Incidence, hospitalization and mortality and their changes over time in people with a first ever diabetic foot ulcer

Røikjer, Johan; Werkman, Nikki C C; Ejskjær, Niels ; van den Bergh, Joop P W; Vestergaard, Peter; Schaper, Nicolaas C. ; Jensen, Morten Hasselstrøm; Klungel, Olaf H; de Vries, Frank; Nielen, Johannes T H; Driessen, Johanna H M

Published in:
Diabetic Medicine

DOI (link to publication from Publisher):
10.1111/dme.14725

Publication date:
2022

Document Version
Accepted author manuscript, peer reviewed version

DR JOHAN RØIKJER (Orcid ID : 0000-0002-4578-1328)

Article type : Research Article

Title:

Incidence, hospitalization and mortality and their changes over time in people with a first ever diabetic foot ulcer

First author:

Johan Røikjer, MD

Steno Diabetes Center North Denmark, Aalborg University Hospital, Aalborg, Denmark

Department of Health Science and Technology, Aalborg University, Aalborg, Denmark

Co-authors:

Nikki C.C. Werkman, PharmD

Cardiovascular Research Institute Maastricht (CARIM), Maastricht, the Netherlands.
Department of Clinical Pharmacy and Toxicology, Maastricht University medical Centre+, Maastricht, the Netherlands.

Division of Pharmacoepidemiology & Clinical Pharmacology, Utrecht Institute for Pharmaceutical Sciences, Utrecht University, Utrecht, the Netherlands.

This article has been accepted for publication and undergone full peer review but has not been through the copyediting, typesetting, pagination and proofreading process, which may lead to differences between this version and the Version of Record. Please cite this article as doi: 10.1111/DME.14725

Niels Ejskjaer, MD, PhD

Steno Diabetes Center North Denmark, Aalborg University Hospital

Clinical Medicine and Endocrinology, Aalborg University Hospital

Joop P.W. van den Bergh, MD, PhD

Department of Internal Medicine, Maastricht University Medical Centre

Department of Internal Medicine, VieCuri Medical Centre

Biomedical Research Centre, Hasselt University

Peter Vestergaard, MD, PhD

Steno Diabetes Center North Denmark, Aalborg University Hospital

Clinical Medicine and Endocrinology, Aalborg University Hospital

Nicolaas C. Schaper, MD, PhD

Division of Endocrinology, Department of Internal Medicine, Maastricht University Medical Centre

Cardiovascular Research Institute Maastricht (CARIM), Maastricht, the Netherlands.

Morten Hasselstrøm Jensen, Ms.c, PhD

Steno Diabetes Center North Denmark, Aalborg University Hospital

Department of Health Science and Technology, Aalborg University

Olaf Klungel, PharmD, PhD

Division of Pharmacoepidemiology & Clinical Pharmacology, Utrecht Institute for Pharmaceutical Sciences, Utrecht University, Utrecht, The Netherlands.

Frank de Vries, PharmD, PhD

Division of Pharmacoepidemiology & Clinical Pharmacology, Utrecht Institute for Pharmaceutical Sciences, Utrecht University, Utrecht, The Netherlands.

Department of Clinical Pharmacy and Toxicology, Maastricht University medical Centre+, Maastricht, the Netherlands.

Cardiovascular Research Institute Maastricht (CARIM), Maastricht, the Netherlands.

Johannes T.H. Nielen, PharmD, PhD

Department of Clinical Pharmacy and Toxicology, Maastricht University medical Centre+, Maastricht, the Netherlands.

Johanna H.M. Driessen, PharmD, PhD
Cardiovascular Research Institute Maastricht (CARIM), Maastricht, the Netherlands.
NUTRIM School for Nutrition and Translational Research in Metabolism, Maastricht University Medical Center, Maastricht, the Netherlands.
Department of Clinical Pharmacy and Toxicology, Maastricht University medical Centre+, Maastricht, the Netherlands.

Division of Pharmacoepidemiology and Clinical Pharmacology, Utrecht Institute of Pharmaceutical Sciences, Utrecht, the Netherlands.

Corresponding author:

Frank de Vries, PharmD, PhD

Division of Pharmacoepidemiology & Clinical Pharmacology, Utrecht Institute for Pharmaceutical Sciences, Utrecht University, Utrecht, The Netherlands.

Address: Universiteitsweg 99, 3584CA Utrecht, The Netherlands

Mail: f.devries@uu.nl

Phone: +31 (0)30-2537324

Conflict of interests: FV supervises three PhD students who are employed with F. Hoffmann La Roche Ltd. (Basel, Switzerland and Welwyn Garden City, UK). He has not received any fees or reimbursements for this. The topics of their work are not related to the current manuscript.

Other authors declare no conflicts of interest.

Word Count (main text):

Word Count (abstract): 250

No. tables and figures: 5+6

Abstract (250/250 words)

Aims: A diabetic foot ulcer (DFU) is a severe condition associated with morbidity and mortality. Population-based studies are rare and limited by access to reliable data. Without this data, efforts in primary prevention cannot be evaluated. Therefore, we examined incidence and changes over time for the first DFU in people with diabetes. We also examined hospitalization and all-cause mortality and their changes over time. **Methods**: From the UK primary care CPRD GOLD database (2007-2017), we identified 129,624 people with diabetes by a prescription for insulin or a non-insulin anti-diabetic drug. DFUs were identified using Read codes and expressed as incidence rates (IRs). Changes over time were described using Poisson and logistic regression and expressed as incidence rate ratios (IRRs) and odds ratios (ORs), respectively. **Results**: The mean IR of first registered DFUs was 2.5 [95% CI: 2.1-2.9] per 1000 person-years for people with type 2 diabetes and 1.6 [1.3-1.9] per 1000 person-years for people with type 1. The IRs declined for people with type 2 diabetes (IRR per year: 0.97 [0.96-0.99]), while no changes were observed for people with type 1 diabetes (IRR per year: 0.96 [0.89-1.04]). Average hospitalization and 1-year mortality-risk for people with type 2 diabetes were 8.2% [SD: 4.7] and 11.7% [SD: 2.2] respectively. Both declined over time (OR: 0.89 [0.84, 0.94] and 0.94 [0.89, 0.99]). **Conclusion**: The decline in all IRs, hospitalizations and mortality in people with type 2 diabetes suggests that prevention and care of the first DFU has improved for this group in primary care in the UK.

