Burden of Diabetes-Related Foot Disease in North Queensland, Australia

Thesis submitted by

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- Golledge J, Fernando M E, Alahakoon C, Lazzarini P A, Wouter B, van Netten J, Bus S A Efficacy of home monitoring of foot temperature for risk reduction of diabetes-related foot ulcer: A meta-analysis. Diabetes-Metabolism and Research Reviews. 2022; 38 (6) e3549

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Abstract

Diabetes-related foot disease (DFD) is defined as infection, ulceration, and soft tissue destruction of the foot in a person with diabetes. It is usually accompanied by peripheral neuropathy and peripheral artery disease (PAD) and occurs in 10-20% of patients with diabetes. DFD is associated with high morbidity, mortality and reduced the quality of life. The increasing incidence and its propensity for recurrence cause a substantial burden to the healthcare system. The burden of DFD in Australia is significant. DFD is known to cost around 1.6 billion Australian dollars per year to the healthcare system. It is estimated that 50,000 people in Australia are living with diabetes-related foot ulcers (DFU), while 300,000 are at-risk of similar ulceration. DFD is more prevalent among first nation Australians (Aboriginal and Torres Strait Islander Australians) compared to the non-Indigenous Australians. The aim of this project was to describe DFD related disease burden in North Queensland Australia. The population of North Queensland has a higher representation of Aboriginal and Torres Strait Islander Australians and varying accessibility to healthcare facilities. The studies were conducted in Townsville University Hospital, a tertiary care hospital in North Queensland.

An initial systematic review was conducted to identify studies that were looking at readmission following an index admission for DFD. Sixteen studies were identified and a total of 124,683 participants were included. The mean total 30-day readmission rate was 22.0% (95% confidence interval; 95% CI 17.0%, 27.0%) while the mean DFD related 30-day readmission rate was 10. 0% (95% CI: 7.0% to 15.0%). We were unable to identify a prospective observational cohort study from Australia that assessed the readmission rate following admission for DFD.

Based on the above finding, we conducted a prospective observational cohort study to quantify the incidence of and risk factors for readmission following and index admission for DFD. A total 190 patients were recruited, of which 41 patients (21.6%) were Aboriginal or Torres Strait Islander Australians. One hundred participants (52.6%) were readmitted to hospital at least once over 12 months. The commonest reason for readmission was for treatment of foot infection (84.0% of first readmission). Absent pedal pulses (unadjusted hazard ratio [HR], 1.90; 95% CI, 1.26, 2.85), loss of protective sensation (LOPS) (unadjusted HR, 1.98; 95% CI, 1.08, 3.62) and male sex (unadjusted HR, 1.62; 95% CI, 1.03, 2.54) were predictive factors of readmission.

Absence of pedal pulses is a surrogate marker of PAD. The anatomical distribution, severity, and outcomes of PAD in Aboriginal and Torres Strait Islander Australians compared with non-Indigenous Australianshas not previously been investigated. We assessed the anatomical distribution and severity of PAD in 73 Aboriginal and Torres Strait Islander and 242 non-Indigenous Australians using a validated angiographic scoring system. We found that Aboriginal and Torres Strait Islander Australians were more likely to present with symptoms of chronic limb threatening ischemia (81% versus 25%, $p<0.001$ respectively), had greater median (Inter quartile range; IQR) angiographic scores for the symptomatic limb (7 [5-10] vs 4 [2-7]) and tibial arteries (5 [2-6] versus 2 [0-4]), and had higher risks of major amputation (HR, 6.1, 95% CI 3.6 to 10.5; $p<0.001$) and major adverse cardiovascular events (MACE; HR 1.5, 95% CI 1.0 to 2.3], $p=0.036$).

We further investigated the association between remoteness and Aboriginal and Torres Strait Islander status with risk of major amputation following initial treatment of DFD by a minor amputation. We were able to include a total of 534 participants of which 306 (57.3%) residing in metropolitan or regional centers, and 228 (42.7%) in rural and remote communities. 144 (27.0%) Aboriginal or Torres Strait Islander Australians were included.

During a median (IQR) follow-up of 4.0 (2.1-7.6) years, 103 participants (19.3%) had major amputation, 230 (43.1%) had repeat minor amputation and 250 (46.8%) died. The risk (HR [95% CI]) of major amputation and death were not significantly higher in participants residing in rural and remote areas (0.97, 0.67-1.47; and 0.98, 0.76-1.26) or those who identified as Aboriginal or Torres Strait Islander people (HR 1.44, 95% CI 0.96, 2.16 and HR 0.89, 95% CI 0.67, 1.18). Ischemic heart disease (IHD), PAD and osteomyelitis and foot ulceration ($p<0.001$ in all instances) were independent risk factors for major amputation.

Overall, we found there is a substantial disease burden associated with DFD in North Queensland. Therefore, we conducted a systematic review and meta-analysis to quantify evidence form randomised controlled trails to assess the best method that can be used to prevent recurrence of DFU. We pooled evidence form three interventions namely, home foot temperature monitoring, offloading footwear and patient education. Participants' who performed home foot temperature monitoring (Odds ratio [OR] 0.51, 95% CI 0.31 to 0.84, n=468) and those provided offloading footwear (OR 0.48, 95% CI: 0.29 to 0.80, n=1438) were less likely to develop DFU. Patient education programs did not significantly reduce DFU incidence (OR 0.59, 95% CI: 0.29-1.20, n=823).

Conclusion: The disease burden related to DFD in North Queensland is substantial. Over 50% of the patients were readmitted within one year following an index admission for DFD. Aboriginal and Torres Strait Islander Australians with PAD tend to present to the hospital with CLTI and significant distal vessel disease and are at higher risk of major amputation. The rates of major amputation following an index minor amputation is not significantly different between those who reside in regional and remote localities or by ethnicity which indicate uniform utilisation of healthcare delivered to people residing in North Queensland Australia. Offloading footwear should be offered to patients with DFD to prevent recurrence of disease.

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List of abbreviations

ABPI	Ankle brachial pressure index
ACEI	Angiotensin converting enzyme inhibitor
ARB	Angiotensin receptor blockers
AUC	Area under the curve
AUD	Australian dollar
BMI	Body mass index
CAD	Coronary artery disease
CHD	Coronary heart disease
CHF	Congestive heart failure
CI	Confidence interval
CKD	Chronic kidney disease
CLTI	Chronic limb threatening ischaemia
COPD	Chronic obstructive pulmonary disease
CRP	C-reactive protein
CTA	Computed tomographic angiography
DFD	Diabetes-related foot disease
DFI	Diabetes-related foot infection
DFU	Diabetes-related foot ulcers
DPN	Diabetes-related peripheral neuropathy
DSA	Digital subtraction angiogram
ESRF	End-stage renal failure

HbA1c	Haemoglobin A1c
HR	Hazard ratio
HREC	Human research ethics committee
HT	Hypertension
ICD	International classification of disease
IHD	Ischaemic heart disease
IQR	Inter-quartile range
IWGDF	International working group of diabetic foot
LOPS	Loss of protective sensation
LOS	Length of stay
LRT	Likelihood ratio test
MACE	Major adverse cardiovascular events
MMM	Modified Monash Model
NA	Not applicable
NHMRC	National Health and Medical Research Council
NR	Not reported
OR	Odds ratio
ORMIS	Operating rooms management system
PAD	Peripheral artery disease
PN	Peripheral neuropathy
PRISAMA	Preferred Reporting Items for Systematic Reviews and Meta-Analysis
PROSPERO	Prospectively registered systematic reviews in health and social care
RCT	Randomised controlled trial

ROC	Receiver operating characteristic curve
SINBAD	Site ischemia neuropathy bacterial infection area depth classification
TIA	Transient ischemic attack
TP	Toe pressure
TUH	Townsville University Hospital
UK	United Kingdom
US/USA	United States of America
UTWCS	University of Texas wound classification system
WIFI	Wound ischemia foot infection classification

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1. Background

1.1 Pathophysiology of Diabetes-related foot disease (DFD)

Diabetes is a broad term given to group of chronic metabolic conditions that occurs following the reduction of insulin production from the pancreas (Type I) or failure of the body to utilize available insulin effectively (Type 2). This results in chronic elevation of blood glucose levels. Chronic elevation of blood glucose concentration damages all body tissues, including nerves and blood vessels, impairing their function mainly following the glycation of proteins that are found in those tissues (1, 2).

The global prevalence of diabetes in 2019 was estimated to be 9.3% (463 million people) and is predicted to be 10.2% (578 million people) by the year 2030 and 10.9% (700 million people) by the year 2045. The prevalence was higher in urban (10.8%) than in rural regions (7.2%), and in high-income (10.4%) than low-income countries (4.0%) (3). The global healthcare costs of managing patients with diabetes were predicted to account for 12% of all healthcare costs by 2030 (4). There was a continuing increase in the total direct costs of diabetes in the U.S over the years; US$116 billion in 2007, US$176 billion in 2012, and US$237 billion in 2017. Care for a single person with diabetes cost an average of US$16,752 per year in 2017 (5). Similar to other countries, the cost of health service utilization by patients with diabetes in Australia was much higher compared to those without diabetes, given the fact that this disease is associated with a high morbidity and mortality (6, 7).

Complications of diabetes can be diverse as it can affect multiple organ systems. Such complications can range from life threatening emergencies such as ketoacidosis to long term complications that involve vasculature. Vascular complications are broadly divided into two, macrovascular and microvascular complications. Macrovascular complications include coronary artery disease (CAD) leading to myocardial ischemia or myocardial infarctions,

peripheral artery disease (PAD) and carotid artery disease leading to strokes (8). Microvascular complications of diabetes include diabetes-related retinopathy involving the eye, diabetes-related nephropathy involving the kidney and diabetes-related peripheral neuropathy (DPN) involving the peripheral nerves (9). PAD and DPN contribute to the development of diabetes-related foot disease (DFD).

DPN is a chronic disease condition that leads to nerve dysfunction. (10). It can be divided into motor neuropathy, sensory neuropathy and autonomic neuropathy (11). Motor neuropathy within the lower limb leads to foot deformities (Charcot deformity: chronic deformity of foot with gradual weakening of bone and surrounding tissue) and subsequent biomechanical abnormalities that alter the shape of the plantar surface of the foot creating areas of high plantar pressure (11). Autonomic neuropathy causes reduced sweating (11). Sensory neuropathy leads to a lack of proprioception, lack of vibration perception and later total sensory impairment (12). Usually, lower limb extremities are affected, and the sensory loss is classically described as “stocking type of sensory loss” and is seen in patients with prolonged uncontrolled diabetes (12). Since lower limbs bear the body weight, the development of calluses and foot ulcers are seen in the lower limbs especially on deformed limbs following motor neuropathy (11). These ulcers can get infected and complicate the outcome of the disease given the low immunity in such patients (13). Very poor blood supply can sometimes precipitate gangrene leading to further loss of tissues (14). An illustration of the development of a diabetes-related foot ulcer (DFU) is provided in Figure 1 (11).

Several pictures of DFD are shown in Figures 2 and 3. Figure 2 illustrates different types of DFU patients present to the hospital with and Figure 3 illustrates ischemic complications of DFD.

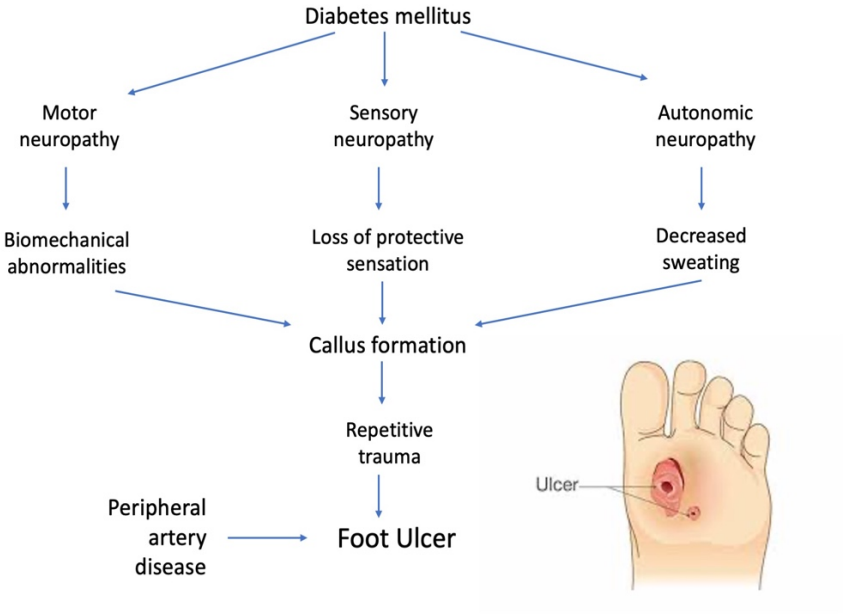

Figure 1-1 Development of a foot ulcer

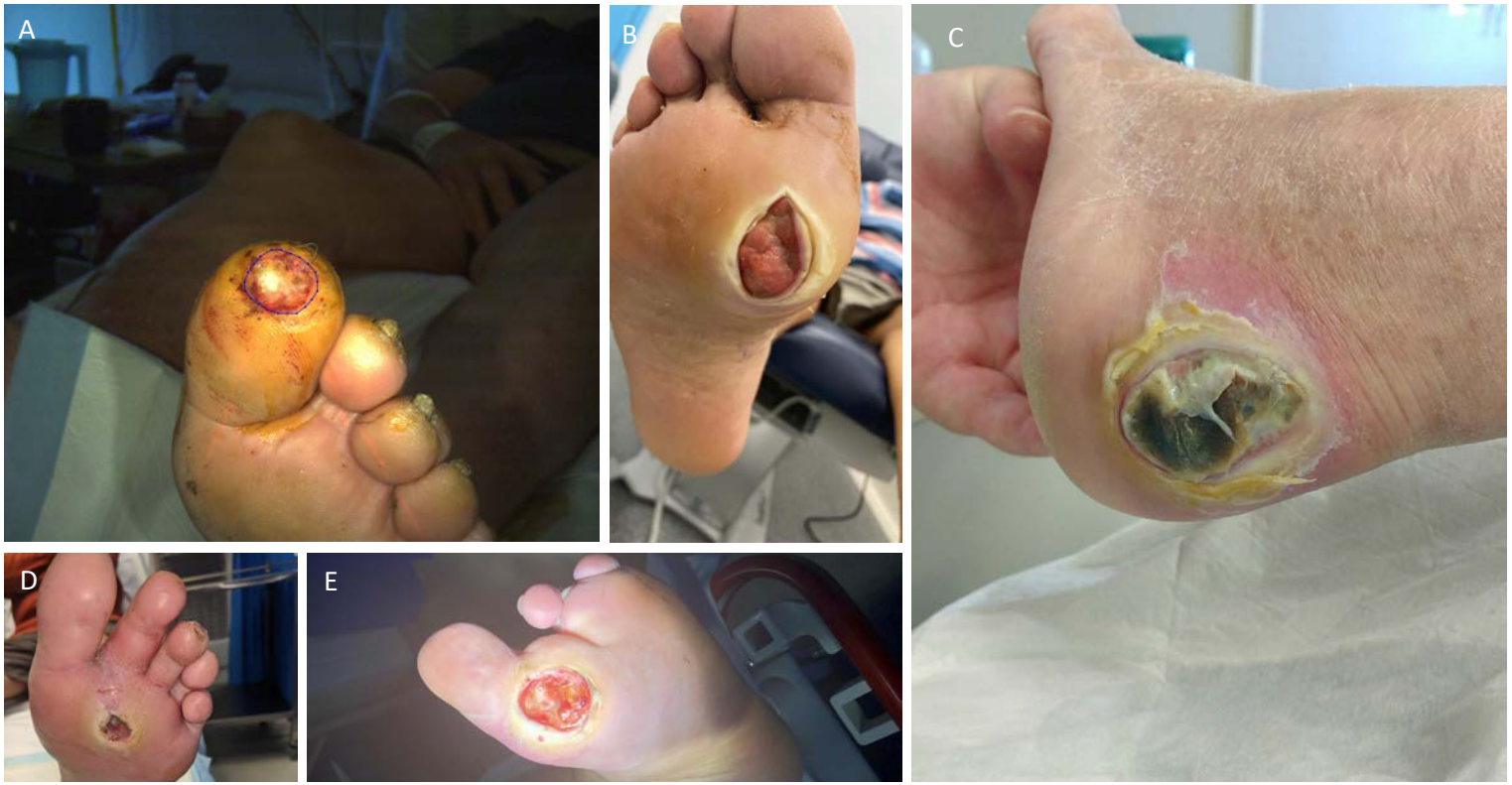

Figure 1-2 Different types of foot ulcers

A, a superficial ulcer in the hallux, B; a deep ulcer reaching the muscle, C; a heel ulcer with necrotic tissue and inflammation in the surrounding tissue, D; a deep ulcer reaching the bone with superimposed infection, E; a superficial ulcer in a person with two previous toe amputations.

