Multiple factors predict longer and shorter time-to-ulcer-free in people with diabetes-related foot ulcers: survival analyses of a large prospective cohort followed-up for 24-months

Short title: Factors predicting time to being ulcer free

Authors

Yuqi Zhang, Msc [a,b,c]*; Susanna Cramb, PhD [a,b,c,d]; Steven M. McPhail, PhD [a,b,e]; Rosana Pacella, PhD [f]; Jaap J. van Netten, PhD [a,g]; Qinglu Cheng, PhD [h]; Patrick H. Derhy, BSc [i]; Ewan M. Kinnear, BSc [j]; Peter A. Lazzarini, PhD[a,b,j]; on behalf of the Diabetic Foot Working Group, Queensland Statewide Diabetes Clinical Network, Australia^.

Affiliations

a School of Public Health and Social Work, Queensland University of Technology, Brisbane, Australia
b Australian Centre for Health Services Innovation & Centre for Healthcare Transformation, Queensland University of Technology, Brisbane, Australia
c Centre for Data Science, Queensland University of Technology, Brisbane, Australia
d Jamieson Trauma Institute, Royal Brisbane and Women's Hospital, Metro North Health, Brisbane, Australia
e Clinical Informatics Directorate, Metro South Health, Brisbane, Australia
f Institute for Lifecourse Development, University of Greenwich, Greenwich, London, UK
g Amsterdam UMC, University of Amsterdam, Department of Rehabilitation Medicine, Amsterdam Movement Sciences, Meibergdreef 9, Amsterdam, the Netherlands
h Kirby Institute, University of New South Wales, Sydney, Australia
i Clinical Access and Redesign Unit, Queensland Health, Brisbane, Australia
j Allied Health Research Collaborative, The Prince Charles Hospital, Brisbane, Australia

*Correspondence to: Yuqi Zhang, School of Public Health and Social Work, Queensland University of Technology, Brisbane, Australia, 60 Musk Ave Kelvin Grove, QLD, 4059, Australia.
yuqi.zhang@hdr.qut.edu.au, +61423580260
^Membership of the Diabetic Foot Working Group, Queensland Statewide Diabetes Clinical Network (Australia) is provided in the Acknowledgments

Word count: 4,445

ABSTRACT

Aims

To investigate factors independently associated with time-to-(being)-ulcer-free, time-varying effects and predict adjusted ulcer-free probabilities, in a large prospective cohort with diabetes-related foot ulcers (DFU) followed-up for 24 months.

Methods

Patients presenting with DFU(s) to 65 Diabetic Foot Services across Queensland, Australia, between July-2011 and December-2017 were included. Demographic, comorbidity, limb, ulcer, and treatment factors were captured at presentation. Patients were followed-up until ulcer-free (all DFU(s) healed), amputation, death or two years. Factors associated with time-to-ulcer-free were investigated using both Cox proportional hazards and flexible parametric survival models to explore time-varying effects and plot predicted adjusted ulcer-free probability graphs.

Results

Of 4,709 included patients (median age 63 years, 69.5% male), median time-to-ulcer-free was 112 days (IQR:40->730), with 68.4% ulcer-free within two years. Factors independently associated with longer time-to-ulcer-free were each year of age younger than 60 years, living in a regional or remote area, smoking, neuropathy, peripheral artery disease (PAD), ulcer size >1cm^2, deep ulcer and mild infection (all $p<0.05$). Time-varying effects were found for PAD and ulcer size limiting their association to six months only. Shorter time-to-ulcer-free was associated with recent DFU treatment by a podiatrist and receiving knee-high offloading treatment (both $p<0.05$). Predicted adjusted ulcer-free probability graphs reported largest differences in time-to-ulcer-free over 24-months for geographical remoteness and PAD factors.

Conclusions

Multiple factors predicted longer and shorter time-to-ulcer-free in people presenting with DFUs. Considering these factors, their time-varying effects and adjusted ulcer-free probability graphs, should aid the prediction of the likely time-to-(being)-ulcer-free for DFU patients.

Keywords

Cohort study; Cox proportional hazard model; diabetic foot; diabetes-related foot ulcer; flexible parametric survival model; ulcer-free.

1. Introduction

Each year an estimated 20 million people worldwide have diabetes-related foot ulcers (DFUs) [1, 2]. Individual DFUs typically take months or years to heal, with around 50% becoming infected [3, 4] and 20% of those requiring an amputation [4]. Thus, it is unsurprising that DFUs are a leading global cause of hospitalisation [5], disability [1, 6], and healthcare costs [2, 7].

Multiple demographic, comorbidity, limb and ulcer factors have been found to be associated with DFU healing, such as renal failure, peripheral artery disease (PAD) and infection [8-22]. These factors though have mostly been identified from studies investigating individual DFUs, healed at a certain fixed point in time, typically three or 12 months, and from patients attending major metropolitan tertiary centres [8, 10, 11, 13-21]. Yet, patients with DFUs often have multiple ulcers [10, 17], can take much longer to heal than 12 months, attend diverse centres, and are most interested in the estimated time it is likely to take until all their ulcers are healed (being 'ulcer-free') [12, 23]. Thus, understanding how different factors may predict the time it takes to become ulcer-free over longer periods in patients presenting with DFU(s) to diverse centres is vital for improving future care and research.

In a brief published letter, we recently reported factors associated with being completely healed ('ulcer-free') at three and 12 months from a large prospective cohort of people with DFU attending diverse centres. We found multiple novel factors, such as a younger age group (18-49 years) and living in a regional or remote area negatively associated with healing, and knee-high offloading treatment positively associated with healing [24]. Further, we confirmed factors found in other studies, such as PAD and ulcer size, but found these factors had significantly different odds ratios for being healed at three and 12 months suggesting they may have an increasingly time-limited association with healing [24]. However, the letter used a binary outcome of healed at fixed points in time, logistic regression models and a maximum

follow-up time of 12 months, which precluded improving our understanding of the vital associations these factors may have on the time to being ulcer-free.

Thus, in this new analysis we aimed to investigate the factors independently associated with the time-to-(being)-ulcer-free, using survival analysis models and exploring for any time-varying effects, in the same prospective cohort with DFU, but this time followed-up for a much longer period of 24 months. We also aimed to utilise the unique functionality that flexible parametric survival models provide to plot novel adjusted ulcer-free probability graphs over 24 months for each identified factor to predict the likely independent association each factor has on the time to becoming ulcer-free.

2. Subjects, Material, and Methods

2.1 Study design

This new analysis was from a prospective multi-site cohort study of patients with DFUs who visited outpatient Diabetic Foot Service sites within Queensland, Australia [24]. Ethical approval was obtained from the Human Research Ethics Committees of the Prince Charles Hospital (HREC/15/QPCH/155) and Queensland University of Technology (1800000722). Legal approvals were obtained from the Queensland Statewide Diabetes Clinical Network Data Access committee, the Queensland Health Statistical Services Branch, and a Queensland Public Health Act 2005 waiver of consent approval (RD007685) to use de-identified data for this study. Results of this study are reported according to the Strengthening the Reporting of Observational studies in Epidemiology (STROBE) statement (eTable 1) [25].