Key words: diabetes mellitus, diabetic foot disease, diabetic foot ulcer, hospitalization, mortality

I. Introduction (324 words)

Diabetic foot ulcers (DFUs) are a severe complication associated with diabetes, a precursor for amputation, and a major cause of patient suffering and high healthcare costs[1,2]. While the continuous efforts of multidisciplinary foot clinics and preventive activities in primary care have reduced the incidence of major lower limb amputations in most countries, the prevention of DFUs remain a major challenge[3–5]. Over the years several risk factors associated with the development of a DFU have been discovered, but despite this, little is known about the factors leading directly to the first ever ulceration[6]. Therefore, the predictive power of even seasoned clinicians in our experience remains low, and combined with the poorly reported, but relatively low, incidence of first ever DFUs, the possibilities for primary prevention is extremely limited[7]. These challenges have led to recurrent DFUs being studied far more than the first ever DFUs, but despite continuous improvements in healing time and the need for total immobilization, the recurrence rate of a DFU is still roughly 40% within 1 year and 60% within 3 years[8]. Therefore, in recent years focus has shifted towards preventing the first ever DFU rather than just treating it, which in turn has led to an increased demand of robust numbers of incidence rate (IR) and their changes over time[9]. The primary aim of this study was to describe the IRs of first ever DFUs and their changes over time in people diagnosed with either type 1 or type 2 diabetes seen in primary care in the UK. An overview of these trends would help determine the effectiveness of the measures applied over the course of the study period, while also providing valuable new insights into an area where reliable data are extremely limited. Furthermore, as there is no new data available regarding hospitalization and mortality following a first ever DFU, these outcomes where also studied as secondary aims alongside characteristics describing the population at the time of the event.

II. Methods (1,134 words)

II.I Data Source

This population-based cohort study used data from the Clinical Practice Research Datalink (CPRD) GOLD (www.cprd.com) formerly known as the General Practice Research Database (GPRD)[10]. This register contains medical records of 674 primary care practices in the United Kingdom (UK), representing approximately 6.9% of the total population in 2013. The general practitioners supplying data to the register are clustered in London, the South, Greater Manchester

and in Birmingham, but the CPRD is still generally considered representative of the UK general population in terms of age, sex and ethnicity[10]. The data recorded in the CPRD includes demographics, medical history, laboratory test results, prescription details, specialist referrals, hospital admissions and major outcomes since 1987, with on-going data collection. In 2004, the British National Health Service introduced the Quality and Outcomes Framework (QOF) to reward general practices for providing good quality of care and registration. The QOF was updated for diabetes in 2006[11].

II.II Study population

To be included, the participants needed to have a record of a diagnosis of either type 1 diabetes or type 2 diabetes in addition to a prescription of either insulin or a non-insulin anti-diabetic drug (NIAD) from the start of the CPRD GOLD database (1987) and until end of study period (2017). As in our experience a record of a diagnosis of diabetes is not always robust in the database, we added the use of insulin/NIAD as a diagnostic criterion. To be included in our cohort, the diagnosis of diabetes needed to be registered before the start of treatment, which was defined as the inclusion date (baseline). When there was no record of a diagnosis, or when there was a record of both type 1 diabetes and type 2 diabetes, the participant was excluded. Moreover, if the first prescription was a NIAD and there was a diagnosis for type 1 diabetes, or if the first prescription was an insulin and there was a diagnosis for type 2 diabetes, the participant was also excluded. Finally, people with a history of a DFU, and people identified as having type 2 diabetes with an age below 30 at the inclusion date, were excluded. See *supplementary figure S1* for flowchart.

Although we included people with diabetes in the full duration of the database (1987-2017), we chose to only analyse our outcomes (DFU, hospitalization, mortality) from 2007 and onwards. This was done as the quality of the data was markedly improved due to the QOF update for diabetes in 2006. Consequently, some of the included people had a first diagnosis and an antidiabetic drug prescription between 1987 and 2007 and outcome analyses for these people all started from 2007. Other people, with a first diagnosis and an antidiabetic drug prescription after 2007, started outcome analyses after the antidiabetic drug prescription (inclusion date). In order to identify newly treated people with diabetes, they needed to have at least one year of valid data

collection before their diabetes diagnosis to be included in the study. We created two cohorts: one for people with type 1 diabetes and another for people with type 2 diabetes.

II.III Outcome

The primary outcome was the average yearly IR of first registered DFU in people with type 1 and type 2 diabetes and its changes over time. DFUs were identified using Read codes in either clinical- or referral files. The secondary outcomes were hospitalization-risk in relation to the first registered DFU, identified using Read codes in the referral files, and all-cause mortality-risk following the first registered DFU (*see supplementary table S1*). A Read code is a clinical code that has been used in UK primary care for coding medical events[12]. Moreover, we analysed changes of the aforementioned variables over time.