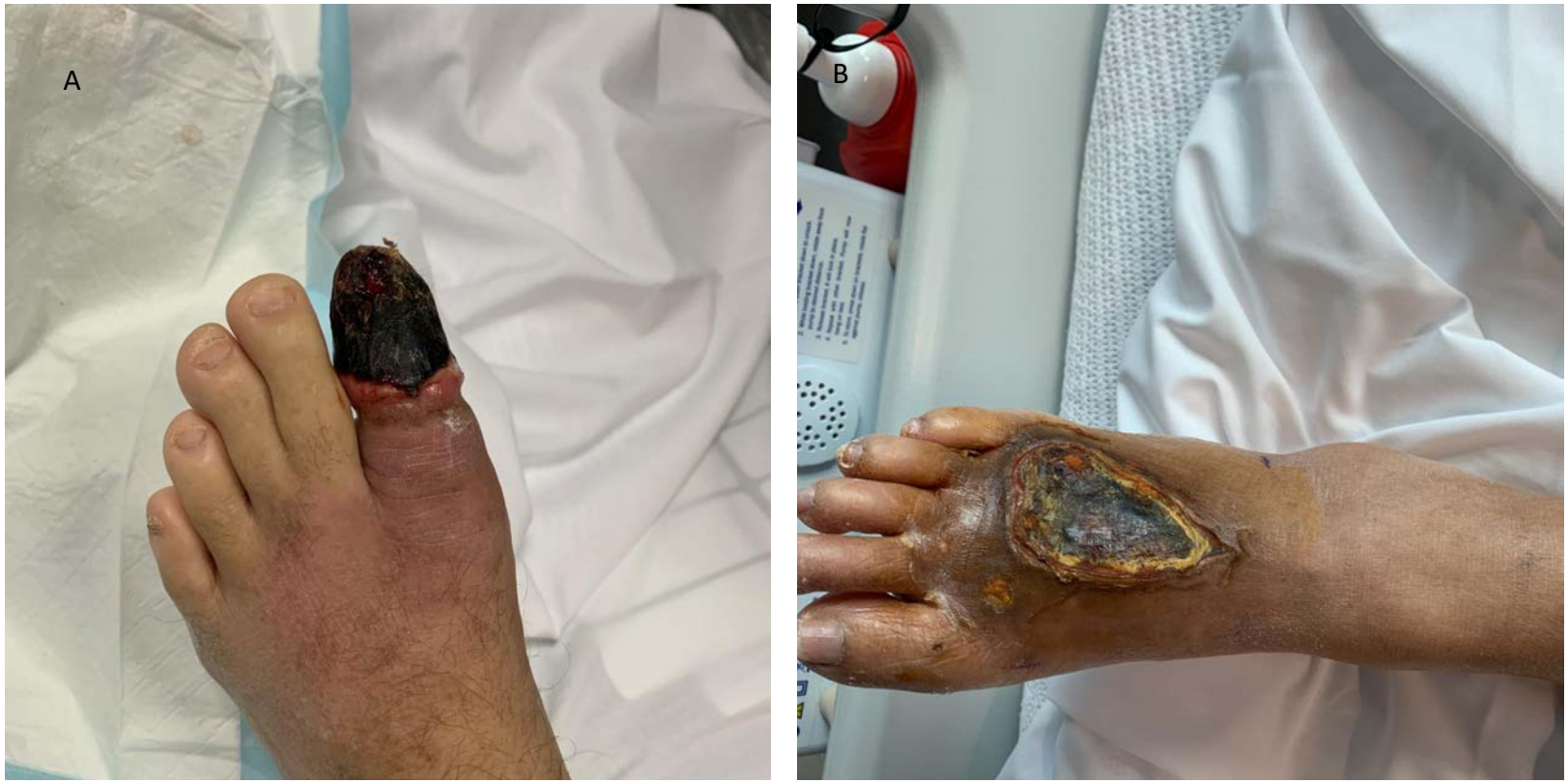

Figure 1-3 Different types of gangrene

A; a gangrenous toe, B; an extensive ischemic foot ulcer in the dorsum of the foot

1.2 Global burden of DFD

DFD is a major complication of long-standing uncontrolled diabetes and was estimated to affect up to 34% of people with diabetes in their lifetime (11). DFD is ranked within the top ten causes of disability of all medical conditions (15). DFD occurs subsequent to DPN (16) which is a sequela of microvascular disease and is usually associated with PAD (17, 18). It was estimated that over 130 million people all around the world are at risk of developing a DFD and that 20 million people worldwide are suffering from diabetes related foot ulcers (DFU) alone (15). It is among the top 40 diseases for global prevalence (11, 19). DFU is the most frequent complication of all DFD (11). The annual incidence of DFU varies between populations and the global incidence is believed to be around 6.3 % for clinical based studies and 4.8% for population-based studies (20). Based on the prevalence data from the International Federation of Diabetes in 2015, it was estimated that foot ulcers would annually develop in 9.1 million to 26.1 million people with diabetes. The same study reported that persons with a history of foot ulceration was believed to be 12.9 million to 49.0 million globally (21). The lifetime incidence of DFU is estimated to be between 19-34% in persons with long standing diabetes (11).

A recent systematic review and meta-analysis reported that the pooled estimate for DFU recurrence was 22.1% per person years (95% Confident interval [CI], 19.0-25.2%). These results were based on 49 studies. The same study reported that the recurrence rates of diabetic foot ulcers before 2002, between 2002 and 2008, and after 2008 were 22.2% per 1000 person years (95% CI, 17.6%-26.8%), 21.9% per person years (95% CI, 17.0%-26.8%), and 21.8% per person years (95% CI, 16.3%-27.2%), respectively. This study also reported that the recurrence rates varied regionally, but these results could be biased by under-reporting with very high rates as seen in Europe and Australia and lower rates seen in Asia and Africa (22) (Figure 4).

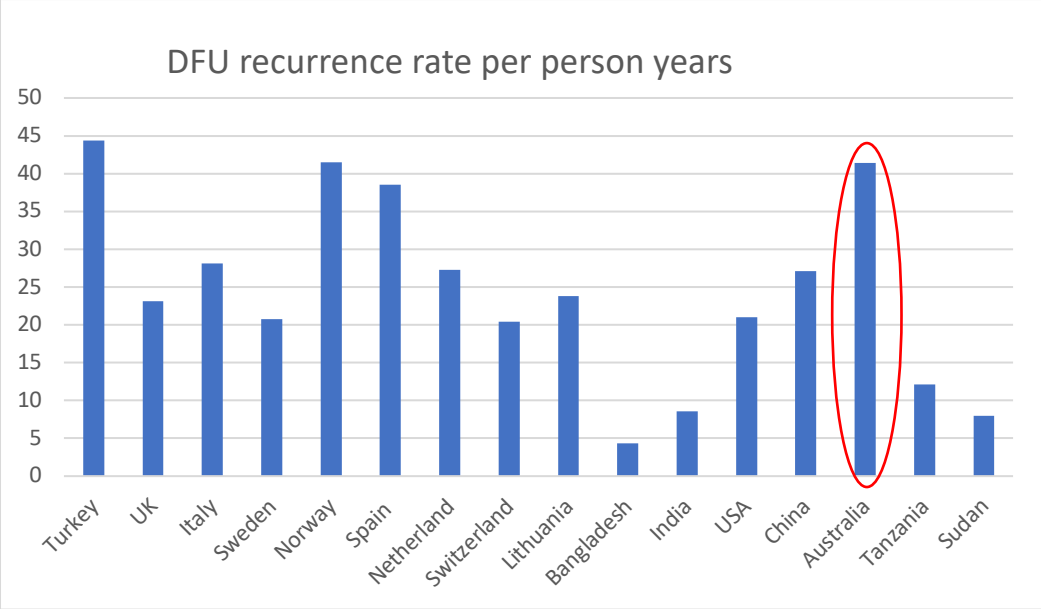

Figure 1-4 DFU recurrence rate per person years

These data were reported for each country by Fu et al. Note a higher recurrence rate in Australian population compared to many countries that reported DFU recurrence rates.

DFU recurrence contributes to DFD related foot amputations. These can be minor amputations (amputations below the level of the ankle) or major amputations (amputations above the level of the ankle in the lower limb) (11). A systematic review conducted on 10 studies that included 871 patients with Charcot's arthropathy reported that the total amputation frequency was 15% (95% CI = 0.067-0.258, I^2 = 93.6%) where 9% where major amputations (95% CI = 0.062-0.127, I^2 = 60%) and 5% were minor amputations (95% CI = 0.004-0.126, I^2 = 94.7%) (23). Similarly, the weighted mean of total re-amputation was reported to be 20.14%, 29.63% and 45.72% at 1, 3 and 5 years respectively (24). Common risk factor for DFD-related amputations includes PAD, DPN, osteomyelitis, postprandial glucose level, white cell count, c-reactive protein, erythrocyte sedimentation rate, low haemoglobin, and albumin (25).

A systematic review conducted to pool the evidence on DFD-related deaths reported that they were able to identify 34 studies, with 124376 participants among whom 51386 died. Twenty-seven studies with 21171 patients were included in the Kaplan-Meier-based meta-analysis and the combined survival rates were 86.9% (95% CI 82.6%-91.5%) at 1 year, 66.9% (95%CI 59.3%-75.6%) at 3 years, 50.9% (95%CI 42.0%-61.7%) at 5 years, and 23.1% (95%CI 15.2%-34.9%) at 10 years. The same study reported that cardiovascular disease, 46.6% (95%CI 33.5%-59.7%) and infection, 24.8% (95% CI 16.0%-33.5%), were the most common causes of death. Patients with older age (per 1-year, Hazard ratio [HR] 1.054, 95%CI 1.045-1.063), PAD (HR 1.882, 95%CI 1.592-2.225), chronic kidney disease (CKD) (HR 1.535, 95%CI 1.227-1.919), end-stage renal disease (ESRF) (HR 3.586, 95%CI 1.333-9.643), previous amputation (HR 2.415, 95%CI 1.323-4.408), and history of cardiovascular disease (HR 1.449, 95%CI 1.276-1.645) had higher mortality risk (26).

In summary, it is important to note DFD is associated with high morbidity and mortality and thus contributes to reducing the quality of life in affected individuals. The risk of death of a person with a history of DFU is 2.5 times more compared to a person who has diabetes only (27, 28) and the risk of death is further increases if the patient has co-existing PAD increasing the risk of non-healing ulcers and amputations even more (29). It has been shown that the mortality of a patient increases by 70% following an amputation related to a DFD in the subsequent 5 years of his or her life (30). Patients who have DFD fear major amputations; a debilitating outcome of DFD perhaps even more than death (31])

1.3 Burden of DFD in Australia

Around 7% of patients in Australia with uncontrolled diabetes tend to develop DFU (32). A recent study conducted in Australia using data from the state of Queensland over five years (2010-2015) showed that DFD causes approximately 27,600 public hospital admissions, around 4,400 amputations and 1,700 deaths. This results in an estimated $1.6 billion direct health care cost (33-39) to the Queensland government. This is not accounting for the indirect healthcare costs associated with the problem. During the period from 2005 to 2010, 4,443 amputations were reported only in Queensland (40). Another study published based on Australian data estimated that over $2.7 billion can be saved over five years by early detection and optimal care of diabetic foot ulcers (41). Therefore, the prevention of complications of DFD such as DFU becomes important in the long-term management of patients with diabetes. The expected prevalence of diabetes in the world is 440 million in 2030 (42) and therefore, along with the rising numbers of patients with diabetes and its complications, the healthcare costs of managing them are also on the rise (4, 32, 37). However, a study protocol published in Australia claims the burden of diabetes-related minor and major amputation rates are not clear and needs to be explored (43).

A comprehensive systematic review was published in 2021 looking at all DFD and its complications; namely prevalence, the incidence of risk factors and the prevalence of different types of DFD and amputations (44). The study found that there were 20 publications from different regions of Australia involving a highly heterogeneous group of populations. According to this study, the prevalence of DFD risk factors ranged from 10.0% to as high as 58.8% among the DFD population. The incidence of DFD related hospitalizations ranged from 5.2-36.3% and the incidence of DFD related amputations ranged from 5.2-7.2 per 1000 person years. The same study reported that the prevalence of risk factors among in-patients with diabetes ranged from

35.3% to 43.3% and that the amputation rates among those who were admitted following DFD were 1.4% -5.8% (44). Overall, they found that the risk factor prevalence of DFD in Australia is similar to that of global statistics which may be an underestimation due to the lack of representative Australian studies from all regions in the country, however, the incidence of hospitalizations and DFD related amputations were higher compared to the global rates (45). This warrants for further studies looking at the epidemiology of DFD in Australia in representative samples mainly related to rates of and risk factors for hospital readmissions following an index admission for DFD. Also, there is room to identify rates of and risk factors for long-term outcomes such as major amputation and death following an index minor amputation for DFD.

1.4 Burden of DFD on Aboriginal and Torres Strait Islander people

The burden of DFD is much greater among Aboriginal and Torres Strait Islander people also known as First Nations people or Indigenous Australians. It is reported that they have very high rates of diabetes and associated PAD (18, 46). It is also noteworthy that Aboriginal and Torres Strait Islander Australians have a 3-6-fold increased likelihood of developing a DFD complication compared to non-Indigenous Australians following uncontrolled diabetes over longer periods, smoking and PAD (47). A retrospective study of public hospital admissions in Queensland between 2005 and 2011 found that ~ 10% of people admitted for treatment of DFD complications identified themselves as Aboriginal and Torres Strait Islander Australians (48). Aboriginal and Torres Strait Islander Australians make up ~ 3% of the Queensland population (estimated from the 2011 Census Data – Table Builder, Australian Bureau of Statistics) (49). A Western Australian study reported that Aboriginal and Torres Strait Islander Australians with diabetes were ~40-times more likely to undergo a major amputation compared to non-Indigenous

Australians with diabetes (50). A similar study performed in North Queensland between 1998 and 2008 supports this finding since 52% of major amputations (below or above knee amputations) occurred in the patients who identified themselves as Aboriginal and Torres Strait Islander Australians (51). A recent study from the Northern Territory reports that the Aboriginal or Torres Strait Islander Australians were 1.8 times more likely to have a minor (amputations that were carried out below the ankle, usually in toes or across metatarsal bones) or major amputation following DFD and that these amputees were about 9 years younger than their non-Indigenous counterparts (52).

While the excess burden of DFD complications amongst Aboriginal and Torres Strait Islander Australians is established, the reasons for this and extensive solutions to closing the gap are unclear. The higher amputation rate amongst Aboriginal and Torres Strait Islander Australians could simply reflect the excess incidence of DFD in this population (48, 53-55). Also contributing to the excess incidence of amputation amongst Aboriginal and Torres Strait Islander Australians could be delayed presentation to the hospital (56, 57). It is established that more severe forms of DFD complications at presentation (58) (e.g., defined as clinical stages 3 or 4 according to the Society of Vascular Surgery Wound Ischemia, foot Infection score (WIFI score) (29, 59) or sepsis (60) are more likely to result in major amputation (32, 33, 35, 37-39, 61). Other contributing factors could be poor control of risk factors such as persistently high blood glucose levels (54), poor adherence to medications and offloading footwear (62), higher rates of smoking (63), higher rates of PAD and ischemia (53, 64) ESRF requiring dialysis (65), previous history of DFU (66), poor knowledge on diabetic foot care (67, 68) or rurality (48, 69). The relative contribution of these factors to the poor outcomes of DFD complication-related hospital admissions, major and minor amputation and major cardiovascular adverse events in Aboriginal

and Torres Strait Islander Australians is unclear and requires further investigation to address the excess burden including larger numbers of Aboriginal and Torres Strait Islanders being included in the studies. Therefore, studying and implementing preventive measures of DFD is crucial, especially in North Queensland, where a substantial population of Aboriginal and Torres Strait Islander Australians live together with a large number of non-Indigenous Australians (70-72). Since PAD is an established cause of major amputations (53, 64), it will be beneficial to investigate the anatomical distribution of PAD in this population and their presentation to the hospital to make decisions about revascularization and further management.