2.2 Settings

Patient information was directly collected from 65 outpatient Diabetic Foot Service sites within 15 of the 17 total Hospital and Health Service regions in the Australian state of Queensland.

These sites ranged from small podiatry-only secondary centres in remote towns, to large multi-disciplinary tertiary centres in major cities, but all were typically the main providers of ongoing DFU care for their relevant catchment area. Queensland is the third largest Australian state in terms of population with approximately 4.5 million residents, second largest in geographical area and the most decentralised state, with a diverse demography, including a comparatively large proportion of Aboriginal and Torres Strait Islander peoples, hereafter respectfully referred to as Indigenous people (4.6% compared with 3.3% nationwide) [26]. The prevalence of diabetes in Queensland is similar to the prevalence of diabetes in Australia (5.0% compared with 5.3% nationwide) [27]. Thus, collectively these 65 Diabetic Foot Service sites provide access to a large cohort of eligible patient participants with DFUs from a large and representative region of Australia.

2.3 Participants

Eligible participants were patients with DFU(s) who presented for their first visit to one of the sites between 1st July 2011 to 31st December 2017. A DFU was defined as a full thickness wound below the ankle on a person with diabetes mellitus [28, 29]. Those who attended only once and did not return were excluded. For any participant with multiple episodes of DFU, only the earliest episode was included so that each participant was included only once.

During each visit to these services, every patient was directly clinically examined according to a standard evidence-based protocol and had their examination data collected for research and clinical benchmarking purposes by trained foot-related health professionals using the Queensland High Risk Foot Form (QHRFF) [3, 30, 31]. The QHRFF aims to facilitate routine ongoing clinical care and prospective data collection for research purposes [30, 31], in alignment with international reporting standards for DFU [23, 28]. The QHRFF development procedures, variable definitions, data collection procedures, training procedures and quality checking procedures have been reported in detail elsewhere [3, 30, 31]. The QHRFF data

collection procedures were established for the primary purpose of prospective research and clinical benchmarking for people with foot ulcers, and have been tested and shown to be valid and reliable for the capture of more than 40 variables [30, 31].

2.4 Variables collected

All variables were obtained via self-report or direct clinical examination for each patient at each visit using the aforementioned QHRFF data collection procedures [3, 24, 30]. Variables were grouped into five domains of demographic, comorbidity, limb, ulcer and treatment-related variables [3, 24, 30]. Table 1 displays the full descriptions of all variables used in this analysis and defined in accordance with international reporting standards for DFU studies [23, 28]. Variables collected at the participant's first visit were used as the baseline characteristics, and variables collected from subsequent visits were used to determine the outcome of interest (being ulcer-free) [24]. If data were missing for a variable, data from the second visit were used for that variable (if available), provided the second visit was within one month of the first visit. For participants with multiple DFUs at baseline, the most severe score for each factor was used for the applicable limb and ulcer variables and a combined ulcer size of all DFUs was calculated (Table 1) [3, 30, 31].

2.5 Outcomes of interest

The outcome of interest in this analysis was time-to-ulcer-free of all DFUs in a participant. Ulcer-free was defined as complete epithelialization of all DFU(s) (on both feet if present) without amputation, death or recurrence within one month, and was obtained from the direct examination of each participant at subsequent visits using the aforementioned QHRFF data collection procedures [23, 28]. Participants were followed up until they were ulcer-free, or for 24 months, whichever came first. Any participant who did not experience the event of interest (ulcer-free) was censored. Participants were considered censored if: 1. they had a lower-extremity amputation before being ulcer-free, including minor amputation (defined as an

amputation procedure below the ankle level) and major amputation (amputation above the ankle level); 2. they died before being ulcer-free; 3. they ceased visiting the service before being ulcer-free and were lost to follow-up; or 4. their ulcer(s) had not healed by the end of the 24 month period. The information on amputation was identified via standard ICD-10-AM amputation procedure codes (provided in Table 1) from linked Queensland Hospital Admitted Patient Data Collection, which captures all hospitalisation procedures in public and private hospitals in Queensland [32]. Time-to-ulcer-free was defined as the time in days between the date of the participant's first visit and the date of the first visit in which all DFUs healed (was ulcer-free), while for censored participants time-to-censoring was defined as between the date of first visit and the date censored.

2.6 Statistical analyses

All variables were initially analysed at a univariable level to determine those crudely associated with time-to-ulcer-free using log-rank tests, Kaplan-Meier curves, and univariable Cox proportional hazard regression models. A multivariable Cox proportional hazards model (model 1) was then developed by entering all categorical and continuous variables that achieved a $p<0.1$ on univariable analysis. The proportional hazards assumptions were checked for the overall model and for each variable using Schoenfeld residuals. Variables that did not meet the proportionality assumption had their time-varying effects explored in model 2.

A flexible parametric survival model (model 2) was then developed by including the same variables as in model 1, plus time-varying coefficients for variables not meeting proportionality assumptions. The advantages of using flexible parametric survival models are that they can readily incorporate time-varying coefficients, model the hazard function smoothly, and also enable prediction of outcomes of interest, such as the probability of being ulcer-free [33]. The best model fit for model 2 was based on Akaike information criterion and Bayesian information criterion, using the hazard scale with three interior knots together with two boundary knots for

the overall model and no interior knots for time-varying coefficients. To improve model flexibility, age was included as a continuous variable and transformed using restricted cubic splines with two degrees of freedom. As time-to-ulcer-free was used as the outcome in the analysis, a hazard ratio (HR) of >1 was associated with a shorter time-to-ulcer-free, while a HR of <1 was associated with a longer time-to-ulcer-free. Model fit was checked using martingale residuals and examining deviance.

Additionally, using the flexible parametric survival model, the probability to become ulcer-free was predicted and plotted for each retained variable. The predicted ulcer-free probability was adjusted for the other covariates, by predicting for each individual as if they had the specific variable of interest (for example, being a smoker), as well as if they did not (for example, not being a smoker), while keeping all other covariates the same. Predictions were then averaged over all individuals to provide the overall adjusted predicted probability among those with and without the variable of interest (for example smokers and non-smokers).

Missing data was handled in model 1 by using multiple imputation for variables with <25% missing data and excluding variables with >25% missing data. However, as imputation is not compatible with the software used for flexible parametric survival models, in model 2 missing data was handled as follows to minimize bias: <10% missing data, the variable was used in further analysis and the missing cases were dropped; 10-25% missing, an extra category for missing data was created for the variable and used in further analysis; and >25% missing data, the variable was excluded from further analysis. All analyses were performed using Stata/SE version 16.1 (StataCorp, TX, USA), and the user-written Stata package stpm2 and stpm2_standsurv [33] for the flexible parametric modelling and predictions.