II.IV Characteristics

Data on sex, age, body mass index (BMI), smoking status and history of diabetes related complications (neuropathy, retinopathy, nephropathy and Charcot neuroarthropathy) were collected at the inclusion date. In the people who developed an ulcer we also collected the most recent data on sex, age, BMI, smoking status, glycated haemoglobin (HbA1c) serum level and history of diabetes related complications on the date of the DFU. Nephropathy was identified by presence of a Read code for nephropathy, a history of an albumin to creatinine ratio of ≥ 30 mg/g or a history of a creatinine-based estimated glomerular filtration rate (eGFR) <60 mL/min/1.73m^2. In addition to the above-mentioned covariates, diabetes duration was determined as the time between the inclusion date (date of first prescription of insulin or a NIAD) and the date of the first registered DFU.

II.V Statistical analysis

For the outcomes DFUs and hospitalization for a foot ulcer, we followed the participants from their inclusion date until the date of the first outcome of interest (first registered DFU or hospitalization for the first registered DFU), death or the end of data collection, whichever came

first. The IRs in each calendar year were calculated as the sum of events (either first registered DFU or hospitalization for the first registered DFU) in that year divided by the total person-time at risk in that given calendar year and expressed as the number of events per 1,000 person-years. Changes over time in the IRs were described using Poisson regression and expressed as an incidence rate ratio per year (IRR)[13]. We also calculated the proportion of DFUs requiring hospitalization by dividing the number of people with a first registered DFU record in the referral file in each calendar year by the total number of people with a first registered DFU in the same year. Changes over time in the proportion of participants hospitalized in relation to their first registered DFU were described using logistic regression and expressed as odds ratios (ORs)[13].

For the outcome all-cause mortality, we used the date of the first registered DFU, and then followed people from this date until either date of death or end of data collection, which ever came first. The mortality rates (MRs) in each calendar year were calculated as the total number of people who died in that year divided by the total person-time at risk in that given calendar year and expressed as the number of events per 1,000 person-years. Changes over time in MRs were described using Poisson regression and expressed as an IRR[13]. Furthermore, we calculated 1- and 5-year mortality-risks by dividing the number of people deceased within 1 or 5 year after their first registered DFU over the total number of people at risk. 1-year mortality risk was calculated for people having their first registered DFU between 2007 and 2016, while the 5-year mortality-risk was calculated for people having their first registered DFU between 2007 and 2012. Changes over time in the proportion of deceased people were described using logistic regression and expressed as ORs[13].

All analyses were performed using SAS 9.4 (SAS Institute, Cary, NC). Graphs were drawn in Microsoft Excel 2013 (build 15.0.5215.100) based on data outputs from SAS. The study protocol was scientifically approved by the independent scientific advisory committee of the Medicines and Healthcare product Regulatory Agency (MHRA) as ISAC protocol No: 19_027A. The MHRA has received ethics approval to receive and supply CPRD data for public health research.

III. Results (536 words)

III.I Demographics

The characteristics of the participants at baseline (the date of the first NIAD or insulin prescription) are depicted by diabetes type and future DFU status in Table 1 (*see supplementary table S4 for characteristics of the population at the start of outcome analysis in 2007*). At baseline, people with type 1 diabetes, who did not develop a DFU, had a mean age of 26.1 years and a mean BMI of 23.5 kg/m^2 with retinopathy as the most common complication (2.9%), while people with type 1 diabetes, who did develop a DFU, had a mean age of 41.2 years with a mean BMI of 25.6 kg/m^2 and retinopathy as the most common complication (6.3%). Those with type 2 diabetes, who did not develop a DFU, had a mean age of 62.8 years, a mean BMI of 31.8 kg/m^2 and nephropathy as the most common complication (31.1%). Those with type 2 diabetes, who did develop a DFU had a mean age of 64.5 years, a mean BMI of 31.3 kg/m^2 and nephropathy as the most common complication (30.2%). Neuropathy as recorded by general practitioners was rare in all groups (0.0-1.9%). The characteristics for those who developed a DFU are depicted at the time of ulceration in table 2.

III.II Incidence

Between 2007 and 2017 the yearly IR of first registered DFU varied from 1.0 [95% Confidence Interval (CI): 0.4, 2.6] to 2.4 [95% CI: 1.3, 4.7] per 1,000 person-years for people with type 1 diabetes. For people with type 2 diabetes these numbers varied from 1.4 [95% CI: 1.2, 1.7] to 3.6 [95% CI: 3.2, 4.1] per 1,000 person-years. This was equivalent to a mean IR of 1.6 [95% CI: 1.3, 1.9] per 1,000 person-years for people with type 1 diabetes and a mean IR of 2.5 [95% CI: 2.1, 2.9] per 1,000 person-years for people with type 2 diabetes over the course of the study period (Figure 1). Furthermore, we did not observe a change in IRs over time for people with type 1 diabetes (IRR: 0.96 [0.89, 1.04]), while the IRs decreased for people with type 2 diabetes (IRR: 0.97 [95% CI: 0.96, 0.99]).

(*Figure 1*)

III.III Hospitalization

Between 2007 and 2017 the average proportion of people with type 2 diabetes hospitalized with their first registered DFU was 8.2% [SD: 4.8] out of the total population with a first ever DFU that year.

As shown in Figure 2 this proportion decreased over time (OR per year: 0.89 [95% CI: 0.84, 0.94]). The IRs (calculated as number people hospitalized with a DFU divided over person-time at risk) are reported in Supplementary table S2. These analyses were only performed on people with type 2 diabetes due to a limited number of events in people with type 1 diabetes.

(*Figure 2*)

III.IV Mortality

Between 2007 and 2017 the average 1-year mortality-risk for people with type 2 diabetes and a first registered DFU was 11.7% [SD: 2.2], while the mean 5-year mortality-risk was 33.1% [SD: 3.5]. As shown in Figure 3 the 1-year mortality risk did change over time (OR per year 0.96 [0.89, 0.99]). The IRs for 1-year mortality are reported in Supplementary table S3. The aforementioned analyses on mortality were only performed in people with type 2 diabetes due to a limited number of events in people with type 1 diabetes.