1.5 Risk factors for developing DFD

There are multiple risk factors that have been established for developing DFD. DFD affects male patients more (73). DFD is also described to be more prevalent among those who require dialysis following ESRF following diabetes-related nephropathy (65, 74). PAD and associated risk factors such as smoking are also more common among those who are affected by DFD (64, 75). According to the Seattle diabetic foot study DPN, past-history of foot amputation, previous foot ulcers, existing Charcot deformities, and poor vision were some of the risk factors associated with DFU (76). The Fremantle diabetic foot ulcer study (Phase 11) reported that DPN, longer durations of diabetes and Aboriginal and Torres Strait Islanders were independent risk factors for developing DFU (55).

Patients with DFU commonly present to the hospital with superimposed foot infections. It can be infections of the foot either in superficial soft tissues or in deeper structures like muscles or bone or even full-blown sepsis (11). Cellulitis is the commonest form of soft tissue infection. Infected deep ulcerations involve the destruction of muscles and tendons. Osteomyelitis; infection of the bone and Charcot's foot cause destruction of the bone (77). Soft

tissue destruction such as nail and bone deformities, calluses, macerated web spaces, gangrene or ulceration superimposed with infections of the foot may lead to possible minor or major amputations (78, 79) requiring hospital admission or readmission (80-82). Around 50% of the DFU become infected (83) and 20% of moderate to severe infections will lead to either a minor or a major amputation (84). Therefore, prevention of DFD is pivotal in managing these patients.

1.6 Prevention of DFD

Reducing even a small amount of the DFD burden and related complications would lead to a substantial reduction in the cost to the health care system, for example a US study reported that the average cost of care for patients requiring readmission following DFD was $79,315 compared to $28,977 for patients who were not readmitted following treatment for DFD ($P<0.001$) (85). This in turn will result in savings in indirect healthcare costs and will benefit all patients in improving the care (41, 86). Identifying the potential gaps in knowledge about factors that could lead to the development of DFD is vital in reducing the future occurrence of such complications. DFD was recently described as "Australia's least known health care problem". Therefore, the implementation of preventive measures individually catered to each and every patient of concern at the appropriate time is pivotal in preventing future DFD (18). Different treatment strategies should be available for different patients who present with different complications and should be delivered in an integrated, objective, quantitative and evidence-based approach (87). Remote management of such patients (88) is also important in areas like North Queensland where access to the nearest tertiary care hospital may take long periods of time (89).

Prevention of DFD plays a key role in improving a patient's quality of life. At the level of policy making the measures that can be implemented to improve the current practices of caring

for a patient with DFD include improving the access of these patients to affordable and effective care such as screening (90-92), delivering multidisciplinary care (a combined treatment approach that involves different specialties such as vascular surgeons, endocrinologists, podiatrist and other health and allied health care specialties depending on the requirement) (92-96), conducting research and provision to update current knowledge and identify new innovative approaches in managing patients (87). However, it is noteworthy that there could be gaps in all areas of care and room for improvement. For example, from the year 2015 to 2019, only two randomized controlled trials were published with regard to the prevention of diabetic foot ulcers (87).

The International working group on diabetic foot guidelines (IWGDF) published in the year 2019 gives 16 recommendations related to preventing DFU in the patient who are at risk of developing such complications (97). These recommendations are for individual patient level care. These recommendations include individualized regular screening of patients, stratification them to risk groups in managing them, delivering patient education, appropriate foot care and offloading footwear or other such interventions to all who are at risk of developing DFU (97). Similar guidelines aiming for patients in Australia were also published recently (98).

IWGDF recommend that all patients with diabetes be screened annually by a trained health care practitioner while maintaining their haemoglobin A1C levels (HbA1C) <7 % (99, 100). Patients with long standing diabetes and who are at risk of developing DFD are categorized into 4 levels based on the presence or absence of DPN and PAD.Based on the risk, those in the higher risk categories are recommended to be followed up more frequently, ranging between 1 and 6 months (97). Remote monitoring of patients can be applied at their homes for follow up (101). Overall, multidisciplinary care is proven to be of benefit in reducing DFD related complications and is the current recommendation (102). The main measures of preventing DFD

in at-risk patients include professional foot treatment, adequate and appropriate footwear (103), tight control of risk factors, and patient education (99). Professional foot treatments include the removal of pre-ulcerative lesions such as calluses, blisters, in-growing or thickened nails, and fungal infections (97, 103) (Figure 5)

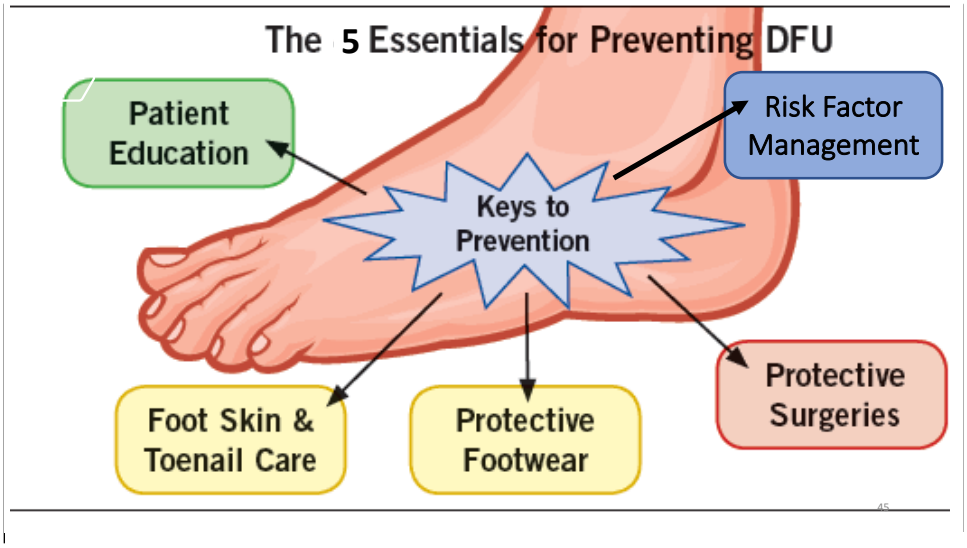

Figure 1-5 Prevention of DFU recurrence

The international guidelines recommend offloading footwear as the most important recommendation to patients with long standing diabetes complicated with DPN, PAD or both to prevent the first occurrence of a foot ulcer (103). Guidelines also recommend that patients with a history of previous ulcers also should wear custom-made offloading footwear (104, 105).

All patients should be educated about improving individual foot care. Advice should include not walking barefoot or with socks or thin-soled shoes, inspecting their feet and the inside of their shoes daily, washing and carefully drying their feet daily (106), avoiding chemical agents and plasters to remove calluses, using emollients, and cutting nails straight across (107). However, the evidence behind these recommendations is scanty (105, 108).

Home foot temperature measurement has also been recommended for early detection of DFU (103). Surgical interventions such as digital flexor tenotomy in preventing toe ulcers, Achilles' tendon lengthening can be performed to offload deformed feet in patients who develop recurrent foot ulcers even after good adherence to offloading footwear (86, 109).

1.7 Important research gaps and rationale

From the extensive research that was conducted, we were able to identify a few areas of research that needs to be addressed. Despite the significant disease burden associated with DFD in Australia, studies looking at hospital admissions following DFD are limited, and we were unable to find studies on readmissions following an index admission to treat DFD. Due to the difficulty in treating DFD and its recurrence, repeated admission to hospital is common and causes substantial healthcare expenditure (110) and was estimated to cost twice as much as the initial admission (110) in the USA. In England, between the years 2014 and 2015, the cost of treating DFU and amputation was estimated to be between 837 and 962 million pounds which were close to 1% of the National Health Service budget (111). But we were not able to find similar studies conducted in Australia. Therefore, our first aim was to conduct a systematic review and a meta-analysis to identify studies looking at hospital readmissions following an index admission to treat DFD and to identify potential risk factors for such readmissions following an index admission for DFD (Chapter 2).

As per IWGDF guidelines we planned to use WIFI classification to classify the DFD/DFU the patient presented to the hospital with (112). During this initial phase we were able to note that despite its recommendation for use, WIFI classification has not been assessed for its reproducibility and its reliability against other foot ulcer classifications. Therefore, our second aim was to conduct a prospective study to compare the inter- and intra-observer reproducibility

of the (WIFI) (29), University of Texas Wound Classification System (UTWCS) (113), Site, Ischemia, Neuropathy, Bacterial Infection, Area of the ulcer and Depth (SINBAD) classification system (114), and Wagner classification (115) using photographs of diabetes-related foot ulcers (Chapter 3).

As stated above, as we could not identify studies reporting on hospital readmissions following an index hospital admission for DFD in Australia, our third aim was to conduct a prospective cohort study in North Queensland to assess the incidence of re-admission for a recurrent DFD following an index admission to treat a DFD and to identify risk factors for such readmission in the Townsville University Hospital (TUH) (Chapter 4).

It is known that Aboriginal and Torres Strait Islander people have a higher burden of DFD and higher rates of major amputations (18, 75). It is established that PAD is a risk factor for the development of DFD and major amputation but the revascularization rates to overcome PAD is shown to be less in the same population (64). Based on this evidence we conducted a retrospective study to identify the distribution of PAD between Aboriginal and Torres Strait Islanders and non-Indigenous populations using a validated tool that objectively grades the stenosis of peripheral arteries (Chapter 5).

Multiple studies on major amputations following PAD or DFD or both are available in the literature (55, 64). However, the number of studies reporting on minor amputations following DFD, and their outcomes are not well understood in Australia, especially in Queensland where the population is highly dispersed in a large geographic area with limitations to access to healthcare in rural areas from where a majority of Aboriginal and Torres Strait Islander Australians reside (49). Therefore, a retrospective study was conducted to look for risk factors

for and repeat rates of minor amputations in patients with DFD in North Queensland over the past 20 years (Chapter 6).

Despite the recommendations by IWGDF on prevention strategies for DFD, collective evidence from randomized controlled trials (RCT) in the form of meta-analyses were not available on preventing recurrent DFU. Therefore, as our final aim a systematic review and a meta-analysis was conducted to pool evidence from RCT looking at, offloading footwear, home foot temperature monitoring and patient education in preventing recurrent DFU (Chapter 7).

1.8 Objectives:

1. To systematically review the incidence and risk factors for readmission to hospital to treat DFD

2. To compare the inter- and intra-observer reproducibility of the Wound Ischemia Foot Infection classification (WIFI), University of Texas Wound Classification System (UTWCS), Site, Ischemia, Neuropathy, Bacterial Infection, Area of the ulcer and Depth (SINBAD) classification system and Wagner classification using photographs of diabetes-related foot ulcers.

3. To prospectively examine the rate and risk factors for DFD related readmission to hospital at a regional tertiary care hospital facility in North Queensland, Australia.

4. To compare the severity and distribution of PAD between Aboriginal and Torres Strait Islander Australians and non-Indigenous Australians presenting with symptomatic PAD

5. To assess the association of remoteness of place of residence with a requirement for repeat amputation (either minor or major) and mortality in residents of North Queensland, Australia.

6. To perform a systematic review and meta-analysis of data from randomized controlled trials (RCT) examining the efficacy of home foot temperature monitoring, patient education and offloading preventing DFU.

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2. A systematic review and meta-analysis of the incidence and risk factors for readmission to hospital in people with diabetes-related foot disease

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What does this study add?

This is the first systematic review and meta-analysis that pooled evidence from studies looking at readmissions following an index admission to treat diabetes-related foot disease (DFD). The findings suggested that about one-fifth of patients are readmitted to hospital within 30 days and readmission was higher among female patients and those presenting with peripheral neuropathy. Having private health insurance was protective of readmission. Coronary artery disease was a risk factor for DFD related readmission.

2.1 Abstract

Introduction: The aim of this study was to systematically review the incidence and risk factors for 30-day readmission to hospital following an index admission to treat diabetes-related foot disease (DFD).

Methods: The study was performed according to the Preferred Reporting Items for Systematic Reviews and Meta-Analysis (PRISMA) guidelines. Studies that reported the rate of total or DFD related 30-day readmissions were included. Meta-analysis was performed using a random effects model to calculate the pooled mean (95% confidence interval, CI) of the proportion of patients readmitted to hospital within 30-days. Meta-regression was performed to determine the association between risk factors and 30-day readmission.

Results: Sixteen retrospective studies with a total of 124,683 participants were included. The mean total 30-day readmission rate was 22.0% (95% CI 17.0%, 27.0%) while the mean DFD related 30-day readmission rate was 10.0% (95% CI 7.0% to 15.0%). Meta-regression found that greater prevalence of peripheral neuropathy (p=0.045) was associated with a higher rate of any 30-day readmission and male sex (p=0.023) and private health insurance (p=0.048)

were associated with lower rates of any 30-day readmission. Coronary artery disease (p=0.025) was associated with a higher rate of DFD-related readmission. All studies had low or moderate risk of bias.

Conclusion: This systematic review suggested that about one-fifth of patients with DFD are readmitted to hospital within 30 days, of which about half are to treat DFD. Risk factors for readmission included female gender, peripheral neuropathy, lack of private health insurance and coronary artery disease.

2.2 Introduction

Diabetes-related foot disease (DFD), such as foot ulcers, infections and gangrene, occur in approximately one-third of patients with diabetes over their lifetime (1, 2). It was estimated that in 2016, 131 million people (~1.7% of the world population) were affected by diabetes-related lower extremity complications. The age-standardized prevalence rates were 1,848 people per 100,000 causing an estimated 16.8 million years lived with disabilities, which was 2.1% of global burden (3).

An important burden related to DFD is hospital admission, with a previous study suggesting that 1 in every 13 hospital admissions were caused by DFD (4). Due to the difficulty in treating DFD and its frequent recurrence, readmission to hospital is very common and was estimated to cost twice as much as the initial admission (5). A US study reported that the average cost of care for patients requiring readmission was $79,315 compared to $28,977 for patients who were not readmitted (P<0.001). The same study reported that readmission costs accounted for approximately 15% of the total costs of treating diabetes-related foot ulceration (DFU) at their institution (5). Between 2014 and 2015, the cost of treating DFU and

amputation were estimated to be between 837 and 962 million pounds in England, which was around 1% of the National Health Service budget (6).

The incidence rates, risk factors and indications for readmission to hospital following an index admission for DFD have not been widely studied. Greater number of comorbidities (7), current smoking (8), failure to perform an amputation during the index admission and Black American ethnicity (9) have been reported to be risk factors for hospital readmission. Reported rates of hospital readmission following treatment of DFD have varied between 10 and 30% (8-10). There has been no previous systematic review of 30-day hospital readmission following an index admission for DFD. The primary aim of this study was to systematically review the incidence and risk factors for total 30-day readmission. Secondary aims were to assess the incidence and risk factors for DFD-related readmission to hospital.

2.3 Methods

This systematic review was undertaken in accordance with the recommendations of the Preferred Reporting Items for Systematic Reviews and Meta-Analysis (PRISMA) guidelines (11). The protocol was developed before searching the literature and made publicly available on the prospectively registered systematic reviews in health and social care

(PROSPERO) database (PROSPERO registration number: CRD42022325739).

2.3.1 Literature Search

To identify eligible studies, a literature search was conducted using Medline/PubMed (1946) Scopus (1970), the Cochrane Library (1951) and CINAHL (1981) databases from database inception until July 2022 and updated again in February 2023 without language or geographic restrictions. Search terms were developed with the assistance of a specialist medical librarian

and individualized for databases. The following search terms (MeSH terms and key words) were used: (“Diabetic foot” OR “diabetic feet” OR “diabetic foot ulcer*” OR “diabetic foot disease” OR “diabetic polyneuropathy” AND (“hospital readmission” OR “readmission” OR” hospitalisation” OR “hospitalization” OR “hospital admission”). Titles and abstracts were screened to identify relevant articles. Full texts of potentially relevant articles were screened using predefined inclusion and exclusion criteria. Hand searching of reference lists of included studies was also performed.