3. Results

3.1 Participant characteristics

Of 4,832 eligible participants identified, 123 (2.5%) were excluded as they did not return for a second visit, with the remaining 4,709 participants included in this study (eFigure 1). The median number of included participants per site was 25 (Interquartile Range, IQR: 6-82). The cohort was followed-up for a median time of 85 days (IQR: 30-237), with a maximum time of 730 days for the purpose of this analysis. The median number of clinic visits per participant was 5 (IQR: 3-11).

Table 2 displays the baseline characteristics of the 4,709 included participants and median time-to-ulcer-free. The included participants had a median age of 63 years (IQR: 54-72), 69.5% were male, 91.0% had type 2 diabetes and 10.5% were of Indigenous status. The median time-to-ulcer-free of the total cohort was 112 days (IQR: 40->730), with the proportion of being ulcer-free at three, 12 and 24 months, being 41.5% (1,956), 64.0% (3,012), and 68.4% (3,221), respectively. eFigure 2 displays the Kaplan-Meier survival graphs for the total cohort and by each categorical variable. Of the remaining 31.6% (1,488) participants, 11.6% (545) had an amputation (8.1% (382) minor and 3.5% (163) major amputation), 6.6% (310) died, 8.5% (399) were lost to follow-up unhealed, and 5.0% (234) were followed up to 24 months but remained unhealed without amputation or death (eFigure 1).

3.2 Factors associated with time-to-ulcer-free

Figure 1 displays the findings from univariable and multivariable analyses for the 18 variables that met our criteria for entry into the multivariable models. The HRs of all these variables from Cox models using multiple imputation, missing category and flexible parametric model using missing category (model 2) were largely consistent (eTable 2). We therefore focus our reporting on the findings of model 2, as it also included the time-varying coefficients for two

variables that did not meet proportionality assumptions (PAD and ulcer size). There were 10 factors identified that associated with time-to-ulcer-free.

Longer time-to-ulcer-free was independently associated with younger age, living in regional or remote areas, being a smoker, having neuropathy, PAD, ulcer size >1 cm^2, deep ulcer and mild infection (all: $p<0.05$; Figure 1). Those of younger age (<60-years) had longer time-to-ulcer-free for each year younger compared with those aged >60 years (Figure 2). PAD (mild-to-moderate PAD and critical PAD) and ulcer size categories (1-3 cm^2 and >3 cm^2) had time-varying effects; both had significantly longer time-to-ulcer-free up to six months after the first visit (both, $p<0.05$), but were not significant after six months (Figure 3; eTable 3).

Shorter time-to-ulcer-free was independently associated with receiving recent DFU treatment by a podiatrist (at baseline or week prior) and receiving a knee-high offloading treatment at baseline (both, $p<0.05$; Figure 1).

3.3 Adjusted probability of being ulcer-free for identified factors

Figure 4 presents the predicted probability of being ulcer-free over 24 months by the identified factor, with all other included factors adjusted. Factors displaying statistically lower adjusted probability of being ulcer-free at any given time during the 24-month follow-up included living in regional or remote areas, smoking, having neuropathy, deep ulcer, and infection (Figure 4; eTable 4). With all other covariates being equal, the probability of being ulcer-free by six months showed largest differences by geographical remoteness and PAD. For geographical remoteness, the adjusted probability of being ulcer-free by six months was 65.0% (63.3-66.7) for people living in a major city, 54.6% (52.6-56.8) in a regional area, and 40.3% (34.6-47.1) in a remote area. Whereas for PAD, the adjusted probability of being ulcer-free by six months was 63.5% (62.0-65.2) for people with nil PAD, 53.9% (51.4-56.6) with mild-to-moderate PAD, and 38.0% (32.3-44.7) with critical PAD. Having PAD and larger ulcer sizes also displayed lower probability of being ulcer-free in the first 12-months, but the difference

narrowed with time and the probability (95% CI) overlapped in the second year, due to the accumulation of the time-varying effects of these two factors. In contrast, factors displaying higher probability of ulcer-free at any given time during the 24-months follow-up included recent DFU treatment by a podiatrist and receiving knee-high offloading treatment at baseline.

4. Discussion

This paper investigated factors associated with the time it takes to become ulcer-free in patients presenting with DFU(s). In nearly 5,000 participants presenting across 65 diverse centres, we observed a median time-to-(being)-ulcer-free of 112 days, with 68% ulcer-free within 24 months. Longer time-to-ulcer-free was found to be independently associated with each year of younger age (<60 years), living in a regional or remote area, smoking, neuropathy, PAD, larger ulcer size, deep ulcers, and mild infection. However, time-varying effects were identified for PAD and larger ulcer sizes which limited their association to six months follow-up time only. Shorter time-to-ulcer-free was associated with recent DFU treatment by a podiatrist and receiving knee-high offloading treatment at presentation. Lastly, novel adjusted ulcer-free probability graphs were plotted for each identified factor, which should aid clinicians and researchers to predict the given time it is likely to take for their patients to become ulcer-free when presenting with these factors.

Apart from confirming that several novel factors reported in our recent brief letter were also associated with time-to-ulcer-free at any given time over 24 months, such as younger age group, living in a regional or remote area and receiving knee-high offloading [24], there are also unique findings in this new analysis. These included that each year of age younger than 60 years was associated with increasingly longer time-to-ulcer free, recent podiatrist treatment was associated with shorter time-to-ulcer-free, PAD and ulcer size had time-limited effects on

being ulcer-free, and adjusted ulcer-free probability graphs were plotted to predict the independent association that each identified factor has on patients becoming ulcer-free at any given time. Furthermore, this new analysis confirmed multiple common factors previously reported to be associated with healing at certain time points up to 12 months, were also associated with being ulcer-free at any given time point up to 24 months, such as smoking, neuropathy, mild infection and deep ulcers.

Every year of younger age, compared to those 60 years or older, was found to be associated with increasingly longer time-to-ulcer-free at any given time up to 24 months. This is a much more specific finding compared to our previous letter that simply compared age categories and found that aged 18-49 years was associated with not healing at three and 12 months, compared 60-69 years [24]. Other recent studies have reported younger age groups to associate with other poor DFU outcomes, such as infection, hospitalisation, and recurrence [3, 24, 34, 35]. These altogether suggest that younger patients may require increasingly intensive care and monitoring when it comes to improving DFU outcomes. We hypothesise that these younger ages may be indicative of younger-onset type 2 diabetes, emerging as a more severe phenotype for diabetes-related complications [24, 34, 35], or being in jobs or lifestyles that require more weight-bearing activity, resulting in higher plantar tissue stress and delayed healing [3]. However, we should point out, whilst we were able to adjust for diabetes type, due to a large proportion of missing data we were unable to adjust for diabetes duration in our analysis which may have been implicated in this finding. Thus, future research should further investigate the influence of age of diabetes onset, diabetes duration, employment and high plantar tissue stress factors on different DFU outcomes.