(Figure 3)

IV. Discussion (1,628 words)

In this study, we found that the IRs of a first ever DFU among people with diabetes in UK primary care varied from 1.0 per 1,000 person-years to 3.6 per 1,000 person-years from 2007 through 2017. This resulted in an average IR of 2.5 per 1,000 person-years in people with type 2 diabetes and 1.6 per 1,000 person-years in people with type 1 diabetes. We also observed a decline in the incidence rate of first ever DFUs over time for people with type 2 diabetes, while there was no change for people with type 1 diabetes. Only a few recent studies are available for comparison and to the best of our knowledge our study is the first to report on general primary care. Among the most recent is a UK study in people at high risk for DFU using a regional community podiatry database from South Devon. In this study, following people between 2003 and 2017, a substantial

decline in development of a first-time DFU was reported, with IRs falling from 11.1 to 6.1 events per 1,000 person-years over the course of the study period[14]. While the decline reported in our study is less pronounced than what was found here, both studies seem to agree on a positive trend with declining incidence rates. The differential event rates are probably related to the marked difference in risk for foot ulceration between a specialized podiatry clinic and general practice. Comparable data is also available from a regional diabetes foot care study among 9,710 people with either type 1 or type 2 diabetes from North-west England (1994-1996). This study showed an average cumulative annual incidence rate of DFUs of 2.2%, and did not provide IRs[15]. Also, it is not completely clear whether this study distinguished between first ever and recurrent DFUs.

Data on DFUs in people with diabetes is also available from a primary care setting in The Netherlands[16] and in Germany[17]. In the Netherlands, a prevalence of 1.8% was reported in a primary care setting in 1997, while the prevalence in Germany in 2008 was 0.8% in both people with type 1 and type 2 diabetes. However, these numbers are not directly comparable with our results, as these are prevalence numbers and do not distinguish between first ever and recurrent DFUs.. In a recent meta-analysis on the global prevalence of foot ulceration in people with diabetes, the prevalence of DFUs was 13.0% in North America, 5.5% in Asia, 5.1% in Europe and 3.0% in Oceania[18]. The same meta-analysis concluded that foot ulcers are more frequent in males than in females, and that foot ulcers are more prevalent in people with type 2 diabetes than in people with type 1 diabetes. It also showed that people suffering from DFUs appear to be older, have a longer diabetes duration, more often hypertension, retinopathy and a history of smoking compared to those not having a DFU. Although not directly tested, these findings appear to be consistent with data from our study, although nephropathy emerged as the most common diabetes complication at the time of a first registered DFU. Surprisingly, neuropathy was only reported in about one out of ten people with a first registered DFU, which is not in line with numbers reported elsewhere[19]. These results are probably the result of inadequate sensory testing and reporting in UK primary care compared to the examinations performed at hospitals or specialized units.

We also found that approximately 8.2% of people with a first ever DFU were hospitalized between 2007 and 2017; furthermore, we observed a decline over time. According to the NICE-guidelines from 2015, people with a relatively uncomplicated DFU should be referred to a multidisciplinary foot team within 24 hours[20]. Although the full guideline was not published until 2015, where a small decline in direct hospitalization is seen (Figure 2*)*, some parts of the original thoughts were

already revealed in 2011, in parallel with the larger decline in the proportion of hospitalized people with type 2 diabetes between 2010 and 2011. It seems plausible, that increased focus and emerging guidelines would help general practitioners to handle the condition in a more standardized way, resulting in a shift from in-patient to out-patient care. However, our results should be interpreted with caution, as they could be biased by parallel changes in the infrastructure of the health care system, where an increased pressure on hospital beds has been reported[21]. Simultaneously, there has also been increasing political pressure on general practitioners not to refer anyone to a hospital if it can be avoided, which might also contribute to the decline observed[21].

Mortality risks found in this study support previous findings of high mortality risks in people with type 2 diabetes following their first ever DFU. In a systematic review from 2016, the average 5-year mortality risk after first ulceration was approximately 40%. This is slightly higher than our findings, but could be explained by the fact that it was estimated in a more mixed population with more comorbidites[22]. Furthermore, the observed decline over time could be attributed to a combination of parameters including better management, awareness, and care of people with type 2 diabetes and a first ever DFU.

In the present study, we have analysed data from people seen in primary care in the UK over a period of 10 years. The primary strength of the study is that it uses a data source with valid and adequate data collection, which grants insight into an area where data are sparse. Furthermore, our study design increases the probability of studying first ever DFUs in the earliest years of disease, although we cannot be completely certain due to potentially lacking registration prior to the QoF update in 2007. The study also has some limitations, which are mostly related to the study design and data source. In order to ensure that the study population consisted of people with diabetes, we used fairly strict definitions. Consequently, this may have limited our statistical power when looking at changes over time, and we were therefore unable to examine our secondary endpoints in people with type 1 diabetes. The short follow-up time also limited our ability to describe the risk of a first ever DFU in the majority of people with type 1 diabetes, as most of the ulcers occurred in people diagnosed with type 1 diabetes later in life, while ulcers amongst those diagnosed earlier would be missed due to the relatively short follow-up time. Therefore, the results regarding people with type 1 diabetes should be interpreted with great caution, as this subpopulation does not necessarily represent the vast majority of people with type 1 diabetes. From table 2 it is also