2.3.2 Eligibility criteria

Studies were eligible for inclusion if they met all the following criteria:

1) included a cohort or a sub cohort of patients with an index admission to treat DFD based on the treating physician’s diagnosis, defined with the international classification of disease (ICD) or Current Procedural Terminology codes or who had an amputation to treat DFD;

2) reported total 30-day hospital readmission rate or DFD related 30-day readmission rate for the cohort or the sub cohort of patients with DFD;

For inclusion the studies need to have included patients who were admitted to hospital to treat DFD which was defined as follows:

- previously diagnosed with either type 1 or 2 diabetes;
- had a foot ulcer defined as a full thickness discontinuation of the epithelium (12);
- or had a foot infection diagnosed by the treating physician according to previously described methods (12);
- or had a gangrenous foot lesion defined as the presence of necrotic tissue in the foot (12).

Total 30-day readmission was defined as any admission to the hospital either planned or unplanned for any cause. DFD-related readmission was defined as readmission to the hospital

within 30 days following recurrent or residual DFD. Only studies written in English were included. Only cohort studies and those reporting minimum data (number of 30-day readmissions, any risk factors and sample size) were included. Studies were excluded if they did not report total or DFD related 30-day readmission as a primary or secondary outcome for the cohort or the sub cohort of patients with DFD, or if the studies did not report a 30-day readmission rate but reported readmission rate for a different period of time for the cohort of patients with DFD.

2.3.3 Data extraction

The following data were extracted from the included studies by two authors (CA and LS): Study design, country, year of publication, sample size, methods of patient identification, inclusion and exclusion criteria, primary outcome, other outcomes, methods of outcome assessment, results, risk factors associated with total 30-day readmission (odds ratio [OR] for univariate and multivariate logistic regression analyses were collected including the number of patients who presented with those risk factors), if the patients were assessed with a wound classification system, reasons for readmission, conclusions and limitations. The total 30-day readmission rates were obtained from the studies and DFD-related 30-day readmission rates were calculated (13).

Risk factors extracted from individual studies based on their definitions included age, sex, ethnicity, hypertension (HT), peripheral artery disease (PAD), current smoking, chronic kidney disease (CKD), peripheral neuropathy (PN), coronary artery disease (CAD), congestive heart failure (CHF), chronic obstructive pulmonary disease (COPD), having private health insurance, C reactive protein (CRP) levels, length of stay (LOS) during the index admission and duration of the study. PAD was defined based on the criteria given by the Wound Ischemia Foot Infection (WIFI) classification (14) or as reported by studies. PN

was defined as positive 10-g mono-filament test (12). Authors of the studies were contacted three times to obtain missing data, but none responded.

2.3.4 Risk of bias assessment

Quality assessment was conducted using the Evidence Based Library and Information Practice and Newcastle and Ottawa scale (15). An additional quality assessment tool was developed using components of the standard quality assessment criteria for evaluating primary research papers incorporating items based on ROBINS-E tool (16,17). This included 20 components which was specifically developed for this study under the subheadings: research question, selection criteria, participant characteristics, sample size, outcome, methods and analysis which is more relevant for DFD and readmission research conducted as observational prospective studies. The questions were first trialled on the excluded articles to assess the tool validity. Two authors (CA and LS) conducted the quality assessment and any discrepancies were resolved by discussion. All 20 questions were equally weighted, and individual scores were calculated based on the proportion of 'yes' answers. Studies that scored <50%, 50% to 75% and >75% were deemed of high, moderate and low risk of bias respectively based on a collective decision taken by the authors in line with ROBINS-E guidelines (17).

2.3.5 Data analysis

Quantitative data analysis was conducted using R software [(R Core Team (2020). R: A language and environment for statistical computing. R Foundation for Statistical Computing, Vienna, Austria. Version: 4.2.1)] using the 'meta' package. Random effects models using inverse variance methods were developed as a significant inter-study heterogeneity was

expected. Meta-analysis calculated the pooled mean (95% confidence interval, CI) of the proportion of patients readmitted to hospital within 30-days. Subgroup analyses were conducted to assess the incidence of total 30-day readmissions in studies reporting patients presenting with DFU, DFI and DFD-related amputation. DFD-related readmissions were calculated assuming that all foot-related complications and surgical-related complications were associated with DFD-related readmission. Heterogeneity was assessed using I^2, with values of 25%, 50% and 75% acknowledged to represent low, moderate and high heterogeneity respectively. Meta-regression was used to determine the association between the rate of 30-day readmission (total or DFD-related) and prevalence of risk factors in the individual studies. Meta-regression was conducted only if three or more studies reported the particular risk factor under investigation. Meta-regression results were presented as scatter plots between percentage of patients with specific risk factor versus logit transformed value of proportion of patients with readmissions. All analysis were performed using 'metaprop' function of the 'meta' package from R software version 4.2.3. P values of <0.05 were considered significant in all analyses.

2.4 Results

2.4.1 Search results

The literature search identified 3365 articles. After removal of duplicates the number of articles screened were 3056 (Figure 1). After title and abstract screening 2511 articles were excluded. After full text evaluation of 545 studies, a total of 16 studies were included for analysis (5,7-10,18-28).

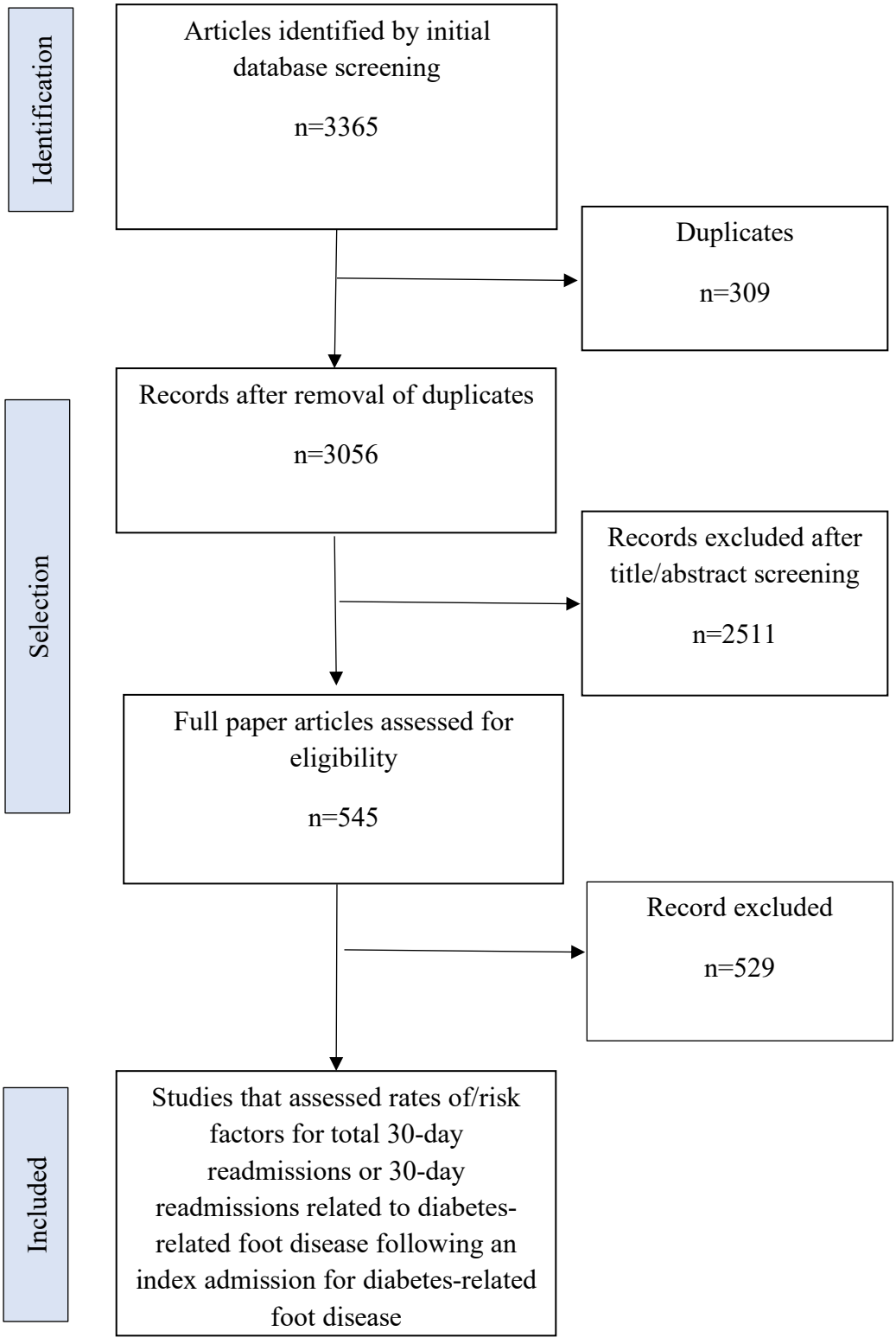

Figure 2-1: PRISMA Diagram

2.4.2 Study characteristics

All included studies were published between 2014 and 2022 and were conducted in the US (5, 7-10, 18-21, 23, 24, 26-28) except one study from Belgium (22) and another study from Australia (25). All studies were retrospective cohort investigations except the study from Belgium (22) and sample sizes of participants with DFD ranged from 116 to 84,653 (Supplementary Table S1). A total of 124,683 participants were included. There were seven single centre studies (5, 7, 8, 10, 18, 22, 24) and nine multi-centre studies (9, 19-21, 23, 25-28). Five studies included patients who were admitted to treat DFU (5, 8, 9, 18, 25) three included patients with diabetic foot infections (DFI) (10, 21,22) and two included patients with chronic limb threatening ischaemia or who had lower limb bypass (23, 26). Six studies included patients who underwent an amputation (7, 19, 20, 24, 27, 28) of which three had a mix of minor or major amputation,(7, 27,28) two major amputations only (20,24) and one minor amputations only (19). Inclusion and exclusion criteria varied between the studies (Supplementary Table S1). All studies extracted data from databases maintained locally (5, 8, 10, 22, 24, 25) or those maintained by Health Services using ICD codes (7, 9, 18-21, 26-28). Thirteen studies reported total 30-day readmission rates (5, 7-10, 18-20, 22-24, 26, 28) and three studies only reported DFD-related readmission rates (21, 25, 27). Overall, ten studies reported 30-day DFD related readmission rates (5, 8-10, 20-22, 24, 25, 27). Six studies did not report reasons for total 30-day readmission (18, 19, 21, 23, 25, 28).

2.4.3 Quality of included studies

Supplementary Table S2 details the quality assessment results. According to the Newcastle-Ottawa scale four studies had a low risk of bias (21, 24, 26, 28). Overall, six out of sixteen studies had a low risk of bias (7, 8, 19, 20, 24, 26) based on the tool developed by the authors. The remaining studies had a moderate risk of bias (5, 9, 10, 18, 21-23, 25, 27, 28). Areas of concern most commonly identified included not reporting the basis of sample size

calculations, (5, 7-10, 18-28) not reporting ethical approval (5, 9, 10, 18, 21, 26, 27) and not reporting the method of outcome data collection in detail (10, 22). All studies reported clear aims, defined the study setting, reported methods of recruitment and defined inclusion and exclusion criteria and all studies included over 100 patients. Sufficient relevant baseline medical and demographic information characterizing participants were provided in all studies (5, 7-10, 18-28).

2.4.4 Rates and risk factors for 30-day readmission

Total 30-day readmission rates varied from 10.6% to 33.0% (Supplementary Table S3). Follow up methods varied and were detailed in Supplementary Table S3. Overall quantitative meta-analysis suggested that 22.0% (95% CI 17.0%, 27.0%) of patients were readmitted for any cause within 30 days (I^2 =99.0%; Figure 2). Sub-analysis suggested that readmission was more common for patients who were initially treated for DFU than those who underwent an amputation (27.0%, 95% CI 15.0% to 43.0%, vs. 17.0%, 95% CI 13.0% to 21.0%, Figure 2). A summary findings table created based on the pooled results according to GRADE criteria is shown in Supplementary Table S4.

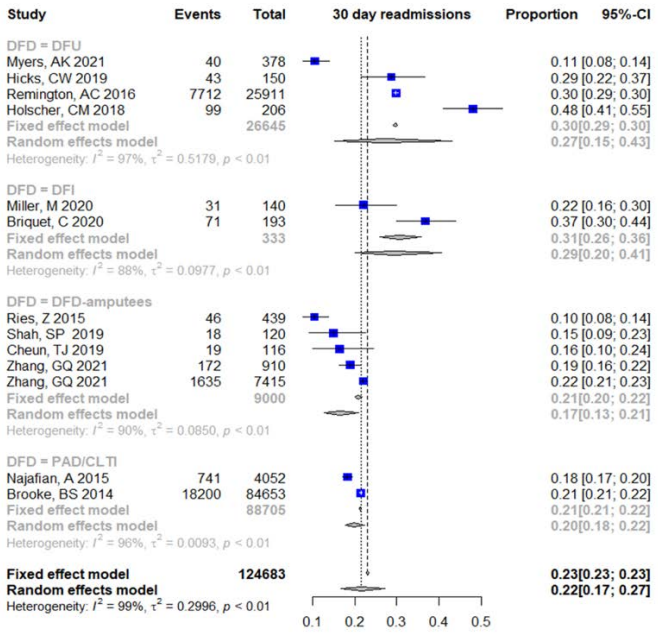

Figure 2-2 Proportions and pooled proportion of patients readmitted within 30 days following index admission for DFD,

2.4.5 Association between risk factors and total 30-day hospital readmission

The following risk factors were reported to be associated with significantly higher rate of readmission: PAD; 4 studies in univariate analyses and 3 out of 4 in multivariate analyses (7, 8, 19, 20), chronic limb threatening ischemia in one study in multivariate analyses adjusted for cardiac comorbidities (26), primary payer being Medicare or Medicaid in 4 studies (8, 9, 19, 20), current smoking in 2 studies (7, 8) ,Black American ethnicity in 4 studies (9, 19, 23, 26), older age in 3 studies (23, 25, 26) and presence of multiple comorbidities in 6 studies (7-9, 19, 21, 26). Three studies reported that longer LOS for the index hospital admission was associated with a significantly higher risk of total 30-day readmission in univariate analyses (9, 10, 21). Overall, ten studies reported (7-10, 19-21, 23, 25, 26) that multiple risk factors were significantly associated with total 30-day readmission (Table 2).

Table 2-1 Risk factors of the 124,683 participants from the 16 included studies

S	N	Risk factor								
		Age	Men	Black	HT	PAD	Smoking*	CAD	PN	PHI
Holscher et al 8	206	58.5	125 (60.7%)	122 (59.2%)	173 (84.0%)	101 (49.0%)	55 (26.7%)	61 (29.6%)	197 (95.6%)	48 (23.3%)
Miller et al 10	140	55 †	106 (75.7%)	NR	NR	45 (32.1%)	47 (33.6%)	NR	NR	NR
Myers et al 18	378	66.1	270 (71.4%)	83 (22.0%)	288 (76.2%)	69 (18.3%)	41 (10.8%)	NR	87 (23.1%)	211 (55.8%)
Remington et al 9	25911	63	17140 (66.2%)	5700 (22.0%)	NR	NR	NR	NR	NR	4664 (18.0%)
Ries 2015 et al 7	439	57.6	297 (67.7%)	NR	335 (76.3%)	73 (16.6%)	89 (20.3%)	NR	246 (56.1%)	NR
Zhang et al 19	7415	NR ‡	5189 (70.0%)	2870 (38.7%)	4765 (64.3%)	3401 (45.9%)	1545 (20.8%)	2518 (34.0%)	1885 (25.4%)	1810 (24.4%)
Zhang et al 20	910	NR ‡	601 (66.0%)	448 (49.2%)	415 (45.5%)	477 (52.4%)	191 (21.0%)	403 (44.3%)	52 (5.7%)	142 (15.6%)
Cheun et al 24	116	58	79 (68.1%)	NR	107 (92.2%)	97 (83.6%)	72 (62.1%)	49 (42.2%)	NR	NR

Hicks et al 5	150	57.7	93 (62.0%)	96 (64.0%)	126 (84.0%)	76 (50.7%)	45 (30.0%)	51 (34.0%)	141 (94.0%)	32 (21.3%)
Najafian et al 26	4052	67.3	2593 (64.0%)	742 (18.3%)	3676 (90.7%)	4052 (100.0%)	1387 (34.2%)	813 (20.1%)	NR	NR
Shah et al 28	120	59.4	86 (71.7%)	72 (60.0%)	71 (59.2%)	28 (23.3%)	NR	35 (29.2%)	NR	NR
Ahn et al 21 §	326	56.0	232 (71.2%)	NR	248 (76.1%)	NR	100	NR	NR	NR
Manewell et al 25 §	749	69.1	525 (70.2%)	NR	NR	NR	75 (10.1%)	NR	NR	NR
Ratliff et al 27 §	15581	63.9	10804 (69.3%)	NR	13389 (85.9%)	7654 (49.1%)	2620 (16.8%)	9844 (63.2%)	4188 (26.9%)	2738 (17.6%)

Reported are mean or number of participants (percentage) having each risk factor unless highlighted. Zhang et al 19 and 20 are two separate studies on different cohorts by the same research group. Briquet et al 22 and Brooke et al 23 did not report any risk factors.