In terms of other novel factors found in this new analysis, those receiving recent podiatrist treatment for their DFU, either in the week prior to or at presentation at a DFU centre, were identified to be independently associated with shorter time-to-ulcer-free. Whilst this factor was

close to achieving significance in our previous letter at three months, and most participants in this cohort received such recent podiatry treatment, this novel finding suggests that early podiatry treatment is beneficial for DFU outcomes, and aligns with growing evidence that DFU patients treated by a podiatrist, prior to or as part of a multi-disciplinary Diabetic Foot Service, have much lower risk of future amputation [36-38]. We hypothesise the reason may be that DFU patients attending a podiatrist are more likely to present with less severe DFU and be referred earlier to a Diabetic Foot Service. Thus, this seems to support the important impact that earlier access to Diabetic Foot Services has on improved DFU outcomes.

In this new analysis, we were able to investigate the time-varying effects of factors for the first time to our knowledge. We found more severe PAD (both critical and mild-to-moderate PAD) and larger ulcer size categories (>3cm^2 and >1cm^2), previously found associated with non-healing at 3 and 12 months [9, 15, 20, 24, 39], to have time-varying associations with time-to-ulcer-free. Our investigation suggests that more severe PAD and larger ulcer sizes have important escalating negative associations on DFU outcomes at baseline, but the association diminishes with time post-presentation until after 6 months they have little-to-no association. For PAD this may potentially be due to subsequent inpatient treatments that we didn't capture, such as revascularization, that can positively modify PAD severity [40]. This time-limited phenomenon may also be due to the patients presenting with more severe PAD or larger ulcer sizes also having more severe comorbidities that were more likely to lead to early amputation or death. Although we did adjust for multiple comorbidities in our models, we didn't adjust for comorbidity severity and the censoring of participants with early amputation or death may also have impacted these findings. Regardless, we recommend that future studies investigate the time-varying effects of these factors alongside subsequent treatments.

Visualising the probability to become ulcer-free is another asset of this new analysis, by using the parametric functionality of the flexible parametric survival model. Unlike other fields

including cancer research [41], most previous time-to-event analyses in the DFU field have used only Cox models. While reporting HRs as the measure of effects, Cox models do not provide any direct information on model-adjusted rate (i.e. adjusted ulcer-free probability) for a person with certain factors like parametric models. The novel probability graphs in this analysis (Figure 4) should help provide clinicians with more precise understanding of the influence that each factor has on predicting the time it may take for their presenting patients to be ulcer-free during their care, information of great value to their patients [23].

The value that these graphs provide is perhaps most evident for the factor of living in a regional or remote area. The adjusted probability shows that with all covariates being equal, for every 100 patients treated over six months in different geographical areas, 65 would become ulcer-free in a major city, 55 in regional area, and only 40 in remote area (Figure 4; eTable 4). We hypothesise, like we did in our previous letter [24] and others have for amputation [42, 43], that geographical remoteness may be indicative of infrequent access to care, reduced socio-economic status or poorer health literacy [42-45]. Whilst we didn't collect socio-economic status or health literacy, in unpublished post-hoc analyses, we did find statistically larger mean number of Diabetic Foot Service visits in those from major cities, which supports infrequent access to care being implicated.

Further, we confirmed that receiving knee-high offloading treatment at presentation was also associated with shorter time-to-ulcer-free in this new analysis as per our previous letter [24]. This is perhaps unsurprising, considering these treatments are supported by high-quality trials and recommended as a gold standard DFU treatment in guidelines [46-48]; however, their use in clinical practice has been disappointingly low [46-48]. These collective findings, suggest that methods to improve earlier access and frequency of guideline-based care for patients with DFU may help shorten time-to-ulcer-free.

Apart from these novel findings, our new analysis confirms several important indicators previously identified from major metropolitan tertiary centres, such as smoking, neuropathy, PAD, ulcer size, depth and infection [9, 10, 13, 15, 17, 39]. Whilst smoking has previously been found to associate with poor DFU healing in only small tertiary centres [49], potentially due to tissue hypoxia [49, 50], our finding seems to also confirm this relationship on time-to-ulcer-free in a larger, diverse, cohort. Additionally, we found mild infection predicted longer time-to-ulcer-free, but perhaps surprisingly moderate-to-severe infection did not. We hypothesise that moderate-to-severe infection is more likely to result in hospitalisation and more aggressive treatments, such as intravenous antibiotics and surgical procedures, which may have helped infection resolution, and in turn shorten time-to-ulcer free compared to mild infection that typically receives a heterogenous array of oral antibiotics [51]. Otherwise, these findings emphasise the need for inclusion of all these important factors in DFU assessment and classification tools for patients attending diverse centres [12].

Several limitations should be considered when interpreting this paper. First, we used some self-reported demographic and comorbidity variables. However, these variables were captured using a valid and reliable standard QHRFF data collection form [30]. Second, while alternative approaches are possible for variable selection, the variables included using the $p<0.1$ entry threshold is consistent with those of clinical importance. Third, missing data existed for some variables. However, for variables with 10-25% missing data we tried to minimise any potential bias by using multiple imputation and missing category methods in both Cox and flexible parametric models, and reassuringly found the HRs were very similar between methods (eTable 2). We did though exclude variables with more than 25% missing data, which meant we had to exclude diabetes duration and HbA1c and this may have been implicated in our younger age findings [9, 17, 39, 52]. Fourth, our definition of moderate PAD (<70mmHg) was a lower threshold than the <60mmHg recommended in guidelines, but we did use <30mmHg

for critical PAD as recommended [12, 40]. Fifth, we did not collect ulcer location, reported to influence individual DFU healing [39], however, this is potentially less of a limitation in patients with multiple DFUs. Lastly, apart from amputation, we did not capture treatments occurring after baseline, such as inpatient interventions, and this may have been a reason why we did not find moderate-to-severe infection to be a factor for time-to-ulcer-free.

Several important strengths should also be considered. First, this study is one of the largest prospective investigations of DFU outcomes in terms of patient numbers, sites, geographical diversity, length of follow-up time and factors explored, capturing around 50% of patients with DFU in Queensland [24]. Second, robust variable selection and analytical methods were applied, including two robust sophisticated multivariable model: Cox proportional hazards, and flexible parametric survival model that appropriately incorporated time-varying effects. Third, in addition to exploring independent factors, we took advantage of the predictive ability of our parametric model to quantify the adjusted probability of being ulcer-free over time. Last, our outcome of being ulcer-free has been recommended as a more important patient-level outcome than healing of an individual ulcer as used in some other studies [23].

In conclusion, we identified both novel and confirmatory factors that were independently associated with time-to-ulcer-free from a large diverse cohort with DFUs followed up for two years. Further, our use of flexible parametric survival model performed similarly well to that of the more-commonly used Cox models and provided the flexibility to investigate the time-varying effects. Adjusted ulcer-free probability graphs show the predicted influence each factor has on being ulcer-free, with largest disparities by geographical remoteness and PAD. Our findings should improve the understanding of patients, clinicians, researchers and policy makers to the influence that these factors have on time-to-ulcer-free in people with DFU.