notable that 6% of those classified with type 1 diabetes did not receive insulin 6 months prior to their ulcer. While this could of course represent coding errors or misclassifications, it could also easily be explained by several other reasons, including long hospital admissions, stays abroad or them only using a small amount of insulin and thus only collecting it once or twice a year. Furthermore, the population of people with type 2 diabetes treated with diet alone were also not included due to our study design, where we chose to improve our certainty of a correct diagnosis over the inclusion of everyone with type 2 diabetes. This also led to a rather large exclusion of people with potential type 2 diabetes. However, our methods were predefined in our ISAC approval, and the excluded population were comparable, although younger, than the included population. This was to be expected, however, as the population was probably diluted by younger people with type 1 diabetes. In addition, our definition of DFUs is limited to Read codes with unexamined validity, and it does not differentiate between severe and mild conditions. This might have influenced the outcomes hospitalization and mortality but may also have presented us with a potential left censoring issue. Changes in areas from which general practitioners supplyed data for the CPRD GOLD occurred during the study. The geographical clustering in London, the South, Greater Manchester and Birmingham could have influenced the trends over time, as previous studies using geospatial mapping have proven DFUs to be more prevalent in areas with poor socioeconomic status and deprivation[23,24]. It is also worth noting, that some people are treated in local podiatry clinics without ever seeing their GP, and while many of these clinics would exchange data with the GPs, we cannot be sure that all DFUs are indeed registered. As the number of such clinics have increased over the course of the study, this could also influence the observed trend. When estimating hospitalization, we also decided to interpret the mentioning of a DFU in the referral file as the reason for hospitalization. While this is probably correct in most cases, some of the referrals might have been due to something else entirely or vice versa the ulcer might not have been mentioned. Lastly, the registration of complications might be limited by insufficient registration or examination in general practice, which might cause underestimation.

In conclusion, we have shown that the average IR of a first registered DFU in people seen in primary care in the UK between 2007 and 2017 was approximately 2.5 per 1,000 person-years for people with type 2 diabetes and approximately 1.6 per 1,000 person-years in people with type 1 diabetes. The IR of first ever DFUs declined for people with type 2 diabetes during the observation period and the proportion of people hospitalized declined substantially. Furthermore,

people with type 2 diabetes had a high mortality-risk following their first registered DFU, which did decline slightly over time. The decline in DFUs, hospitalizations and mortality, suggests that prevention and care of the first ulcer has improved for this group in primary care in the UK.

V. Contributions and acknowledgement (127 words)

J.R. wrote the manuscript, researched data, and contributed to the idea and study design. F.V., N.E., J.B., P.V., N.S., M.H. and O.K. contributed to the idea and study design, reviewed the manuscript, and conducted critical editing of written text. N.W. and J.N. reviewed the manuscript and conducted critical editing of written text. J.D. analysed data, contributed to the idea, study design, reviewed the manuscript, and conducted critical editing of written text. Each author is accountable for his own contribution, disclosure of potential interests and approved the final version of the manuscript. F.V. is responsible for all aspects of the manuscript.

The authors would like to acknowledge and thank Prof. Dr. William Jeffcoate from the Nottingham University Hospitals Trust for his feedback, insights, and guidance on several versions of this manuscript.

VI. References

1 Lepäntalo M, Apelqvist J, Setacci C, Ricco JB, De Donato G, Becker F *et al.* Chapter V: Diabetic foot. *Eur J Vasc Endovasc Surg* 2011; **42**: S60–S74.

2 Cavanagh P, Attinger C, Abbas Z, Bal A, Rojas N, Xu ZR. Cost of treating diabetic foot ulcers in five different countries. *Diabetes Metab Res Rev* 2012; **28**: 107–111.

3 Røikjer JB, Jensen MH, Vestergaard P, Sørensen AM, Laursen HVB, Ejskjær N. Twenty years with diabetes and amputations: a retrospective population-based cohort study. *Diabet Med* 2020; : dme.14251.

4 Paisey RB, Abbott A, Levenson R, Harrington A, Browne D, Moore J *et al.* Diabetes-related major lower limb amputation incidence is strongly related to diabetic foot service provision and improves with enhancement of services: peer review of the South-West of

England. *Diabet Med* 2018; **35**: 53–62.

5 van Netten JJ, Raspovic A, Lavery LA, Monteiro-Soares M, Rasmussen A, Sacco ICN *et al.* Prevention of foot ulcers in the at-risk patient with diabetes: a systematic review. *Diabetes Metab Res Rev* 2020; **36**. doi:10.1002/dmrr.3270.

6 Crawford F, Cezard G, Chappell FM, Murray GD, Price JF, Sheikh A *et al.* A systematic review and individual patient data meta-analysis of prognostic factors for foot ulceration in people with diabetes: The international research collaboration for the prediction of diabetic foot ulcerations (PODUS). *Health Technol Assess (Rockv)* 2015; **19**: 1–207.

7 Jeffcoate WJ, Vileikyte L, Boyko EJ, Armstrong DG, Boulton AJM. Current challenges and opportunities in the prevention and management of diabetic foot ulcers. Diabetes Care. 2018; **41**: 645–652.

8 Armstrong DG, Boulton AJM, Bus SA. Diabetic Foot Ulcers and Their Recurrence. *N Engl J Med* 2017; **376**: 2367–2375.

9 Kerr M, Barron E, Chadwick P, Evans T, Kong WM, Rayman G *et al.* The cost of diabetic foot ulcers and amputations to the National Health Service in England. *Diabet Med* 2019; **36**: 995–1002.

10 Herrett E, Gallagher AM, Bhaskaran K, Forbes H, Mathur R, van Staa T *et al.* Data Resource Profile: Clinical Practice Research Datalink (CPRD). *Int J Epidemiol* 2015; **44**: 827–836.

11 NHS. Quality and Outcomes Framework (QOF) - 2016-17 - NHS Digital. NHS Digit. 2017.https://digital.nhs.uk/data-and-information/publications/statistical/quality-and-outcomes-framework-achievement-prevalence-and-exceptions-data/quality-and-outcomes-framework-qof-2013-14%0Ahttp://digital.nhs.uk/catalogue/PUB30124 (accessed 8 Jun2020).