Reference study; S, number of participants in each study; N, hypertension; HT, peripheral artery disease; PAD, coronary artery disease; CAD, peripheral neuropathy; PN, private health insurance; PHI, not reported; NR. Black refers to Black American ethnicity.

*Refers to current smoking, † Age was reported as median, ‡ age was reported in categories, § These studies only reported diabetes-related foot disease specific 30-day readmission only.

Table 2-2 Reported risk factors for any readmission within 30-days of an index hospital admission to treat diabetes-related foot disease in the included studies.

S	Risk factor								
	Age	Men	Black	HT	PAD	Smoking*	CKD	CAD	PHI
Holscher et al 8	1.00 [0.97-1.02]	0.98 [0.59-1.63]	1.69 [0.88-3.25]	2.36 [1.00-5.55]	1.22 [0.69-2.15]	1.95 [1.02-3.73]	NR	1.66 [0.94-2.91]	0.56 [0.26-1.21]
Remington et al 9	1.00 [1.00-1.00]	0.98 [0.92-1.04] ‡	1.21 [1.13-1.29]	NR	NR	NR	NR	NR	1.48 [1.36-1.61] §
Ries et al 7	NR	NR	NR	NR	2.47 [1.08-5.67]	3.22 [1.40-7.36]	2.82 [1.30-6.15]	NR	NR
Zhang et al 19	0.95 [0.68-1.31] †	1.13 [1.00-1.27]	1.21 [1.07-1.38]	0.93 [0.82-1.05]	1.38 [1.22-1.56]	NR	1.29 [1.14-1.46]	1.26 [1.11-1.43]	1.43 [1.20-1.69] §
Zhang et al 20	NR	1.45 [1.01-2.06] ‡	1.18 [0.82-1.70]	NR	1.49 [1.04-2.12]	1.07 [0.67-1.70]	1.17 [0.82-1.69]	0.96 [0.66-1.38]	1.76 [1.01-3.06] §
Brooke et al 23	1.21 [1.13-1.30]	NR	1.11 [1.03-1.19]	NR	NR	NR	NR	NR	NR
Najafian et al 26	1.24 [1.04-1.47]	1.03 [0.89-1.20]	1.07 [0.88-1.29]	1.06 [0.87-1.30]	1.17 [1.01-1.36]	1.01 [0.86-1.18]	NR	NR	NR

Shown are multivariate logistic regression analyses odds ratios [95% CI] for risk factors by the included studies. Risk factors that were adjusted for during these analyses are given in Supplementary Table 3.

Zhang et al 19 and 20 are two separate studies on different cohorts by the same research group.

Study; S, hypertension; HT, peripheral artery disease; PAD, chronic kidney disease; CKD, coronary artery disease; CAD, private health insurance; PHI, not reported; NR.

Black refers to Black American ethnicity.

Myers et al study was not included in the table as none of the risk factors were significantly associated with total 30-day readmissions in univariate logistic regression analyses and therefore multivariate analyses were not done.

* Current smoking.

† Reported for age category >65 years.

‡ Reported for female sex.

§ Reported for Medicare holders compared to those with private health insurance.

None of the studies assessed DFD-related readmissions.

Odds ratios given in the study reported by Najafian et al [26] were for 30-day unplanned readmission after infra-inguinal bypass surgery stratified by cardiac comorbidities.

Meta regression suggested that studies with greater prevalence of PN (intercept= 0.0129, SE= 0.0064, p= 0.045) had significantly higher rates of total 30-day readmission. Having private health insurance (intercept= -0.0294, SE= 0.0149, p= 0.048) and male sex (intercept= -0.0776, standard error; SE= 0.0342, p= 0.023) were associated with lower total 30-day readmission (Supplementary Table S5 and Supplementary Figure 1).

2.4.6 DFD-related readmission

Quantitative meta-analysis suggested that 10.0% (95% CI: 7.0% to 15.0%) patients were readmitted within 30 days for a DFD-related complication (I^2 =100.0%; Figure 3). Meta regression suggested that CAD (intercept = 0.0475, SE= 0.0211, p= 0.025) was associated with a higher rate of DFD related readmission (Supplementary Table S5 and Supplementary Figure 2). Assessment of publication bias was not possible due to the small number of studies.

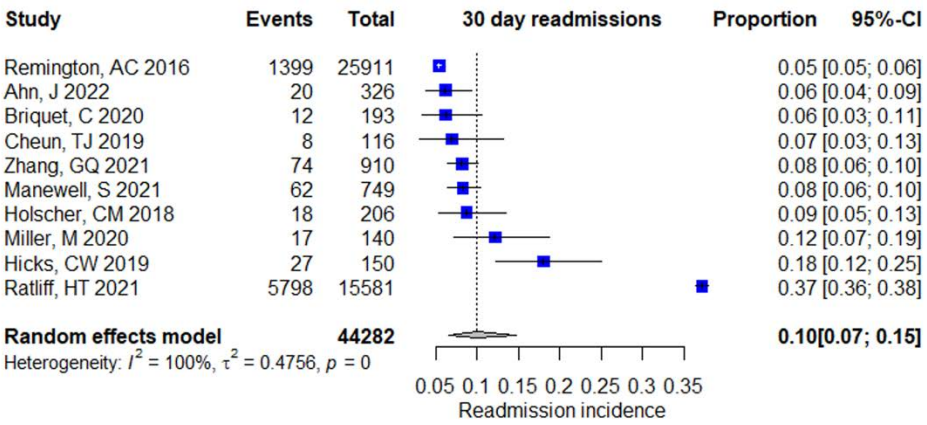

Figure 2-3 Proportion of participants readmitted within 30 days for DFD related problem.

2.4.7 Reasons for readmissions

Reasons for readmission were reported in 10 studies but the results could not be pooled due to heterogeneity (5, 7-10, 20, 22, 24, 26, 27). Common reasons for readmission included foot infections and related causes such as worsening of foot infection (10) recurrent foot infection (20, 22) cellulitis or sepsis (27) foot ulcers and related complications such as recurrent ulceration (9, 29) or worsening of ulcers (22, 26) cardiac causes (8, 9, 20, 26) and renal problems (5, 8, 9, 20).

2.5 Discussion

This systematic review suggests that total 30-day readmission following hospital treatment of DFD occurs in approximately one fifth of patients with 10% of patients readmitted to treat recurrent DFD. Meta-regression suggested that women and patients with PN had significantly increased risk of 30-day readmission and that CAD was a risk factor for DFD-related readmission. Having private health insurance appeared protective against total 30-day readmission. It is important to note that most of the studies were conducted in US and were of retrospective design (5, 7-10, 18-28). There is a need for prospective cohort studies conducted in other populations to assess risk factors for DFD-related readmission.

Hospital admissions to treat DFD is common and causes enormous burden in the US30 and other countries (31). In a study conducted in US, it was estimated that neuropathy and infections caused 90% of DFU-related hospital admissions costing approximately $1.4 billion/year (5). There has been increasing focus on hospital readmission in the US since the introduction of the Affordable Care Act (32, 33). Identifying risk factors for readmission may provide targets to reduce cost and morbidity. Meta-regression suggested that female sex and PN were risk factors for increased total 30-day readmissions. Other risk factors that were identified by multiple different studies included presence of multiple comorbidities, Black American ethnicity and smoking but meta-regression analyses did not conform these findings. Multiple studies also reported that having private insurance was protective from readmission, a finding confirmed in the meta-regression (8, 9, 19, 20). It is possible that PN is a surrogate marker of poorly control diabetes over a long period of time and patients may have concurrent macrovascular complications such as PAD and microvascular complications such as diabetes-related nephropathy which increase the risk of readmission to the hospital (7). Socio-economic aspects are important determinants of health status with deprived patients more likely to have poor outcomes possibly due to poor living conditions and limited

access to care (34, 35). Studies assessing patients over longer follow-up periods are needed to fully understand the role of other risk factors. It is noteworthy that patients with DFD are usually admitted for multiple reasons and a significant proportion of patients included in this systematic review were readmitted for cardiac reasons (8, 9, 20, 26).

The 30-day readmission rates specifically related to DFD varied from 5.0% to 37.0% (mean 10.0%). Meta-regression found that CAD was a risk factor for DFD-related readmission. Patients with CAD usually have other co-morbidities as well as PAD which play an important role in development of DFD (1, 2). Assessment and reporting of presence of PAD was not consistent among the studies and may be the reason why it was not found to be a risk factor for total or DFD-related readmission. Patients with CAD may present with peripheral oedema of the limbs and even a minute injury to the leg can cause foot infection and cellulitis which is a common reason for admission to the hospital in these patients (4, 36).

This systematic review has several limitations. There was substantial heterogeneity in the design of the included studies and populations studied which limits interpretation of the regression analyses. Most studies reported total 30-day readmissions rate (5, 7-10, 18-20, 22-24, 26, 28) but not DFD-related readmission rate which was calculated by secondary analyses. Studies with longer follow-up periods may have been beneficial to assess risk rates per 100 person years and summarise the readmission rates over a longer period. Some studies did not report the reasons for readmissions (18, 19, 21, 23, 25, 28). It is also noteworthy that most of the studies were conducted only in the US5 (7-10, 18-21, 23, 24, 26-28), which limits the generalisability of the results to other populations. The included studies had multiple limitations including retrospective design which may have led to missed outcome events and inconsistent definition of risk factors. Many studies had small sample sizes (5, 8, 10, 28) and single centre design (5, 7, 8, 10, 18, 22, 24).

2.6 Conclusion

This systematic review identified that total 30-day readmission rate among patients who were discharged from an index admission to treat DFD was 22% and was higher in female patients and those with PN. Having private health insurance was protective of total 30-day readmission. Thirty-day DFD related readmission rate was 10%. CAD was a risk factor for DFD-related readmission. Future research is needed to develop effective ways to reduce readmission and examine rates in different populations.

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2.8 Conflict of interest statement/Funding

The authors have no conflicts of interest to declare.

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2.10 Supplementary Material

Supplementary Table 1: Characteristics of the studies

Study	Study period	Study design	Single centre of Multicentre	Sample size	Methods of patient identification	Inclusion criteria	Exclusion criteria	Primary Outcome and other outcomes
Holscher 2018 [8]	1st of July 2012 to 31st of June 2017	Retrospective cohort study	Single centre	206	Data were extracted from a prospectively maintained data base	All patients presenting to our multidisciplinary diabetic limb preservation service, who were admitted for any lower extremity related problem with DFU	Not stated	Risk factors for unplanned 30-day readmissions
Miller 2020 [10]	1st of July 2012-1st of July 2015	Retrospective cohort study	Single centre	140	Data were extracted from a prospectively maintained data base by manual extraction	Patients with DFI (Only 35% were selected from a larger group).	Absence of DFI Pregnancy Incarcerated DFD Transferred to another facility. Withdrawal from care	Risk factors for all cause 30-day hospital readmission

Myers 2021 [18]	1st of January 2014 to 31st of December 2018	Retrospective cohort study	Single centre	378	Data were collected form Sunrise health record system using ICD 9 and 10 codes	Patients with type 11 diabetes Those with DFU, Age >18,	Patients with no DM Non-diabetic foot ulcers Outpatients Those who died during the initial admission Patient charts with missing data	Risk factors for all cause 30 day and 90-day readmissions
Remington 2016 [9]	1st of January 2011 to 31st of December 2012	Retrospective cohort study	Multicentre	25911	Patient discharge records were identified using ICD 9 codes	Patients with DFU (diabetes and distal foot ulcers)	If patients had missing link data on readmission rates or race or those with higher level amputations. Discharges that were not at risk of 30-day readmission Those who died during index admission	Risk factors for all cause 30-day readmissions

							Those who were transferred to nursing care facilities Those admitted in the last month of the study period	
Ries 2015 [7]	1st of January 2012 to 31st of December 2013	Retrospective cohort study	Single centre	439	Current Procedural Terminology codes and ICD 9 codes	Patients with a diagnosis of diabetes undergoing primary lower-extremity amputation Orthopaedic department admissions >18 years, Initial amputation is not for trauma, primary amputation only	Patients with multiple amputations/previous major amputations	Incidence, risk factors, and causes for unplanned 30-day readmissions following primary lower-extremity amputation

Zhang 2021(Minor Amputations) [19]	1st of January 2012 to 31st of December 2019	Retrospective cohort study	Multicentre	7415	All patients from the Maryland Health Services Cost Review Commission database using ICD 9/10 codes	Any patient with minor amputation following DFD (53 hospitals) Age> 18	Patients with major amputations Those with missing residential codes Those who missing data in key variables	Association of geographic socioeconomic disadvantage with short- and long-term outcomes after minor amputation in patients with diabetes: all cause 30-day readmission and 1-year re-amputation.
Zhang 2021(Major Amputations) [20]	1st of July 2015- 1st of July 2017	Retrospective cohort study	Multicentre	910	All patients from the Maryland Health Services Cost Review Commission database using ICD 9/10 codes	Any patient with major amputation (AKA or BKA) following DFD, (53 hospitals) Age >18	Patients with minor amputations Those with missing residential codes Those who missing data in key variables Patients who died during the index admission were also excluded.	Association of geographic socioeconomic disadvantage with all cause 30-day readmission and 1-year major amputation

Ahn J 2022 [21]	1st of January 2012 to 31st of January 2017.	Retrospective cohort study	Multicentre	562 of which 326 had diabetes.	Data were extracted from a prospectively maintained data base: American College of Surgeons-National Surgical Quality Improvement Program Database (ACS-NSQIP)	Diagnosis of necrotizing fasciitis based on ICD 9 and 10 codes from ACS-NSQIP combined with current procedural terminology codes (CPT) to identify the involvement of lower limb.	Patients with CPT codes for involvement of other regions except lower limbs, those who has CPT codes for surgeries in abdomen and upper regions, and age over 90 years. Planned readmissions or reoperations unrelated to the condition were excluded.	Unplanned reoperation and readmission related to necrotising fasciitis.
Briquet C 2020 [22]	1st of September 2013 to 31st of December 2017	Prospective cohort study	Single centre	193 of which 19 were patients with diabetic foot infections.	Through multi-disciplinary team, local database	Patients on intravenous antibiotics following confirmed diagnosis of an existing infection by means of clinical or biochemical sampling or	Patients on vancomycin	Number of days of hospitalization saved, number of readmissions during OPAT and reasons, readmissions within 30 days after OPAT finishes and

						through imaging, projected remaining duration of ab treatment at home is at least 6 days, no change to oral antibiotics. Patient was discharged after agreement with the family. Included 19 patients with diabetic foot infections.		complications related to OPAT
Brooke 2014 [23]	1st of January 2004 and 31st of December 2007	Retrospective cohort study	Multicentre	172,134, of which 84,653 patients had diabetes	Data were extracted from a prospectively maintained data bases: Centres for Medicare and Medicaide Services (CMS) ,	Diabetes, a revascularisation procedure and chronic limb threatening ischemia (CLI) identified by ICD 9 codes.	Records with missing values for primary outcome, gender, age and race, patients with intermittent claudication (IC) and upper extremity revascularisation were excluded.	Amputation free survival and major adverse limb events following lower extremity (LE) revascularisation

					Medicare Provider Analysis and Review (MedPAR) data bases were screened with ICD 9 codes for identification to assess if routine annual HbA1c and serum cholesterol measurement improved subsequent amputation or death?			
Cheun 2019 [24]	1st of January 2014 to 31st of	Retrospective cohort study	Single centre	116, 61 had staged amputations and 55 had	Locally maintained database/electronic medical records	Diabetes, age >18, foot gangrene and denovo major amputation.	Diabetes, age >18, foot gangrene and denovo major amputation.	30-day unplanned ipsilateral re-amputation rate