Acknowledgements

The research on which this paper is based was conducted using the Queensland High Risk Foot Form Database resource. We are most grateful to the Diabetic Foot Working Group, Queensland Statewide Diabetes Clinical Network (Australia) and to the individual centers that provided the data. The authors acknowledge the participants of the Diabetic Foot Working Group: Kimberley Canning, Danielle Charles, Patrick Derhy, Pankaj Jha, Achamma Joseph, Ewan Kinnear (chair), Amy Langley, Shireen Lazaro, Peter Lazzarini, Rebecca Mann, Helen Martin, Sharon O'Rourke and Helen Sheahan.

Funding

This work was supported by the Chinese Scholarship Council and Australian National Health and Medical Research Council (Grant numbers 1143435 and 1161138). The funding sources had no role in study design, collection, analysis, interpretation, writing or decision to submit this manuscript for publication.

Declarations of interest

The authors declare that they have no relevant competing interests

Authors' contributions

YZ contributed to conception and design of the study, data acquisition, analysis and interpretation, drafted and critically reviewed the paper for intellectual content. SC contributed to conception and design of the study, data analysis and interpretation, drafted and critically reviewed the paper for intellectual content. SMM contributed to conception and design of the study, data interpretation and critically reviewed the paper for intellectual content. RP

contributed to conception and design of the study, data acquisition, and critically reviewed the paper for intellectual content. JJvN and QC contributed to data analysis and interpretation and critically reviewed the paper for intellectual content. PHD and EMK contributed to conception and design of the study, data acquisition, and critically reviewed the paper for intellectual content. PAL contributed to conception and design of the study, data acquisition, analysis and interpretation, drafted and critically reviewed the paper for intellectual content. All authors reviewed and approved the final version of the article. The corresponding author had full access to all the data and final responsibility for publication submission.

Data statement

The data that support the findings of this study are available from the Queensland Statewide Diabetes Clinical Network and Queensland Health Statistics Branch, but restrictions apply to the availability of these data, which were used under approvals for the current study, and so are not publicly available. This data was made available to the authors following successful applications for Human Research Ethics Committee Approval and a Public Health Act waiver, a legal act of the Queensland Government. Thus, the data has been obtained from the data custodians, the Queensland Statewide Diabetes Clinical Network and Queensland Health Statistics Branch; only after an ethics application and Public Health Act waiver application were successfully approved. Data are however available to other researchers who follow this same process and contact the Queensland Health Statistics Branch at HSBresearch@health.qld.gov.au .

Table 1: Definitions of included variables.

Variables	Definitions
Demographics (from self-report)	
Sex	Participant identifies as male, female or indeterminate/intersex
Age	Participant's age in years at time of the first visit
Indigenous status	Participant identifies as being of Aboriginal and/or Torres Strait Islander origin and is respectfully referred to as being Indigenous for the purpose of the study
Geographical remoteness	Participant's residential postcode was transformed into geographical remoteness areas (major city, regional area (inner or outer regional area), remote area (remote or very remote area)), according to Remoteness Areas Index of Australia (Australian Bureau of Statistics) [53]
Comorbidity (from self-report)	
Diabetes type	Participant has been diagnosed with Type1 or Type 2 diabetes mellitus
Diabetes duration (years)	Year participant was diagnosed was used to calculate diabetes duration
Glycated haemoglobin (HbA1c)	The participant's most recent reported glycated haemoglobin level (HbA1c). HbA1c % was converted into mmol/mol.
Hypertension	Participant has been diagnosed with hypertension: Blood pressure of >140mmHg systolic and/or >90mmHg diastolic.
Dyslipidemia	Participant has been diagnosed with dyslipidemia: Lower-density lipoprotein cholesterol >2.5 mmols/L, Triglycerides >2.0mmol/L or Cholesterol >6.2mmol/l.
Cardiovascular disease	Participant has been diagnosed with cardiovascular disease: All diseases and conditions of the heart and blood vessels, including myocardial infarction, angina or stroke.
Chronic kidney disease	Participant has been diagnosed with chronic kidney disease: Estimated Glomerular filtration rate (eGFR) <90mL/min.
End stage renal failure	Participant has been diagnosed with end stage renal failure: Estimated Glomerular filtration rate (eGFR) <15 mL/min, on dialysis and/or had a kidney transplant.
Smoker	Participant smokes tobacco regularly or has smoked in the previous 4 weeks.
Limb (from clinically diagnoses)	
Previous foot ulcer	History of a previous healed foot ulcer. Participant self-report is acceptable.
Previous amputation	The participant has had an amputation procedure through (part of) the lower limb confirmed on clinical examination
Neuropathy	Lack of protective sensation to a 10-gram monofilament on at least 2 of 3 plantar forefoot locations
Peripheral artery disease	Mild to moderate PAD: Toe systolic pressure 30-70mmHg

	Critical PAD: Toe systolic pressure <30mmHg
Foot deformity	Scored at least 3 points on a 6-point foot deformity score (one point each scored if small muscle wasting, Charcot foot deformity, bony prominence, prominent metatarsal heads, hammer/claw toes, or limited joint mobility present).
Acute Charcot foot	Suspected Acute Charcot foot due to currently having a red, hot, swollen, unilateral neuropathic foot joint without an ulcer in close proximity.
Ulcer (from clinically diagnoses)	
Ulcer size	Ulcer surface area was estimated by multiplying length of ulcer in mm by width of ulcer in mm. Participants with multiple ulcers had the surface area of all ulcers summed together for a combined ulcer surface area in mm^2. Ulcer surface area was then categorized into: $<1cm^2$, $1\text{-}3cm^2$, $>3cm^2$
Deep ulcer	Ulcer penetrating to tendon, capsule, bone or joint, including University of Texas Wound Classification system depth categories of 2 or 3
Infection	At least 2 of the following signs or symptoms were present around the ulcer: erythema, swelling, warmth, tenderness or pain, purulent discharge. Mild infection: Erythema extends <2cm from the edge of the ulcer Moderate or systemic infection: Erythema extends >2cm from the edge of the ulcer +/or systemic signs or symptoms of infection.
Recent DFU treatment by*:* (from self-report)	
Podiatrist	A podiatrist provided treatment for the participant's foot complication in the week prior to, or at, the current visit to a Diabetic Foot Service.
General practitioner (GP)	A GP provided treatment for the participant's foot complication in the week prior to, or at, the current visit to a Diabetic Foot Service.
Surgical specialist	A surgical specialist provided treatment for the participant's foot complication in the week prior to, or at, the current visit to a Diabetic Foot Service.
Medical specialist	A medical specialist physician provided treatment for the participant's foot complication in the week prior to, or at, the current visit to a Diabetic Foot Service.
Nurse	A nurse provided treatment for the participant's foot complication in the week prior to, or at, the current visit to a Diabetic Foot Service.
Others	Other health professionals provided treatment for the participant's foot complication in the week prior to, or at, the current visit to a Diabetic Foot Service.
Current DFU treatment (from clinically diagnoses)	
Debrided	Sharp debridement of ulcer performed in the current visit.
Dressing appropriate	Dressing applied during current visit was considered appropriate if it promoted a moist wound healing environment unless clinically contraindicated.
Antibiotics prescribed	Antibiotic therapy commenced in the current visit if needed (in participants with ulcers that are infected or non-healing) or medical practitioner has prescribed or been contacted to prescribe antibiotic therapy
Knee-high offloading	Knee-high offloading device (removable or non-removable) is already used or has been prescribed in the current visit.
Footwear appropriate	Footwear was considered appropriate for the contralateral foot in the current visit if it protects against injury, allowed appropriate offloading if required (such as insoles) and encouraged safe mobility.
Patient educated	Participant was provided education on foot-related self-care in the current visit.
Amputation identified from hospital dataset	
Minor amputation	ICD-10-AM (the International Statistical Classification of Diseases and Related Health Problems, Tenth Revision, Australian Modification) procedure codes 4433800,4435800,9055700,4436100,4436101,4436400,4436401
Major amputation	ICD-10-AM procedure codes: 4436701,4436702,4437000,4437300,4436700