12 Benson T. The history of the Read Codes: The inaugural James Read memorial lecture 2011. Inform. Prim. Care. 2012; **19**: 173–182.

13 Ely JW, Dawson JD, Lemke JH, Rosenberg J. An Introduction to Time-Trend Analysis. *Infect Control Hosp Epidemiol* 1997; **18**: 267–274.

14 Paisey RB, Abbott A, Paisey CF, Walker D. Diabetic foot ulcer incidence and survival with improved diabetic foot services: an 18-year study. *Diabet Med* 2019; **36**: 1424–1430.

15 Abbott CA, Carrington AL, Ashe H, Bath S, Every LC, Griffiths J *et al.* The North-West Diabetes Foot Care Study: Incidence of, and risk factors for, new diabetic foot ulceration in a community-based patient cohort. *Diabet Med* 2002; **19**: 377–384.

16 De Sonnaville JJJ, Colly LP, Wijkel D, Heine RJ. The prevalence and determinants of foot ulceration in type II diabetic patients in a primary health care setting. *Diabetes Res Clin Pract* 1997; **35**: 149–156.

17 Sämann A, Tajiyeva O, Müller N, Tschauner T, Hoyer H, Wolf G *et al.* Prevalence of the diabetic foot syndrome at the primary care level in Germany: A cross-sectional study. *Diabet Med* 2008; **25**: 557–563.

18 Sunyinyan Tang DZ& YBPZJLYJ. Global epidemiology of diabetic foot ulceration: a systematic review and meta-analysis†. *Ann Med* 2017; **49**: 106–116.

19 Oyibo SO, Jude EB, Voyatzoglou D, Boulton AJM. Clinical characteristics of patients with diabetic foot problems: changing patterns of foot ulcer presentation. *Pract Diabetes Int* 2002; **19**: 10–12.

20 NICE. Diabetic foot problems: pre Diabetic foot problems: prev vention and ention and management management NICE guideline-and-conditions#notice-of-rights. 2015www.nice.org.uk/guidance/ng19 (accessed 4 Nov2019).

21 Smith P, McKeon A, Blunt I, Edwards N. NHS hospitals under pressure: trends in acute activity up to 2022. 2014.

22 Jupiter DC, Thorud JC, Buckley CJ, Shibuya N. The impact of foot ulceration and amputation on mortality in diabetic patients. I: From ulceration to death, a systematic review. *Int Wound J* 2015; **13**: 892–903.

23 Kontopantelis E, Stevens RJ, Helms PJ, Edwards D, Doran T, Ashcroft DM. Spatial distribution of clinical computer systems in primary care in England in 2016 and implications for primary care electronic medical record databases: a cross-sectional population study. *BMJ Open* 2018; **8**: e020738.

24 Hurst JE, Barn R, Gibson L, Innes H, Bus SA, Kennon B *et al.* Geospatial mapping and data linkage uncovers variability in outcomes of foot disease according to multiple deprivation: a population cohort study of people with diabetes. *Diabetologia* 2020; **63**: 659–667.

Table 1: Baseline characteristics

	T1DM without DFU (N = 5,756)		T1DM who later develops a DFU (N =63)		T2DM without DFU (N =121,791)		T2DM who later develops a DFU (N =2,014)	
	N	%	N	%	N	%	N	%
No. of women	2,339	40.6	22	34.9	53,142	43.6	713	35.4
Age								
Mean age (years, SD)	26.1	19.6	41.2	17.1	62.8	12.4	64.5	12.7
< 18 years	2,763	48.0	8	12.7				
18-29 years	895	15.5	8	12.7				
30-39 years	698	12.1	11	17.5	3,831	3.1	60	3.0
40-49 years	534	9.3	17	27.0	14,799	12.2	203	10.1
50-59 years	380	6.6	11	17.5	29,113	23.9	427	21.2
60-69 years	297	5.2	< 5	6.3	35,682	29.3	567	28.2
70-79 years	147	2.6	< 5	6.3	27,570	22.6	510	25.3
80+ years	42	0.7	0	0.0	10,796	8.9	247	12.3
BMI								
Mean BMI (kg/m2, SD)	23.5	5.8	25.6	5.8	31.8	6.5	31.3	6.8
<20 kg/m2	1,493	25.9	12	19.0	1,023	0.8	23	1.1
20-24.9 kg/m2	1,834	31.9	22	34.9	12,939	10.6	264	13.1
25-29.9 kg/m2	1,116	19.4	15	23.8	39,216	32.2	665	33.0
30-34.9 kg/m2	427	7.4	10	15.9	36,307	29.8	591	29.3
≥35 kg/m2	193	3.4	> 5	6.3	31,537	25.9	456	22.6
Missing	693	12.0	0	0.0	769	0.6	15	0.7
Smoking status								
Current	1,163	20.2	25	39.7	23,115	19.0	470	23.3
Former	791	13.7	10	15.9	62,940	51.7	1,004	49.9
Non-smoker	2,787	48.4	28	44.4	35,622	29.2	539	26.8
Missing	1,015	17.6	0	0.0	114	0.1	< 5	0.0
History of comorbidities								
Neuropathy	28	0.5	0	0.0	868	0.7	39	1.9
Retinopathy	168	2.9	< 5	6.3	7,943	6.5	120	6.0
Nephropathy	163	2.8	< 5	3.2	37,839	31.1	608	30.2