	March 2017			primary amputations				
Hicks 2019 [5]	1st of June 2012 to 1st of June 2016	Retrospective cohort study	Single centre	150	All patients presenting to the multidisciplinary diabetic limb preservation service- collected from the local database.	All patients with diabetic foot ulcers	Patients without diabetic foot ulcers, those without hospital admissions, those with missing cost data and those with unsalvageable limbs (WIFI stage 5)	Inpatient hospital charges, costs, professional fees for index admissions and readmission (only unplanned readmissions for any cause were included)
Manewell 2021 [25]	1st of July 2012 to 30th June 2017	Retrospective cohort study	Two centres	749	All patients admitted with DFU recruited from hospital data bases.	Hospital admission for DFU during the study period as per ICD 10 codes and over 18 years.	Not stated	Readmission planned or unplanned and related to DFU (28 days and 12 months) and cumulative length of stay in hospital

Najafian 2015 [26]	1st of January 2011 to 31st of December 2012	Retrospective study conducted on a prospectively maintained data base.	Multicentre	4052	All patients with lower extremity bypass for PAD-diabetic patients were a sub-cohort (insulin dependent or not) were identified from the American College of Surgeons National Surgery Quality Improvement Program data base using current procedure terminology codes	Patients undergoing infra-inguinal bypass during the study period.	Concomitant supra inguinal procedures, primary post operative diagnosis of acute ischemia, death over the follow up period, planned readmission, hospitalisation for >30 days during the index admissions, if the patients were missing age, diabetes status	30-day unplanned readmission rate following lower extremity bypass surgery between those with and without diabetes

Ratliff 2021 [27]	1st of January 2016 to 31st of December 2017	Retrospective study conducted on a prospectively maintained data base.	Multicentre	15581	Data collected from National Readmission Database using ICD 10 codes.	All patients who had an amputation (minor or major) following diabetes during 2016 to 2017 were collected from National Readmission Database using ICD 10 codes.	Patients with bilateral index amputations were excluded, and those who died during index admission were excluded.	6-month readmission rate by type of amputation (major vs minor). Does not specify if the admissions were planned or unplanned. All are related to DFD.
Shah 2019 [28]	1st of August 2011 to 1st of August 2016	Retrospective cohort study	Multicentre	120	All patients who underwent an amputation secondary to DFI from corporate financial services database using ICD 9 codes	Patients over 18 years, inpatient admission for DFI, and an amputation secondary to DFI.	Documented history of major amputation	Post of length of stay in the hospital following no antibiotics, oral antibiotics and parenteral antibiotics.

Foot note: International Classification of Disease, ICD; diabetes-related foot disease, DFD; diabetes-related foot ulcers, DFU; diabetic foot infections, DFI; above knee amputation, AKA; below knee amputation, BKA

Supplementary Table S2: Quality Assessment of the included studies

Quality Category	Questions	Holscher 2018	Miller 2020	Myers 2021	Remington 2016	Ries 2015	Zhang Min 2021	Zhang Maj 2021	Ahn 2022	Briquet 2020	Brooke 2014	Cheu 2020	Hicks 2019	Manewell 2022	Najafian 2015	Ratliff 2021	Shah 2019
Newcastle-Ottawa Scale																	
Selection																	
	Representativeness of the Exposed Cohort	*	*	*	*	*	*	*	*	*	*	*	*	*	*	*	*
	Selection of the Non-Exposed Cohort	No	No	No	No	No	No	No	*	No	*	*	No	No	No	No	*
	Ascertainment of Exposure	*	*	*	*	*	*	*	*	*	*	*	*	*	*	*	*

	Demonstration that the outcome of interest was not present at study entry.	No	No	No	No	No	No	No	*	No	No	*	No	No	*	No	*
Comparability																	
	Comparability of cohorts on the basis of the design analysis (If the relative risk for the exposure of interest is adjusted for the confounders listed, then the groups will be considered to be comparable on each variable used in the adjustment). 2 points	No	No	No	No	No	No	No	*	No	*	*	No	No	*	*	*
Outcome																	
	Assessment outcome	*	*	*	*	*	*	*	*	*	*	*	*	*	*	*	*
	Adequacy of follow-up for the event to occur.	*	*	*	*	*	*	*	No	*	No	*	*	*	*	*	No
	Adequacy of follow-up of cohorts for both groups	No	No	No	No	No	No	No	*	No	*	*	No	No	*	*	*

Risk		High	High	High	High	High	High	High	Low	High	High	Low	High	High	Low	High	Low
Quality Assessment Tool Developed for Observational Cohort Studies by the authors																	
Selection of participants																	
Research question	Did the study report clear aims (including all of the following: population, exposure, and outcome of interest)?	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y
	Was the study setting defined (eg, hospital based; single centre or multicentre)?	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y
	Was the study reported as a prospective study (eg, hypothesis/research question defined before recruitment of patients)	N	N	N	N	N	N	N	N	Y	N	N	N	N	N	N	N
Selection criteria	Were the methods for recruitment /sampling detailed in the study?	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	N	Y	Y	Y

	Was the diagnosis of DFD adequately defined (ie, positive diagnosis of DFD by one or several of the following: presence of DM type 1 or 2 with presence of ulcer; discontinuation of the epithelium, infection: local signs of infection or systemic features of infection or gangrene; presence of black necrotic tissue with clinical examination or presence of OM; probing to bone or medical imaging with or without biochemical confirmation of infection)	N	Y	Y	Y	Y	Y	Y	Y	N	Y	Y	Y	Y	Y	Y	Y
	Confirmation of an index admission following a DFD	N	Y	Y	Y	Y	Y	Y	N	Y	N	Y	Y	Y	Y	Y	Y
	Were inclusion and exclusion criteria detailed?	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	N	Y	Y	Y
Sub total		4/7	6/7	6/7	6/7	6/7	6/7	6/7	5/7	6/7	5/7	6/7	6/7	4/7	6/7	6/7	6/7
Comparability of studies																	

Participant characteristics	Was DFD severity defined in the cases? (ie, based on WIFI, SINBAD, Texas or any similar DFD classifications)	Y	N	N	N	N	N	N	N	N	N	Y	Y	N	N	N	N
	Sufficient relevant baseline medical and demographic information characterizing participants was provided (or reference to previously published baseline data provided). Defined as including ≥5 of the following: age, gender, ethnicity, smoking, PN, HTN, ABI, DM, previous AMI/CAD, PN, renal impairment.	Y	Y	Y	N	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y
Sample size	Was the sample size >100 participants?	Y	Y	Y	Y	Y	Y	Y	Y	N	Y	Y	Y	Y	Y	Y	Y
	Was the basis of sample size/calculation reported in methodology?	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N
Sub total		3/4	2/4	2/4	1/4	2/4	2/4	2/4	2/4	1/4	2/4	3/4	3/4	2/4	2/4	2/4	2/4
Outcomes																	

Outcome	Was the primary outcome defined as readmission to a hospital as an inpatient ≤30 days after the index DFD related admission?	Y	Y	Y	Y	Y	Y	Y	N	Y	N	N	N	Y	Y	N	N
	Was the indication for readmission noted	Y	N	N	Y	Y	N	Y	N	Y	N	Y	Y	N	Y	Y	N
	Was it reported whether readmission was planned or unplanned	Y	N	N	N	Y	N	N	Y	N	N	Y	Y	N	Y	N	N
Methods	Process by which follow-up was performed to identify outcomes described (eg, ICD 9/10 codes, dataset, hospital records, prospective phone calls, patient reports etc)	Y	N	Y	Y	Y	Y	Y	Y	Y	N	Y	N	N	Y	Y	Y
	Ethical issues (eg, consent, patient confidentiality, ethics approval) addressed	Y	N	N	N	Y	Y	Y	N	Y	Y	Y	N	Y	N	N	Y
Analysis	Did the study exclude or adjust for ≥2 confounders using one or several statistical methods (eg, logistic regression): age, gender, HTN, IHD, ABI, BMI, DM, smoking, dyslipidaemia impaired	Y	Y	Y	Y	Y	Y	Y	Y	N	Y	N	N	Y	Y	N	N

	renal function, previous stroke, preoperative wound, ASA classification vs readmissions																
	Measure of association (eg, odds ratio) included for each risk factor	Y	Y	Y	Y	Y	Y	Y	Y	N	Y	N	N	Y	Y	Y	N
	Whether the association was statistically significant (eg, *P* value) included	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y
	Did the study report findings in the context of the existing literature?	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y
Sub total		9/9	5/9	6/9	7/9	9/9	7/9	8/9	6/9	6/9	5/9	6/9	4/9	6/9	8/9	5/9	4/9
Individual score (Y)		16	13	14	14	17	15	16	13	13	12	15	13	12	16	13	12
Averaged score (%)		80%	65%	70%	70%	85%	75%	80%	65%	65%	60%	75%	65%	60%	80%	65%	60%

Note: There are 8 items under three domains in the Newcastle and Ottawa scale with two stars for comparability. Studies with a score of 7-9 is considered to have low risk of bias, a score of 4-6 is considered to have a high risk of bias and a score of 0-3 is considered to have a very high risk of bias.

Supplementary Table S3: Outcomes and results of included studies

Study	Method of follow-up	Duration of follow-up	30-day readmission rate of DFD: unplanned, related, overall	Risk factors associated with readmission in univariate logistic regression analysis (OR, 95% CI)	Risk factors associated with readmission in multivariate logistic regression analysis (OR, 95% CI)	Reasons for readmissions (percentage)	Conclusions
Holscher 2018 [8]	Prospectively maintained data base and from home care or patient reports	1st of July 2012 to 31st of June 2017	Total 30-day readmissions: 21.5% (99 readmissions out of 460 admissions in 206 patients), unplanned readmission rate: 17.6%.	HT (OR, 2.80; 95% CI, 1.19-6.59; PAD (OR, 1.80; 95% CI, 1.09-2.99) and open vascular surgery (OR, 2.64; 95% CI, 1.34-5.17) were associated with higher risk and insurance was (OR, 0.52;95%CI,	HT (OR, 2.80; 95%CI, 1.19-6.59) and current smoking (OR, 1.95; 95% CI, 1.02-3.73) were independently associated with 30-day unplanned readmissions after adjusting for age, gender, race,	Foot wound related complications (40.7%), vascular complications (14.8%), gastrointestinal (9.9%), cardiac causes (8.6%), acute kidney injury (8.6%), pulmonary causes (4.9%), diabetes related complications (3.7%), contra-lateral leg complications	17% unplanned 30-day readmission rate was seen in this prospective cohort of DFU patients enrolled in a multidisciplinary diabetic foot service. Only current smoking and hypertension were independent predictors of readmission after risk adjustment. WIFI score was not associated with readmissions.

				0.28-0.97) was protective	insurance status, hypertension, CAD, PAD, smoking status, open vascular operations, WIFI composite score and wound status at discharge	(3.7%) and other (4.9%).	
Miller 2020 [10]	Manual extraction of data from a prospectively maintained data base	1st of July 2012-1st of July 2015	Total 30-day readmissions: 22%	Length of stay (p=0.03), CRP level (p=0.009) and treatment failure (p=0.009) were significantly different between those who were readmitted or not. OR not mentioned.	Length of stay (OR, 1.08; 95% CI 1.01-1.16) and treatment failure (OR, 2.67; 95% CI, 1.15-6.21) were independent risk factors of 30-day readmissions after adjusting	Worsening of the DFI (55.0%), exacerbation of the chronic condition (19.0%), antibiotic relate (3.0%) and other causes (23.0%).	The 30-day readmission rate for patients with DFI is high. Treatment failure and length of stay are independently associated with readmission.

					for length of stay, treatment failure and homelessness.		
Myers 2021 [18]	By REDCap electronic data capture tool hosted at the institution	1st of January 2014 to 31st of December 2018	Total 30-day readmissions:10.6% Total 90-day readmissions: 26.7%	None of the factors were associated with 30-day readmissions	None of the factors were associated with 30-day readmissions. Discharge location to home with health care (OR, 2.62; 95% CI, 1.39-4.95), anticoagulant use (OR, 2.36, 95% CI, 1.27-4.39) and insulin use (OR, 2.08, 95% CI 1.20-3.61) were risk factors for 90-day readmissions	Not reported	None of the variables examined were associated with 30-day readmission; however, potential predictors for 90-day readmission included anticoagulation or insulin use and discharge home with healthcare services.

					after adjusting for discharge location, anticoagulant use, and insulin use.		
Remington 2016 [9]	Patients were followed up using current Procedural Terminology codes and ICD 9 codes	1st of January 2011 to 31st of December 2012	Total 30-day readmissions: 30%	Age, Elixhauser comorbidities, index length of stay in the hospital, initial surgical procedure, amputation procedure, sex, race, primary payer status and hospital state was significantly different between those who were readmitted or not.	Patients with a previous amputations (OR, 0.78; 95% CI 0.73-0.84) was protective of 30 day readmissions while, Elixhauser comorbidities (OR, 1.13; 95% CI, 1.12-1.15), Black American ethnicity (OR, 1.21; 95% CI, 1.13-1.29), Hispanic ethnicity (OR,	DM and related complications (19.4%), infection or post-operative complications (12.6%), ulcerations (5.4%), cardiac disease (6.1%), respiratory disease (2.5%), renal disease (1.9%)	Overall readmission rate was 30%. The study suggests that there are many factors that affect readmission rates for diabetic foot ulcer patients.

					1.11; 95% CI, 1.03-1.21) compared to White American ethnicity , Medicare (OR, 1.48; 95% CI, 1.36-1.61), and Medicaid (OR, 1.51; 95% CI, 1.37-1.67) holders compared to Private insurance holders were as more likely to be readmitted after adjusting for age, female sex, Elixhauser comorbidities, elective, amputation procedure, race		

					and payer status.		
Ries 2015 [7]	Current Procedural Terminology codes and ICD 9 codes were used	1st of January 2012 to 31st of December 2013	Unplanned 30-day readmissions:10.5%	In univariate analyses, discharge of antibiotics, smoking, chronic kidney disease, peripheral vascular disease, higher Charlson Comorbidity Index were associated with higher risk of readmission ($p<0.005$). Odds ratios were not given.	Gangrene (OR, 2.95; 95% CI, 1.37-6.35), discharge on antibiotics (OR, 4.48; 95% CI 1.71-11.74), smoking (OR, 3.22; 95% CI, 1.40-7.36), CKD, (OR, 2.82; 95% CI, 1.30-6.15) and PAD (OR, 2.47; 95% CI, 1.08-5.67) were independently associated with unplanned readmissions after adjusting for factors with $p<0.1$ in	Major surgical events (37.0%), minor surgical events (28.3%), medical events (28.3%) and psychiatric events (6.4%).	Thirty-day readmission rates following primary lower-extremity amputation in patients with diabetes were high at >10%. Both medical and surgical complications, many of which were unavoidable, contributed to readmission.

					univariate analyses.		
Zhang 2021(Minor Amputations) [19]	ICD 9 and 10 codes for readmissions and Clinical Modification procedure code for either major or minor lower extremity amputation	1st of January 2012 to 31st of December 2019	Total 30-day readmissions: 22.1%	ADI 2 (OR, 1.16; 95% CI 1.01-1.32), ADI 3 (OR, 1.33; 95% CI 1.14-1.55), ADI 4 (OR, 1.31; 95% CI 1.03-1.66), age >65 (OR, 1.42; 95% CI, 1.05-1.91), females (OR, 1.23; 95% CI, 1.09-1.38), Black American ethnicity (OR, 1.23; 95% CI 1.15-1.45), Medicare (OR, 1.88; 95% CI, 1.62-2.17), Medicaid (OR, 1.47; 95% CI, 1.23-1.75), HT (OR, 0.86; 95%	ADI 3 (OR, 1.28; 95% CI 1.09-1.50), Black American ethnicity (OR, 1.21; 95% CI 1.07-1.38), Medicare (OR, 1.43; 95% CI, 1.20-1.69), Medicaid (OR, 1.48; 95% CI, 1.15-1.66), CHF (OR, 1.50; 95% CI, 1.31-1.72), CAD (OR, 1.26; 95% CI, 1.11-1.43), PAD (OR, 1.38; 95% CI, 1.22-1.56), CKD (OR, 1.29; 95% CI,	Not reported	Geographic socioeconomic disadvantage is independently associated with both short- and long-term outcomes after minor diabetic amputations in Maryland. Incidence of 30-day readmission was 22.1% and increased with ADI quartile. Incidence of re-amputation was 23.6% and increased with ADI. Multivariate logistic regression showed that ADI3, black race, Medicare, Medicaid, CHF, CAD, PAD, CKD, and COPD were associated with readmissions.