Table 2: Participant baseline characteristics (number (%) unless otherwise stated and median time-to-ulcer-free (95% CI)

Variable	n	Total	Median time-to-ulcer-free[†]
Total participants	4,709	4,709 (100%)	112 (105-119)
Demographics			
Male	4,709	3,275 (69.5%)	113 (105-121) vs. 106 (97-124)[¶]
Age (years)*	4,708	63 (54-72)	-
Indigenous status	4,709	495 (10.5%)	181 (147-235) vs. 106 (100-114)[¶]
Geographical remoteness	4,559		
Major city		2,486 (54.6%)	88 (84-98)
Regional area		1,857 (40.7%)	140 (126-154)
Remote area		216 (4.7%)	315 (184-659)
Comorbidities			
Diabetes type	4,709		
Type 1		425 (9.0%)	113 (91-140)
Type 2		4,284 (91.0%)	112 (105-119)
Diabetes duration (years)*	1,736	15 (8-22)	-
HbA1c*	1,203	8 (6.9-9.7) %; 64 (52-82) mmol/mol[‡]	-
Hypertension	4,709	2,502 (53.1%)	119 (107-126) vs. 106 (98-116)[¶]
Dyslipidemia	4,709	1,701 (36.1%)	112 (100-126) vs. 112 (104-119)[¶]
Cardiovascular disease	4,709	986 (20.9%)	126 (112-149) vs. 108 (100-116)[¶]
Chronic kidney disease	4,709	620 (13.2%)	125 (105-155) vs. 112 (104-118)[¶]
End stage renal failure	4,709	185 (3.9%)	233 (138-312) vs. 111 (102-117)[¶]
Smoker	4,709	494 (10.5%)	168 (142-216) vs. 106 (99-114)[¶]
Limb			
Previous foot ulcer	4,709	3,621 (76.9%)	111 (102-118) vs. 123 (105-142)[¶]
Previous amputation	4,697	1,428 (30.4%)	140 (125-152) vs. 101 (94-110)[¶]
Neuropathy	3,866	3,319 (85.9%)	124 (115-132) vs. 88 (70-112)[¶]
Peripheral artery disease	3,800		
Nil		2,214 (58.3%)	91 (85-100)
Mild to moderate		1,357 (35.7%)	155 (135-181)
Critical		229 (6.0%)	261 (189-360)
Foot deformity	3,039	1,910 (62.8%)	126 (116-140) vs. 118 (102-134)[¶]
Acute Charcot foot	3,768	69 (1.8%)	168 (85-330) vs. 119 (112-126)[¶]
Ulcer			
Ulcer size (cm^2)*	3,597	0.70 (0.16-2.38)	-
Ulcer size			
<1cm²		2,038 (56.7%)	70 (63-74)
1-3cm²		818 (22.7%)	138 (118-160)
>3cm²		741 (20.6%)	231 (189-273)
Deep ulcer	4,654	728 (15.6%)	193 (165-223) vs. 98 (91-105)[¶]
Infection	4,702		
Nil		3,106 (66.1%)	97 (91-105)
Mild		994 (21.1%)	148 (151-173)
Moderate to systemic		602 (12.8%)	135 (119-160)
Recent DFU treatment by			
Podiatrist	4,709	4,491 (95.4%)	111 (104-117) vs. 193 (145-257)[¶]
General practitioner	4,709	420 (8.9%)	102 (83-116) vs. 113 (105-121)[¶]
Surgical specialist	4,709	266 (5.6%)	175 (142-248) vs. 109 (102-115)[¶]
Medical specialist	4,709	557 (11.8%)	149 (126-189) vs. 106 (100-114)[¶]
Nurse	4,709	1,124 (23.9%)	140 (126-156) vs. 104 (97-112)[¶]
Others	4,709	565 (12.0%)	119 (98-142) vs. 112 (105-119)[¶]
Current DFU treatment of			
Debrided ulcer	3,772	3,357 (89.0%)	112 (102-119) vs. 175 (128-222)[¶]
Dressing appropriate	3,772	3,644 (96.6%)	114 (106-124) vs. 120 (83-244)[¶]
Antibiotics prescribed	4,699	1,697 (36.1%)	147 (133-164) vs. 97 (89-105)[¶]
Knee-high offloading	4,706	1,835 (39.0%)	102 (92-113) vs. 126 (114-139)[¶]

Footwear appropriate	4,686	2,743 (58.5%)	99 (91-109) vs. 124 (113-140) ¶
Patient educated	3,772	3,721 (98.6%)	104 (91-115) vs. 114 (106-124) ¶

458 * Continuous variables are presented as median (IQR).
459 † Median time-to-ulcer-free is the time when 50% of the participants had become ulcer-free. eFigure2 displays more details in
460 the corresponding unadjusted Kaplan-Meier survival graphs.
461 ¶ Median time-to-ulcer-free for variables with two categories (Yes and No) are presented in sequence of Yes and No and
462 connected by "vs.".
463 ‡ HbA1c mmol/mol is converted from HbA1c % based on American Diabetes Association (ADA) recommendations
464 (http://www.ngsp.org/convert1.asp)
465

Figure 1 Univariable and multivariable analysis of factors associated with time-to-ulcer-free of diabetes-related foot ulcers within 2 years.

[^]The results of the category of Yes is presented, with the category of No used as the reference group for this variable. All included variables are those with $p<0.10$ on the univariable analysis.

A missing category was included when there were between 19%-25% missing values, for variables including Neuropathy, PAD, Ulcer size and Debrided ulcer.

Multivariable flexible parametric survival model (n=4,486) included all the listed variables, with PAD and ulcer size included as time varying coefficients (tvc), as they had non-proportional hazards.

Figure 2 Hazard ratio (95% CI) of continuous age, with a reference of 60 years old

Figure 3: Hazard ratio (95% CI) of PAD and ulcer size (as time-varying coefficients).

A: PAD. Hazard ratio (95% CI) of PAD as time-varying coefficients. no PAD was the reference category;

B: Ulcer size. Hazard ratio (95% CI) of ulcer size (cm^2) as time varying coefficients. Ulcer size, $<1cm^2$ was the reference. Number at risk was presented below the graph.