History of CN	> 5	0.0	0	0.0	21	0.0	< 5	0.0
Hba1c (most recent in year before index)								
Mean HbA1c (%, SD)	10.8	2.6	10.4	3.0	8.4	1.6	8.7	1.8
<6%	21	0.4	0	0.0	911	0.7	11	0.5
6.0 – 6.9%	54	0.9	0	0.0	11426	9.4	108	5.4
7.0 – 7.9%	50	0.9	< 5	1.6	29,688	24.4	352	17.5
8.0 – 8.9%	86	1.5	0	0.0	17,985	14.8	241	12.0
≥9.0%	641	11.1	< 5	3.2	21,593	17.7	349	17.3
Missing	4,904	85.2	60	95.2	40,188	33.0	953	47.3
Mean follow-up time (years, SD)	8.6	5.9	13.6	5.5	7.8	4.9	10.4	4.9

Abbreviations: BMI: Body Mass Index. **T1DM**: Type 1 diabetes. **T2DM**: Type 2 diabetes. **DFU**: Diabetic foot ulcer **No:** Number. **SD**: Standard Deviation. **NIAD**: Non-insulin antidiabetic drug. <5: exact number not shown due to CPRD's data confidentiality policy.

Legend: Characteristics for all participants at inclusion (first NIAD or insulin prescription) by diabetes type and weather they later developed an ulcer or not. For characteristics of the population in 2007, when the trend analysis started, see supplementary table S4.

Table 2: Characteristics at first registered diabetic foot ulcer				
	T1DM (N =63)		**T2DM** (n =2,014)	
	N	%	N	%
No. of women	22	34.9	713	35.4
Age				
Mean, (years, SD)	50.7	16.7	71.3	12.5
By category (years)				
<18 years	8	12.7		
18-29	10	15.9		
30-39	8	12.7	13	0.6
40-49	18	28.6	99	4.9
50-59	10	15.9	272	13.5
60-69	7	11.1	432	21.4
70-79	<5	3.2	616	30.6
80+	0	0.0	582	28.9
BMI				
Mean (kg/m^2, SD)	27.2	5.9	30.6	7.1
By category (kg/m^2)				
<20.0	6	9.5	59	2.9
20.0-24.9	17	27.0	318	15.8
25.0-29.9	24	38.1	691	34.3
30.0-34.9	10	15.9	518	25.7
≥35.0	6	9.5	413	20.5
Missing	0	0.0	15	0.7
Smoking status				
Current	17	27.0	311	15.4
Former	26	41.3	1,281	63.6
Non-smoker	20	31.7	421	20.9
Missing	0	0	< 5	0.0
Median Diabetes Duration (years, IQR)	9.6	6.0 – 13.2	6.3	2.8 – 10.0

History of diabetes complications				
Neuropathy	5	7.9	203	10.1
Retinopathy	37	58.7	724	35.9
Nephropathy	32	50.8	1,363	67.7
Charcot Neuroarthropathy	< 5	3.2	13	0.6
Use of insulin in 6 months prior	59	93.7	368	18.3
Most recent HbA1c recording in the year before the first diabetic foot ulcer				
Mean, by category (%, SD)	9.6	2.0	7.7	1.6
By category				
<6.0%	0	0	163	8.1
6.0 – 6.9%	5	7.9	518	25.7
7.0 – 7.9%	7	11.1	464	23.0
8.0 – 8.9%	6	9.5	264	13.1
≥9.0%	29	46.0	321	15.9
Missing	16	25.4	284	14.1

Abbreviations: BMI: Body Mass Index. **HbA1c**: Glycated haemoglobin. **T1DM**: Type 1 diabetes. **T2DM**: Type 2 diabetes **No.:** Number. SD: Standard Deviation. **IQR:** Interquartile range

<5: exact number not shown due to CPRD's data confidentiality policy.

Legend: Characteristics for people with diabetes at the time of their first registered diabetic foot ulcer.

Figure 1: Annual incidence rates per 1,000 person-years for a first registered diabetic foot ulcer in people with type 1 and type 2 diabetes.