				0.77-0.96), CHF (OR, 2.05, 95% CI; 1.81-2.32), CAD (OR, 1.65; 95% CI, 1.47-1.84), PAD (OR, 1.62; 95% CI, 1.45-1.80), CKD (OR, 1.71; 95% CI, 1.53-1.92), COPD (OR, 1.70; 95% CI, 1.45-1.99).	1.14-1.46), COPD (OR, 1.38; 95% CI, 1.16-1.62).		
Zhang 2021(Major Amputations) [20]	ICD 9 and 10 codes for readmissions and Clinical Modification procedure code for either major or minor lower extremity amputation	1st of July 2015 to 1st of July 2017	Total 30-day readmissions: 18.9%	Female sex (OR, 1.52; 95% CI, 1.08-2.13), Medicare (OR, 1.96; 1.15-3.23), dyslipidaemia (OR, 1.43; 95% CI, 1.02-1.99), PAD (OR, 1.59; 95% CI, 1.13-2.23)	Female sex (OR, 1.45; 95% CI, 1.01-2.06), Medicare (OR, 1.76; 95% CI, 1.01-3.06), PAD (OR, 1.49; 95% CI 1.04-2.12)	Amputation stump complication (23.0%), infection (20.0%), diabetes complication (13.0%), cardiovascular disease (12.0%), gastrointestinal disease (8.0%), respiratory disease (7.0%), neurological disease (3.0%),	Major amputations were more prevalent in more deprived. 30-day readmission rate was 18.9% and this did not change with increasing ADI. Re-amputation occurred in 14.4% and increased with increasing ADI quartile and was confirmed with KM analyses. In multivariate female sex, Medicare and PAD

						genitourinary disease (2.0%), haematological disease (2.0%), renal disease (2.0%), psychiatric disease (2.0%), pain (1.0%), rheumatologic disease (1.0%), skin disease (1.0%), convalescence (0.6%), stroke (0.6%)	remained significant risk factor for readmission.
Ahn J 2022 [21]	Current Procedural Terminology codes	1st of January 2012 to 31st of January 2017.	Unplanned readmissions related to necrotising fasciitis. Readmission rate among diabetes	BMI >30kg/m2 0.36 [0.16-0.83}	BMI >30kg/m2 0.36 [0.13-0.92], time form hospital admission to surgery > 8.5 days 7.9 [1.91-32.9], amputation 4.53 [1.20-	Not reported	Overall, 30-day readmission rate was 5.3 % and the rate in patients with diabetes was 6.1%. Higher BMI was protective of readmission and any amputation and time form admission to surgery >8.5 days were

			patients is 6.1%.		29.6] were significantly associated with unplanned readmission.		significant risk factors for readmission
Briquet C 2020 [22]	Patients were followed-up-specific method not mentioned.	1st of September 2013 to 31st of December 2017	Overall, 32.6% (For DFD patients:63. 2%, 12% were related to OPAT)	Not done	Not done	Unfavourable evolution or relapse (12.7%), unfavourable wound evolution (14.1%), Clostridium difficile infection (2.8%), antibiotic toxicity (2.8%), picc line (4.2%), related readmissions (36.6%), new infection (15.5%), unrelated readmissions (14.1%), planned readmissions for interventions (33.8%).	Diabetic foot infections resulted in a significantly higher rate of readmission compared to other conditions that required OPAT.OPAT is found to be efficacious in saving hospitalization's days, with a low rate of readmissions and complications and a high patients' level of satisfaction.

Brooke 2014 [23]	Not stated clearly. Possible follow up using current Procedural Terminology codes and ICD 9 codes.	1st of January 2004 and 31st of December 2007. All patients were subsequently followed up for two years.	All readmissions: between 20.3% (better DM care) to 22.2% (Poor DM care), Common rate: 21.25%.	Low rates of readmission for those presenting from regions with better diabetic care (0.91 [0.85-0.97]. Age over 80 years 1.21 [1.13-1.30], black American ethnicity 1.11 [1.03-1.19], higher Charlson comorbidity index 2.61 [2.32-2.94] were risk factors and baseline endovascular procedures 0.82 [0.77-0.88] were protective for 30-day readmission.	Not done	Not reported	Readmission rates were significantly lower in areas with routine annual testing of HbA1C and serum lipids.

Cheun 2019 [24]	Retrospective chart review/ access of electronic medical records	1st of January 2014 to 31st of March 2017 and all patients were followed up for 5 years.	16.4% for the entire cohort	Not done	Not done	9% for medical causes and 7% for stump-related complications	Staged lower extremity amputations achieve better outcomes including readmission.
Hicks 2019 [5]	Not stated clearly. Possible follow up using current Procedural Terminology codes and ICD 9 codes.	1st of June 2012 to 1st of June 2016	28.70%	Not done	Not done	Reasons for readmissions include foot wounds (48.8%), bypass wounds (14.0%), renal complications (9.3%) and other medical conditions.	Readmissions following DFU are common and is associated with a substantial burden (twice as much as the initial admission)
Manewell 2021 [25]	Not stated clearly. Possible follow up using current	1st of July 2012 to 30th June 2017	8.30%	Age 1.03 [1.00-1.05], unplanned status 1.72 [0.92-3.19], higher rate of	Age 1.02 [1.00-1.05] and Modified Charlson Comorbidity	Not reported	There is significant disease burden related to hospital readmission

	Procedural Terminology codes and ICD 9 codes.			modified Charlson Comorbidity counts 1.38 [1.03-1.85] were risk factors in univariate analyses	count 1.38 [1.02-1.88] were significant in multivariable analysis.		following DFU in Australia.
Najafian 2015 [26]	ICD 9 codes and current procedure terminology codes	1st of January 2011 to 31st of December 2012	Unplanned readmission was observed in 16.0% of the patients.	Insulin dependent diabetes mellitus 1.55 [1.36-1.76](p<0.001), age more than 75th centile 1.14 [1.00-1.29], black race 1.25 [1.08-1.44], obesity 1.31 [1.13-1.51], femoral-tibial 1.43 [1.26-1.61], tibial-tibial/popliteal - tibial level bypass 1.36	In patients without concomitant cardiac diseases insulin dependent diabetes mellitus (OR 1.23; 95% CI 1.03-1.47; p=0.01), bleeding disorders 1.20 [1.02-1.40], chronic limb threatening ischemia 1.17	Reported for non-diabetic patients, non-insulin-dependent diabetes mellitus patients and insulin-dependent diabetes mellitus patients respectively. Any infectious complication (5%, 8%, 9%), any wound complication (33%, 34%, 33%), any cardiac complications (3%, 5%, 7%),	Insulin-dependent diabetes mellitus was independently associated with unplanned readmission only in those without cardiac disease.

				[1.11-1.67], American Society of Anaesthesiologist class 3 1.66 [1.22-2.25], class 4-5 2.55 [1.85-3.50] and functional dependency 1.63 [1.37-1.94] were associated with increased odds of 30-day unplanned readmission ($p<0.05$).	[1.01-1.36] and wound infection 1.22 [1.04-1.43] were associated with 30-day readmission.	pulmonary complications (4%, 5%, 5%), bleeding (30%, 35%, 35%), renal failure (2%, 1%, 1%) and deep vein thrombosis (2%, 2%, 1%).	
Ratliff 2021 [27]	Diagnosis related group codes and ICD 10 codes	1st of January 2016 to 31st of December 2017	37.21%	Not done	Not done	Re-amputation 12.8%, major re-amputation 10.2%, wound debridement 4.2%, soft-tissue procedure 2.2%, osteomyelitis 0.4%, cellulitis 1.2%,	48.8% were readmitted within 6 months and 12.8% had a subsequent amputation. Patients with minor amputation were at greater odds of readmission (OR 1.25; 95% CI 1.18-1.31), re-amputation (OR 3.71;

						post-operative infection 1.7% and sepsis 6.5%. 3.5% of the patients died.	95% CI 3.34-4.12) and more proximal re-amputation (OR 2.61; 95% 2.33-2.93).
Shah 2019 [28]	Documented history in electronic medical records/post-operative notes	1st of August 2011 to 1st of August 2016	14.17%	Not done	Not done	Not reported	Oral antimicrobial therapy following amputation for DFI has the potential to decrease post-operative length of stay without increasing the risk of readmission.

Supplementary Table S4: Summary findings table based on GRADE criteria applied to the pooled results of total 30-day readmission rate and 30-day readmission rate related to diabetes-related foot disease following an index admission for diabetes-related foot disease.

Patients of population: Patients who were admitted to hospital for treatment of diabetes-related foot disease.

Setting: Hospital.

Intervention: None

Comparison: None

30-day readmission outcome	**Mean 30-day readmission (95%CI)**	**Number of participants (studies)**	**Certainty of evidence (GRADE)**	**Comments**
Total	22.0 (17.0-27.0)	124,683 (16)	Low	Due to inconsistency and concern about generalisability of the studies as most are from USA and wide confidence interval.
Diabetes related foot disease	10.0 (7.0-15.0)	44,282 (10)	Low	

Supplementary Table S5: All risk factors of the participants in the included studies and meta regression findings

Study	Age (mean)	Sex (number of males)	Black	HT	PAD	Dyslipidaemia	Smoking *	CKD	PN	CAD	CHF	COPD	PHI	LOS (Median)
Holscher 2018 [8] (n=206)	58.5	125 (61%)	122 (59%)	173 (84%)	101 (49%)	106 (52%)	55 (27%)	43 (21%)	197 (96%)	61 (30%)	34 (17%)	NR	48 (23%)	9
Miller 2020 [10] (n=140)	55 †	106 (76%)	NR	NR	45 (32%)	NR	47 (34%)	NR	NR	NR	NR	NR	NR	7
Myers 2021 [18] (n=378)	66.1	270 (71%)	83 (22%)	288 (76%)	69 (18%)	NR	41 (11%)	81 (21%)	87 (23%)	NR	NR	NR	211 (56%)	11.9
Remington 2016[9] (n=25911)	63	17140 (66%)	5700 (22%)	NR	NR	NR	NR	NR	NR	NR	NR	NR	4664 (18%)	6
Ries 2015 [7] (n=439)	57.6	297 (68%)	NR	335 (76%)	73 (17%)	NR	89 (20%)	141 (32%)	246 (56%)	NR	137 (31%)	137 (31%)	NR	7.6

Zhang 2021(Minor Amputations[19] (n=7415)	NR ‡	5189 (70%)	2870 (39%)	4765 (64%)	3401 (46%)	3702 (50%)	1545 (21%)	2949 (40%)	1885 (25%)	2518 (34%)	1590 (21%)	835 (11%)	1810 (24%)	NR
Zhang 2021(Major Amputations) [20] (n=910)	NR ‡	601 (66%)	448 (49%)	415 (46%)	477 (52%)	437 (48%)	191 (21%)	448 (49%)	52 (6%)	403 (44%)	275 (30%)	145 (16%)	142 (16%)	NR
Briquet C 2020 [22] (n=193)	NR	NR	NR	NR	NR	NR	NR	NR	NR	61 (30%)	NR	NR	NR	NR
Brooke 2014 [23] (n=84653)	NR	NR	NR	NR	NR	NR	NR	NR	NR	NR	NR	NR	NR	NR
Cheun 2019 [24] (n=116)	58	79 (68%)	NR	107 (92%)	97 (84%)	78 (67%)	72 (62%)	35 (30%)	NR	NR	26 (22%)	NR	NR	12.6

Hicks 2019 [5] (150)	57.7	93 (62%)	96 (64%)	126 (84%)	76 (51%)	74 (49%)	45 (30%)	35 (23%)	141 (94%)	NR	27 (18%)	NR	32 (21%)	NR
Najafian 2015 [26] (n=4052)	67.3	2593 (64%)	742 (18%)	3676 (91%)	4052 (100.0 %)	NR	1387 (34%)	383 (9%)	NR	NR	137 (3%)	442 (11%)	NR	NR
Shah 2019 [28] (n=120)	59.4	86 (72%)	72 (60%)	71 (59%)	28 (23%)	NR	NR	37 (21%)	NR	2518 (34%)	NR	NR	NR	9.6
Ahn J 2022 [21] § (n=326)	56.0	232 (71%)	NR	248 (76%)	NR	NR	100	37 (11%)	NR	403 (44%)	19 (6%)	18 (6%)	NR	NR
Manewel l 2021 [25] § (n=749)	69.1	525 (70%)	NR	NR	NR	NR	75 (10%)	55 (7%)	NR	NR	NR	NR	NR	10.0
Ratliff 2021 [27] § (15581)	63.9	10804 (69%)	NR	13389 (86%)	7654 (49%)	NR	2620 (17%)	6727 (43%)	4188 (27%)	NR	NR	NR	2738 (18%)	NR

Meta regression for total readmissions

	Age (mean)	Sex (number of males)	Race (Black)	HT	PAD	Dyslipidaemia	Current smoking	CKD	PN	CAD	CCF	COPD	Private Insurance	Length of stay in hospital in days
Intercept	-0.0348	-0.0776	0.0132	0.0072	0.0060	-0.0287	0.0060	-0.0014	0.0129	-0.0103	-0.0244	0.0349	-0.0294	-0.0419
Standard error	0.0523	0.0342	0.0106	0.0136	0.0068	0.0345	0.0149	0.0178	0.0064	0.0255	0.0240	0.0706	0.0149	0.0671
P value	0.51	0.023	0.21	0.60	0.38	0.41	0.69	0.94	0.045	0.69	0.31	0.62	0.048	0.53

Meta regression for DFD related readmissions														
Intercept	0.0210	0.0047	0.0114	0.0150	-0.0176	-0.0266	-0.0170	0.0265	-0.0001	0.0475	0.0.0416	0.0291	-0.0074	-0.0186
Standard error	0.0598	0.0565	0.0067	0.0205	0.0201	0.0295	0.0176	0.0165	0.0105	0.0211	0.0381	0.0250	0.1387	0.0543
P value	0.72	0.29	0.088	0.47	0.38	0.37	0.33	0.11	0.99	0.025	0.28	0.24	0.96	0.73

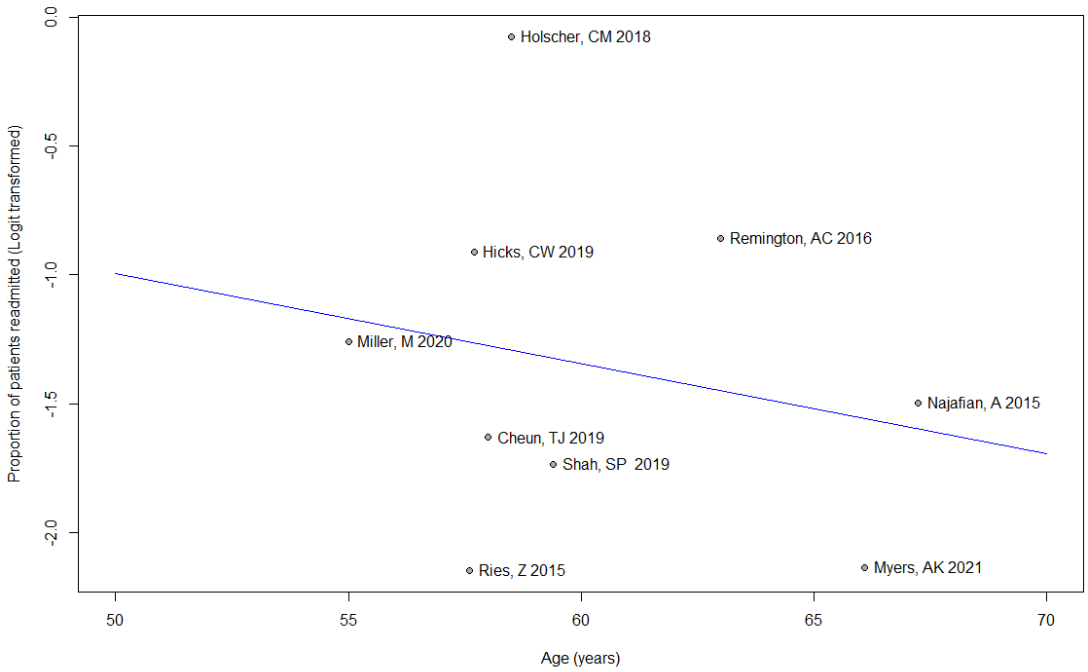
Reported are mean or number of participants (percentage) having each risk factor unless highlighted.