Note: the missing category overlaps with both categories and is not presented; the HR is fully adjusted for all other included variables. CI: Confidence Interval; PAD: Peripheral Artery Disease.

Figure 4: Predicted probability of ulcer-free (95% CI) by demographics, comorbidity, limb and treatment characteristics over time (in months).

Probability of being ulcer free in all graphs were adjusted for all included variables in the flexible parametric survival model. Graphs for variables that were not significant ($p>0.05$) in the multivariable model 2 are not presented. CI: Confidence Interval

REFERENCES

[1] Zhang Y, Lazzarini P, McPhail S, van Netten J, Armstrong D, Pacella R (2020) Global Disability Burdens of Diabetes-Related Lower-Extremity Complications in 1990 and 2016. Diabetes Care 43(5): 964-974. 10.2337/dc19-1614

[2] Armstrong D, Boulton A, Bus S (2017) Diabetic Foot Ulcers and Their Recurrence. New England Journal of Medicine 376(24): 2367-2375

[3] Jia L, Parker C, Parker T, et al. (2017) Incidence and risk factors for developing infection in patients presenting with uninfected diabetic foot ulcers. PloS one 12(5): e0177916

[4] Pickwell K, Siersma V, Kars M, et al. (2015) Predictors of Lower-Extremity Amputation in Patients With an Infected Diabetic Foot Ulcer. Diabetes Care 38(5): 852-857. 10.2337/dc14-1598

[5] Lazzarini P, Hurn SE, Kuys SS, et al. (2016) The silent overall burden of foot disease in a representative hospitalised population. Int Wound J 14(4): 716-728. 10.1111/iwj.12683

[6] Lazzarini P, Pacella R, Armstrong D, van Netten J (2018) Diabetes-related lower-extremity complications are a leading cause of the global burden of disability. Diabet Med 35(9): 1297-1299. 10.1111/dme.13680

[7] Kerr M, Barron E, Chadwick P, et al. (2019) The cost of diabetic foot ulcers and amputations to the National Health Service in England. Diabet Med 36(8): 995-1002. 10.1111/dme.13973

[8] Prompers L, Schaper N, Apelqvist J, et al. (2008) Prediction of outcome in individuals with diabetic foot ulcers: focus on the differences between individuals with and without peripheral arterial disease. The EURODIALE Study. Diabetologia 51(5): 747-755

[9] Pickwell KM, Siersma VD, Kars M, Holstein PE, Schaper NC, Eurodiale Consortium (2013) Diabetic foot disease: impact of ulcer location on ulcer healing. Diabetes Metab Res Rev 29(5): 377-383. 10.1002/dmrr.2400

[10] Örneholm H, Apelqvist J, Larsson J, Eneroth MJWR, Regeneration (2015) High probability of healing without amputation of plantar forefoot ulcers in patients with diabetes. Wound Repair Regen 23(6): 922-931

[11] National Diabetes Foot Care Audit (2019) National Diabetes Foot Care Audit Fourth Annual Report. Available from https://digital.nhs.uk/data-and-information/publications/statistical/national-diabetes-footcare-audit/2014-2018. Accessed 9 May 2021

[12] Monteiro-Soares M, Boyko EJ, Jeffcoate W, et al. (2020) Diabetic foot ulcer classifications: A critical review. Diabetes Metab Res Rev 36(S1): e3272. 10.1002/dmrr.3272

[13] Leese G, Schofield C, McMurray B, et al. (2007) Scottish foot ulcer risk score predicts foot ulcer healing in a regional specialist foot clinic. Diabetes Care 30(8): 2064-2069

[14] Jeffcoate WJ, Chipchase SY, Ince P, Game FL (2006) Assessing the outcome of the management of diabetic foot ulcers using ulcer-related and person-related measures. Diabetes Care 29(8): 1784-1787. 10.2337/dc06-0306

[15] Holman N, Young B, Stephens H, Jeffcoate W (2015) Pilot study to assess measures to be used in the prospective audit of the management of foot ulcers in people with diabetes. Diabet Med 32(1): 78-84

[16] Ha Van G, Amouyal C, Bourron O, et al. (2020) Diabetic foot ulcer management in a multidisciplinary foot centre: one-year healing, amputation and mortality rate. Journal of Wound Care 29(8): 464-471

[17] Gershater MA, Löndahl M, Nyberg P, et al. (2009) Complexity of factors related to outcome of neuropathic and neuroischaemic/ischaemic diabetic foot ulcers: a cohort study. Diabetologia 52(3): 398-407. 10.1007/s00125-008-1226-2

[18] Fife CE, Horn SD, Smout RJ, Barrett RS, Thomson B (2016) A Predictive Model for Diabetic Foot Ulcer Outcome: The Wound Healing Index. Advances in Wound Care 5(7): 279-287. 10.1089/wound.2015.0668
[19] Beckert S, Witte M, Wicke C, Königsrainer A, Coerper S (2006) A new wound-based severity score for diabetic foot ulcers: a prospective analysis of 1,000 patients. Diabetes Care 29(5): 988-992
[20] Oyibo SO, Jude EB, Tarawneh I, et al. (2001) The effects of ulcer size and site, patient's age, sex and type and duration of diabetes on the outcome of diabetic foot ulcers. Diabet Med 18(2): 133-138. 10.1046/j.1464-5491.2001.00422.x
[21] Margolis DJ, Allen-Taylor L, Hoffstad O, Berlin JA (2002) Diabetic neuropathic foot ulcers: the association of wound size, wound duration, and wound grade on healing. Diabetes Care 25(10): 1835-1839. 10.2337/diacare.25.10.1835
[22] Akturk A, van Netten JJ, Scheer R, Vermeer M, van Baal JG (2019) Ulcer-free survival days and ulcer healing in patients with diabetic foot ulcers: A prospective cohort study. Int Wound J 16(6): 1365-1372. 10.1111/iwj.13199
[23] Jeffcoate WJ, Bus SA, Game FL, Hinchliffe RJ, Price PE, Schaper NC (2016) Reporting standards of studies and papers on the prevention and management of foot ulcers in diabetes: required details and markers of good quality. Lancet Diabetes Endocrinol 4(9): 781-788. 10.1016/s2213-8587(16)30012-2
[24] Zhang Y, Cramb S, McPhail S, et al. (2021) Factors associated with healing of diabetes-related foot ulcers: observations from a large prospective real-world cohort. Diabetes Care 44(7): e1-e3. 10.2337/dc20-3120
[25] von Elm E, Altman DG, Egger M, et al. (2007) The Strengthening the Reporting of Observational Studies in Epidemiology (STROBE) Statement: Guidelines for Reporting Observational Studies. PLOS Medicine 4(10): e296. 10.1371/journal.pmed.0040296
[26] Australian Bureau of Statistics (2019) Data by region, 2013-18. Available from https://www.abs.gov.au/AUSSTATS/abs@.nsf/Lookup/1410.0Main+Features12013-18?OpenDocument. Accessed March 1 2020
[27] National Diabetes Service Scheme (2019) The Australian diabetes map. Available from https://map.ndss.com.au/. Accessed 1 May 2020
[28] van Netten J, Bus S, Apelqvist J, et al. (2020) Definitions and criteria for diabetic foot disease. Diabetes Metab Res Rev 36(S1): e3268. 10.1002/dmrr.3268
[29] Armstrong D, Lavery L, Harkless L (1998) Validation of a Diabetic Wound Classification System: The contribution of depth, infection, and ischemia to risk of amputation. Diabetes Care 21(5): 855-859. 10.2337/diacare.21.5.855
[30] Lazzarini P, Ng V, Kinnear EM, et al. (2014) The Queensland high risk foot form (QHRFF)–is it a reliable and valid clinical research tool for foot disease? Journal of foot and ankle research 7(1): 7
[31] Queensland Health (2011) Queensland High Risk Foot Form Guideline: Statewide Diabetic Foot Working Group. In: Statewide Diabetes Clinical Network (ed), Brisbane, Australia
[32] Lazzarini P, O'Rourke S, Russell A, Derhy P, Kamp M (2015) Reduced Incidence of Foot-Related Hospitalisation and Amputation amongst Persons with Diabetes in Queensland, Australia. Plos One 10(6). 10.1371/journal.pone.0130609
[33] Lambert PC, Royston P (2009) Further Development of Flexible Parametric Models for Survival Analysis. the Stata Journal 9(2): 265-290. 10.1177/1536867x0900900206
[34] Hamilton EJ, Davis WA, Siru R, Baba M, Norman PE, Davis TME (2021) Temporal Trends in Incident Hospitalization for Diabetes-Related Foot Ulcer in Type 2 Diabetes: The Fremantle Diabetes Study. Diabetes Care 44(3): 722-730. 10.2337/dc20-1743