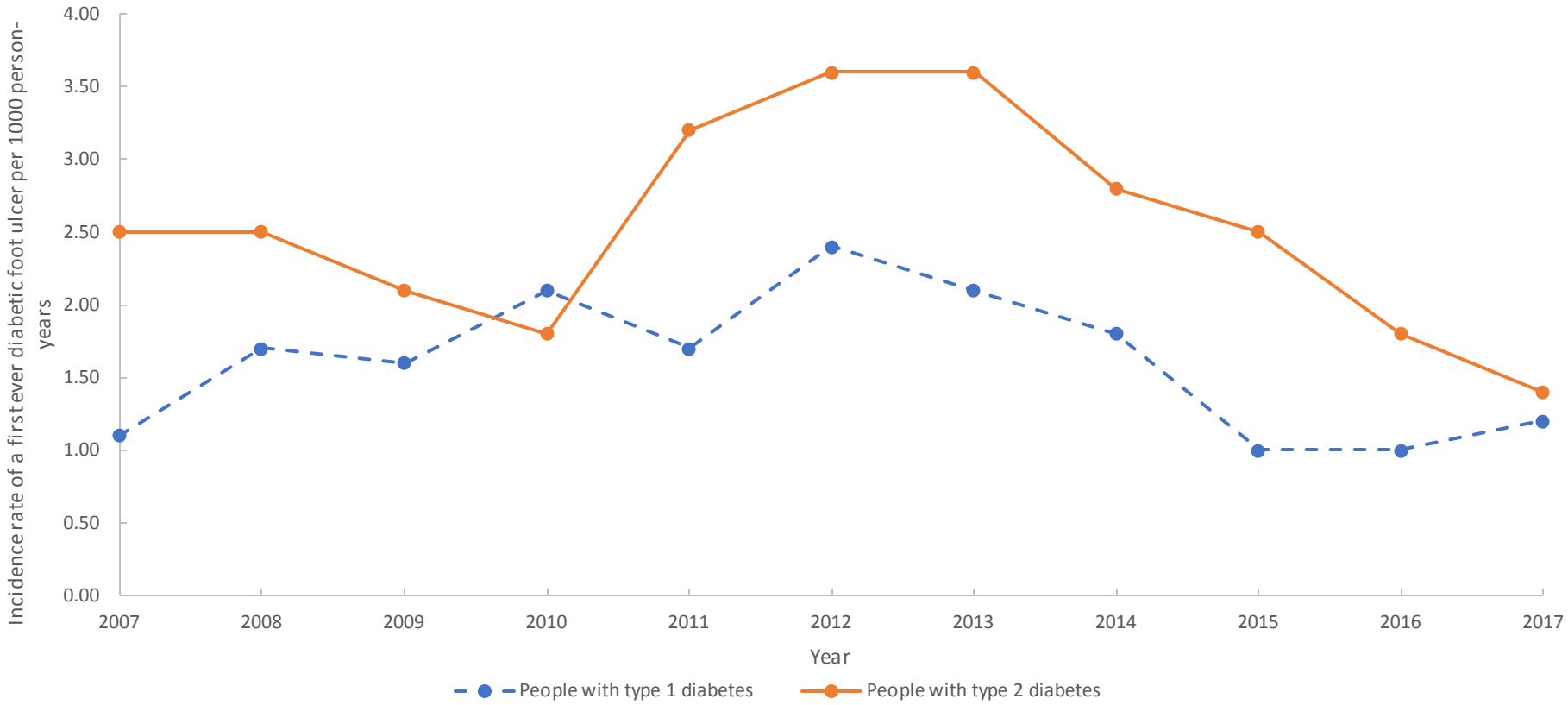

Figure 2: Proportion (%) of people with type 2 diabetes hospitalized in relation to their first registered diabetic foot ulcer. People with type 1 diabetes were not included in the analysis as the number of events was too small. As illustration the trend over time is presented by using a linear regression line but was analysed using logistic regression. A graph of the expected probabilities and confidence intervals from the logistic regression model is presented as supplementary figure S3.

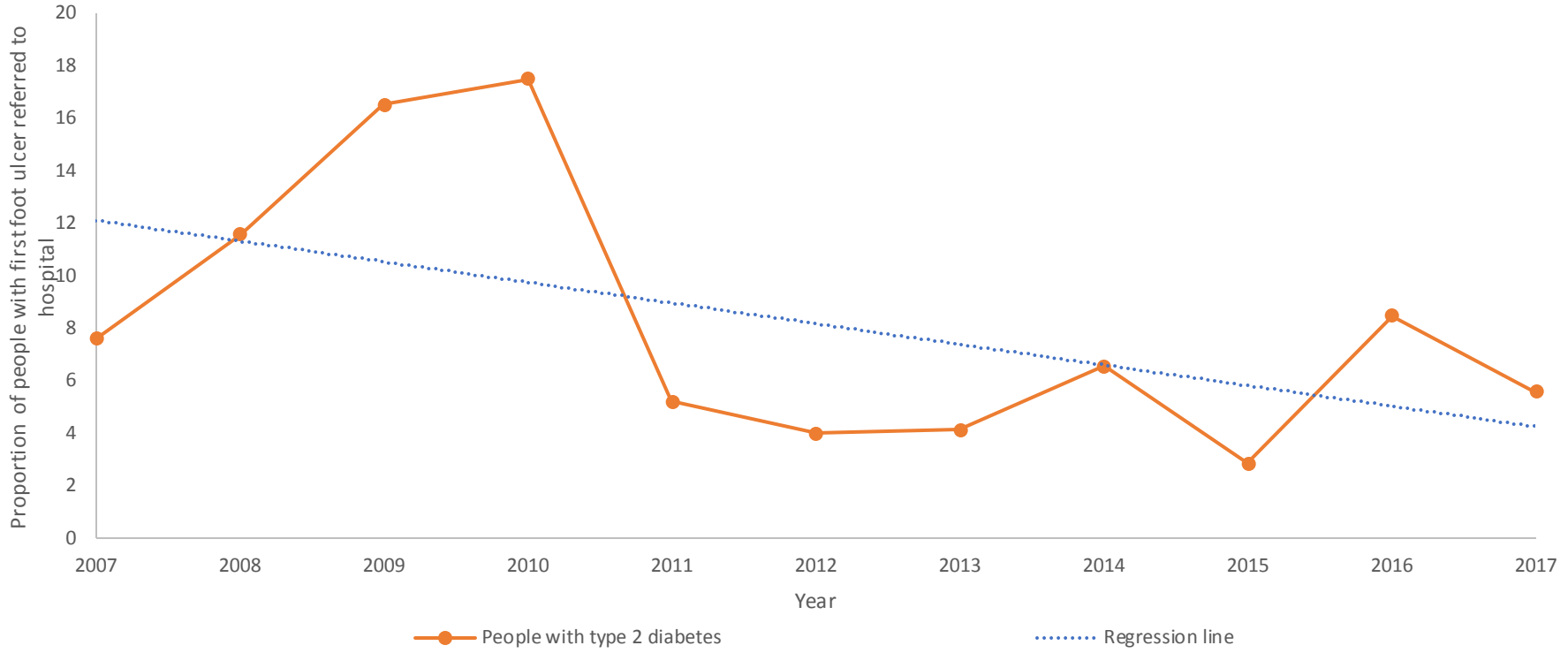

Figure 3: 1-year mortality-risk (%) after the first registered diabetic foot ulcer, by calendar time. People with type 1 diabetes were not included in the analysis as the number of events was too small. As illustration the trend over time is presented by using a linear regression line but was analysed using logistic regression. A graph of the expected probabilities and confidence intervals from the logistic regression model is presented as supplementary figure S2.