity and associated cardiovascular risk in millennials than in older people with type 2 diabetes, inappropriate spillover of less strict glycemic control strategies from older age-groups with the push for individualized targets, and perhaps greater adverse metabolic effects in younger individuals as a result of the economic recession that started in 2008–2009 (34). It is also possible that younger people at risk for, or with, DFUs spend

more time on their feet while working or during leisure activities than older individuals with type 2 diabetes.

Other baseline independent predictors of incident DFU hospitalization were HbA<sub>1c</sub>, insulin use, ln(uACR), height, PSN, absent foot pulse, and history of peripheral revascularization. These variables are predominantly established risk factors for DFU and largely reflect the findings of a recent large-scale meta-analysis that identified loss of protective sensation, at least one absent pedal pulse, and a past history of foot ulceration as the factors most predictive of risk of future DFU (35). A history of revascularization and absent foot pulses were among the strongest predictors of incident hospitalization with DFU in the Cox model, consistent with results from the U.K. National Diabetes Foot Care Audit, which found ischemia to have the strongest association with hospitalization for DFU, delayed DFU healing, and major LEA (36). The finding that PSN was a significant independent predictor in the present Cox model is consistent with previous findings from our group for prevalent DFU (12). The association with height, independently of PSN, for which height is a recognized risk factor (37), suggests that nonneuropathic factors such as changes in vascular pressure dynamics (38) and perhaps even the ability to implement foot self-care, including regular inspections, may be implicated in this association. A link between uACR and DFU has been reported previously (39).

The current study had limitations. Any study of incident DFU should be interpreted in the context of the population, numerator, denominator, definitions, and clinical setting (28). In the current

Table 3—Most parsimonious Cox model of independent predictors of hospital admission for/with DFU in the pooled FDS type 2 diabetes cohorts and the same model with FDS1 vs. FDS1 participation added

	csHR (95% CI)	P value	csHR (95% CI)	P value
Age at diabetes diagnosis (increase of year)	0.96 (0.94–0.99)	0.008	0.97 (0.94–0.997)	0.033
Insulin therapy	3.36 (1.74–6.48)	<0.001	2.98 (1.53–5.83)	0.001
HbA <sub>1c</sub> (increase of 1% or 11 mmol/mol)	1.19 (1.02–1.40)	0.031	1.23 (1.04–1.44)	0.014
ln(uACR) (mg/mmol)*	1.40 (1.17–1.67)	<0.001	1.42 (1.20–1.70)	<0.001
Height (increase of 1 cm)	1.04 (1.01–1.08)	0.008	1.04 (1.01–1.08)	0.010
History of peripheral revascularization	7.96 (3.28–19.30)	<0.001	6.58 (2.67–16.24)	<0.001
Any foot pulse absent	2.46 (1.28–4.71)	0.007	3.14 (1.56–6.31)	0.001
PSN	4.10 (1.87–8.97)	<0.001	3.38 (1.51–7.57)	0.003
FDS2 vs. FDS1 participation			2.15 (0.98–4.70)	0.056

csHR, cause-specific HR. \*A 2.72-fold increase in uACR corresponds to an increase of 1 in ln(uACR).



study, we used a community-based sample of people with type 2 diabetes from a representative Australian urban setting, but our end point of incident DFU hospitalizations meant that we did not capture less severe DFUs managed in the community or through hospital outpatient clinics. It is possible that DFU ICD coding practices changed between FDS phases, with improved detection of associated hospitalizations, but our chart reviews and the magnitude of the difference in incidence between FDS1 and FDS2 suggest that this would not, if present, have been a major confounding factor. Temporal changes in diabetes diagnostic criteria and local diabetes prevalence, as well as awareness of DFU management and its consequences, including referral patterns and thresholds for hospitalization, may have influenced our findings, but a detailed assessment of these factors was beyond the scope of our data collection and analyses. The strengths of the current study include its use of well-characterized community-based cohorts, long-duration follow-up, and validation of the majority of individual DFU hospitalizations.

In conclusion, FDS data collected over a long duration of follow-up have allowed identification of temporal trends in the incidence of hospitalization for DFU in community-based people with type 2 diabetes. Established DFU risk factors, including PSN, PAD, nephropathy, and poor glycemic control, were independent predictors of incident DFU hospitalization irrespective of FDS phase, but we cannot exclude a temporal change in management practices that could favor increased inpatient DFU care. The burden of DFU has started to shift to younger age-groups, and foot care education and preventive management strategies may need to be modified in response to this.

**Acknowledgments.** The authors thank the FDS staff, investigators, and participants, the staff at the Western Australian Data Linkage Branch, the Hospital Morbidity Data Collection, the Registry for Births, Deaths and Marriages, and National Coronial Information System.

**Funding.** Seeding funding for FDS1 was provided by the Raine Medical Research Foundation of the University of Western Australia, and FDS2 was funded by the National Health and Medical Research Council of Australia (project grants 513781 and 1042231). T.M.E.D. is supported by a Medical Research Future Fund Practitioner Fellowship. E.J.H. is supported by a Raine Clinician Research Fellowship.

The funding bodies had no involvement in the study design, data collection, analysis and interpretation of results, or writing of this manuscript.

**Duality of Interest.** No potential conflicts of interest relevant to this article were reported.

**Author Contributions.** E.J.H. coordinated the analysis and interpretation of data and produced the first draft of the manuscript. W.A.D., a co-investigator of the FDS, organized data linkage, performed all statistical analyses, and edited the manuscript. R.S., M.B., and P.E.N. assisted with data validation and edited the manuscript. T.M.E.D., the principal investigator of the FDS2, provided clinical interpretation and produced the final version of the manuscript. T.M.E.D. is the guarantor of this work and, as such, had full access to all the data in the study and takes responsibility for the integrity of the data and the accuracy of the data analysis.

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