[35] Aan de Stegge WB, Schut MC, Abu-Hanna A, van Baal JG, van Netten JJ, Bus SA (2021) Development of a prediction model for foot ulcer recurrence in people with diabetes using easy-to-obtain clinical variables. BMJ Open Diabetes Res Care 9(1). 10.1136/bmjdrc-2021-002257
[36] Tan T-W, Armstrong DG, Concha-Moore KC, et al. (2020) Association between race/ethnicity and the risk of amputation of lower extremities among medicare beneficiaries with diabetic foot ulcers and diabetic foot infections. BMJ Open Diabetes Research & Care 8(1): e001328. 10.1136/bmjdrc-2020-001328
[37] Driver VR, Goodman RA, Fabbi M, French MA, Andersen CA (2010) The impact of a podiatric lead limb preservation team on disease outcomes and risk prediction in the diabetic lower extremity: a retrospective cohort study. Journal of the American Podiatric Medical Association 100(4): 235-241. 10.7547/1000235
[38] Blanchette V, Brousseau-Foley M, Cloutier L (2020) Effect of contact with podiatry in a team approach context on diabetic foot ulcer and lower extremity amputation: systematic review and meta-analysis. Journal of Foot and Ankle Research 13(1). 10.1186/s13047-020-0380-8
[39] Ince P, Kendrick D, Game F, Jeffcoate W (2007) The association between baseline characteristics and the outcome of foot lesions in a UK population with diabetes. Diabet Med 24(9): 977-981. 10.1111/j.1464-5491.2007.02189.x
[40] Hinchliffe RJ, Forsythe RO, Apelqvist J, et al. (2020) Guidelines on diagnosis, prognosis, and management of peripheral artery disease in patients with foot ulcers and diabetes (IWGDF 2019 update). Diabetes Metab Res Rev 36(S1): e3276. 10.1002/dmrr.3276
[41] Cramb SM, Mengersen KL, Lambert PC, Ryan LM, Baade PD (2016) A flexible parametric approach to examining spatial variation in relative survival. Statistics in Medicine 35(29): 5448-5463. https://doi.org/10.1002/sim.7071
[42] Lazzarini P, Fitridge R (2019) Regional variations in amputation rates: are regional diabetic foot services the reason? ANZ Journal of Surgery 89(7-8): 796-797. 10.1111/ans.15161
[43] Margolis DJ, Hoffstad O, Nafash J, et al. (2011) Location, location, location: Geographic clustering of lower-extremity amputation among medicare beneficiaries with diabetes. Diabetes Care 34(11): 2363-2367. 10.2337/dc11-0807
[44] Disler R, Glenister K, Wright J (2020) Rural chronic disease research patterns in the United Kingdom, United States, Canada, Australia and New Zealand: a systematic integrative review. BMC public health 20(1): 7. 10.1186/s12889-020-08912-1
[45] Chen PY, Elmer S, Callisaya M, Wills K, Greenaway TM, Winzenberg TM (2018) Associations of health literacy with diabetic foot outcomes: a systematic review and meta-analysis. Diabet Med 35(11): 1470-1479. 10.1111/dme.13694
[46] Lazzarini P, Jarl G, Gooday C, et al. (2020) Effectiveness of offloading interventions to heal foot ulcers in persons with diabetes: a systematic review. Diabetes Metab Res Rev 36(S1): e3275. 10.1002/dmrr.3275
[47] Bus SA, Armstrong DG, Gooday C, et al. (2020) Guidelines on offloading foot ulcers in persons with diabetes (IWGDF 2019 update). Diabetes Metab Res Rev 36(S1). 10.1002/dmrr.3274
[48] Lazzarini P, Crews RT, van Netten JJ, et al. (2019) Measuring Plantar Tissue Stress in People With Diabetic Peripheral Neuropathy: A Critical Concept in Diabetic Foot Management. Journal of diabetes science and technology 13(5): 869-880. 10.1177/1932296819849092
[49] Fu XL, Ding H, Miao WW, Chen HL (2018) Association Between Cigarette Smoking and Diabetic Foot Healing: A Systematic Review and Meta-Analysis. Int J Low Extrem Wounds 17(4): 247-257. 10.1177/1534734618809583

[50] Xia N, Morteza A, Yang FY, Cao H, Wang AP (2019) Review of the role of cigarette smoking in diabetic foot. J Diabetes Investig 10(2): 202-215. 10.1111/jdi.12952
[51] Commons RJ, Raby E, Athan E, et al. (2018) Managing diabetic foot infections: a survey of Australasian infectious diseases clinicians. Journal of Foot and Ankle Research 11(1): 13. 10.1186/s13047-018-0256-3
[52] Fernando ME, Seneviratne RM, Tan YM, et al. (2016) Intensive versus conventional glycaemic control for treating diabetic foot ulcers. The Cochrane database of systematic reviews(1): Cd010764. 10.1002/14651858.CD010764.pub2
[53] Australian Bureau of Statistics (2016) Australian Standard Geographical Classification (ABS Cat No.1270.0). Available from https://www.abs.gov.au/AUSSTATS/abs@.nsf/Lookup/1270.0.55.005Explanatory%20Notes1July%202016?OpenDocument. Accessed 23 June 2019