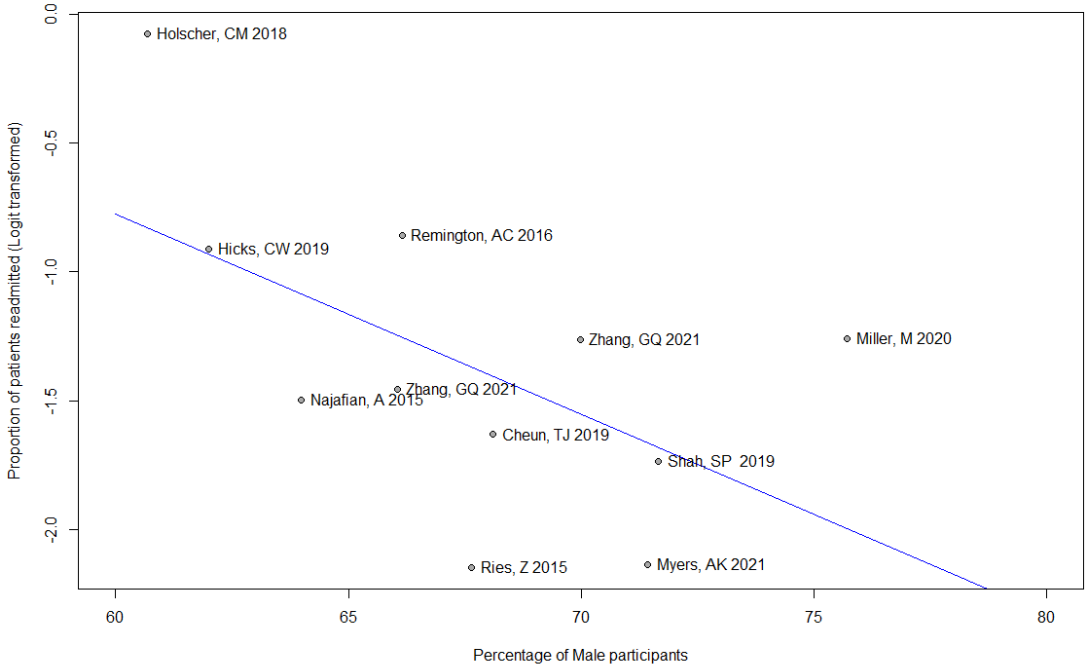
Zhang et al 19 and 20 are two separate studies on different cohorts by the same research group.

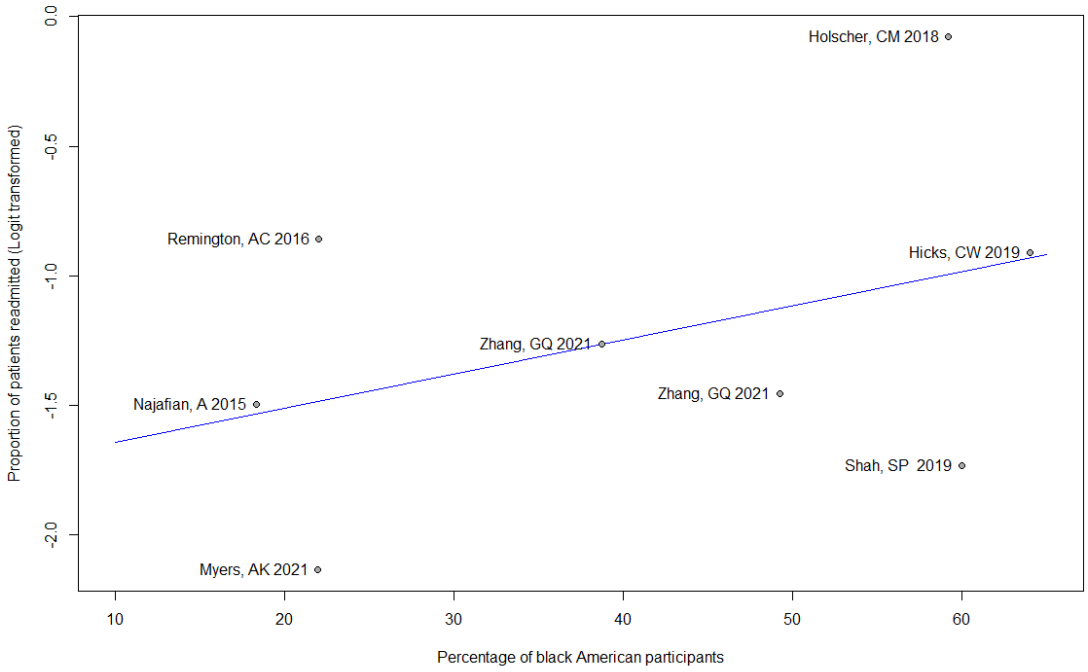
Hypertension; HT, peripheral artery disease; PAD, chronic kidney disease; CKD, peripheral neuropathy; PN, coronary artery disease ; CAD, congestive heart failure; CHF, chronic obstructive pulmonary disease; COPD, private health insurance; PHI, length of stay in hospital in days; LOS, not reported; NR. Black refers to Black American ethnicity.

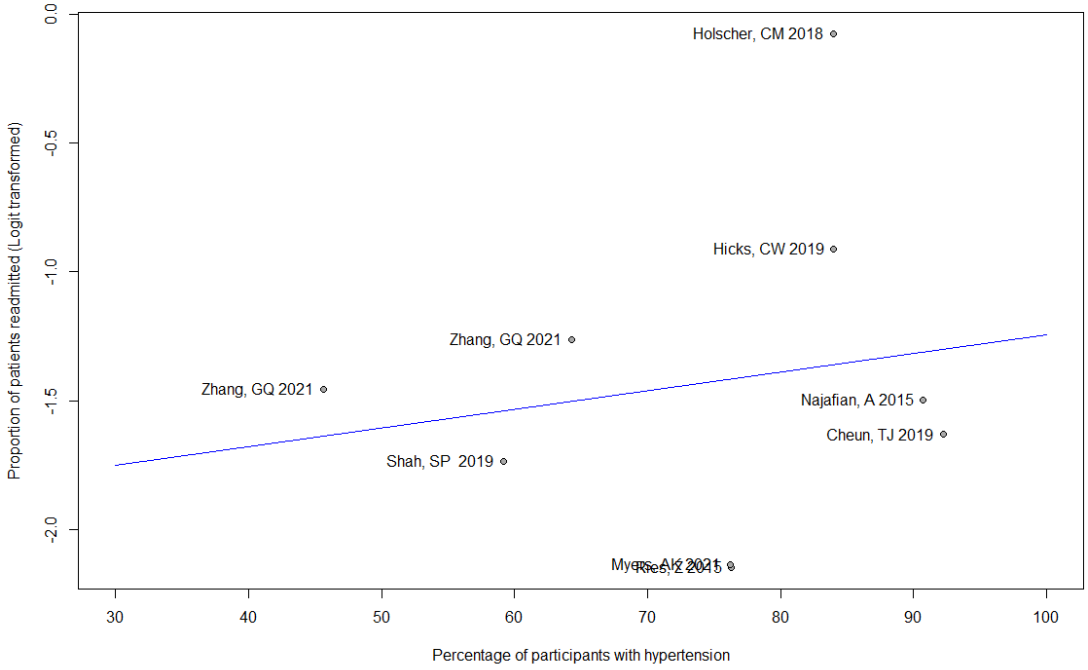
*Refers to current smoking, † Age was reported as median, ‡ age was reported in categories, § These studies only reported diabetes-related foot disease specific 30-day readmission only.

Supplementary Figure 1: Scatter plots of meta regression analysis for risk factors: age, male sex, Black American ethnicity, hypertension, peripheral artery disease, dyslipidaemia, current smoking, chronic kidney disease, peripheral neuropathy, coronary artery disease, chronic cardiac failure, chronic obstructive pulmonary disease, private insurance and length of stay in the hospital during index admission for total readmissions.






Holscher, CM 2018
Remington, AC 2016
Hicks, CW 2019
Zhang, GQ 2021
Najafian, A 2015
Zhang, GQ 2021
Shah, SP 2019
Myers, AK 2021
Proportion of patients readmitted (Logit transformed)
0.0
-0.5
-1.0
-1.5
-2.0
10
20
30
40
50
60
Percentage of black American participants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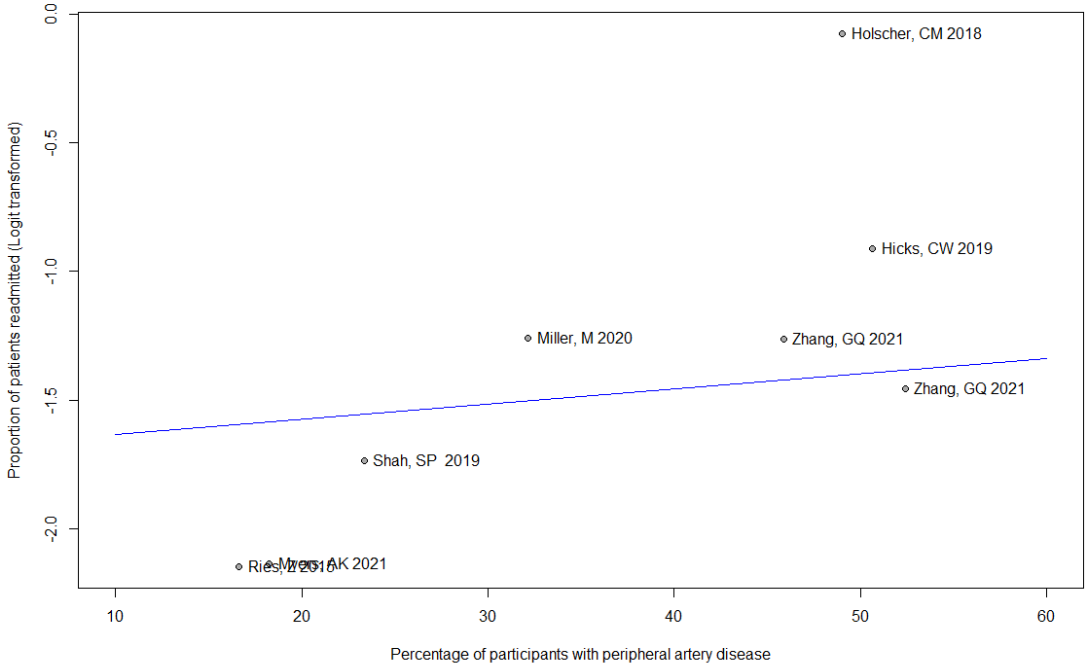
Hicks, CW 2019
Zhang, GQ 2021
Zhang, GQ 2021
Najafian, A 2015
Cheun, TJ 2019
Shah, SP 2019
Myers, AK 2021
Rhee, Z 2015
Proportion of patients readmitted (Logit transformed)
0.0
-0.5
-1.0
-1.5
-2.0
30
40
50
60
70
80
90
100
Percentage of participants with hypertension


Holscher, CM 2018
Hicks, CW 2019
Miller, M 2020
Zhang, GQ 2021
Zhang, GQ 2021
Shah, SP 2019
Ries, J 2018
Myers, AK 2021
Proportion of patients readmitted (Logit transformed)
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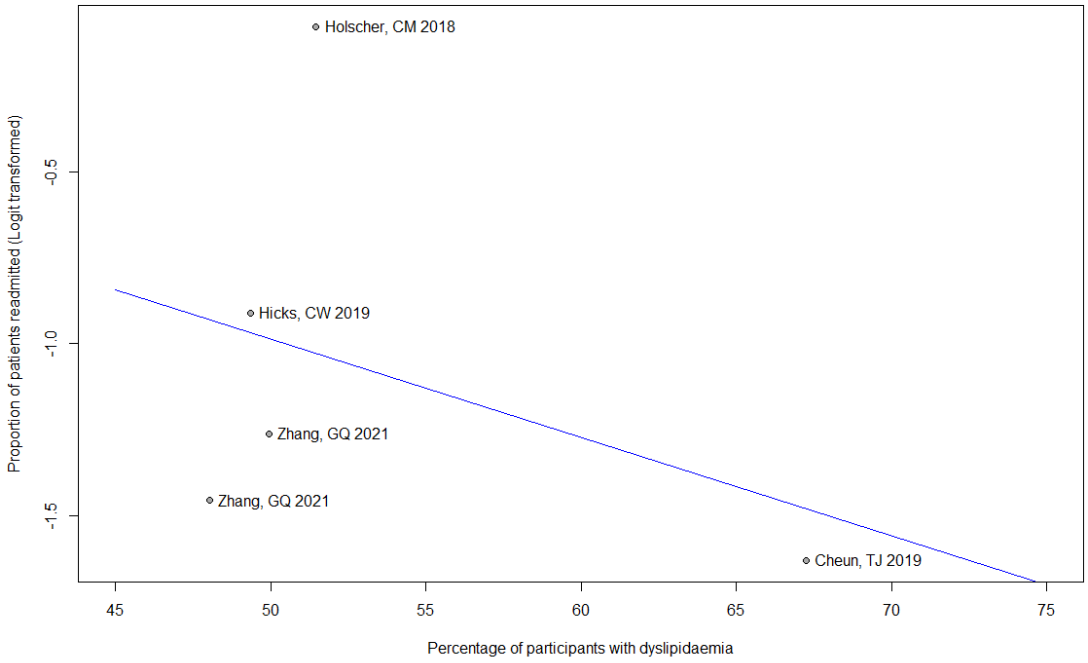
-1.0
-1.5
-2.0
10
20
30
40
50
60
Percentage of participants with peripheral artery disease


Holscher, CM 2018
Hicks, CW 2019
Zhang, GQ 2021
Zhang, GQ 2021
Cheun, TJ 2019
Proportion of patients readmitted (Logit transformed)
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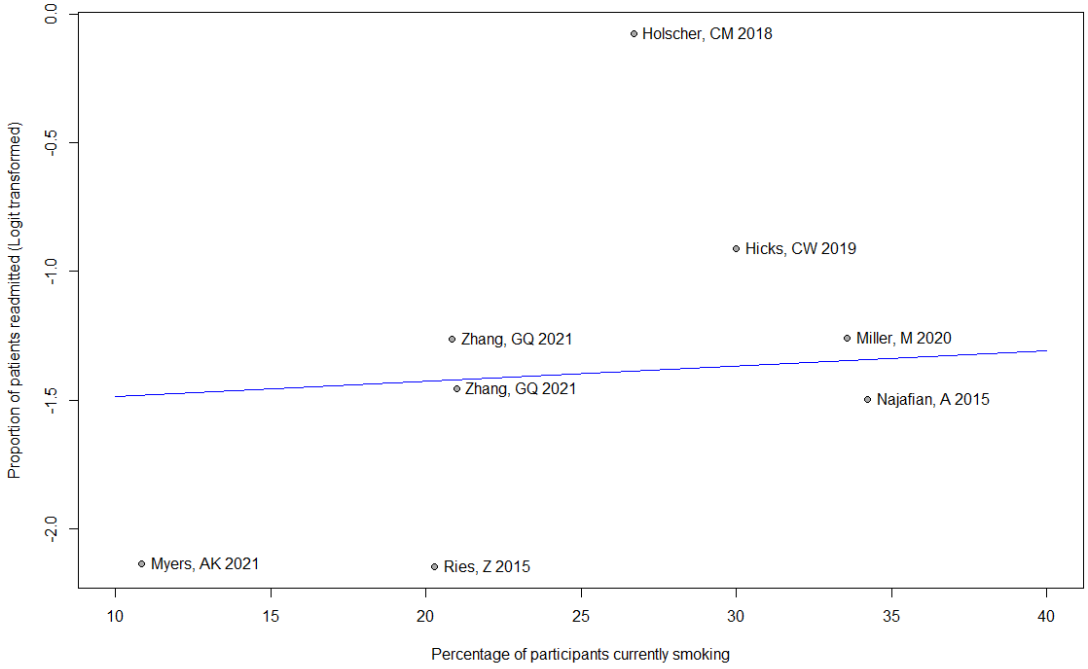
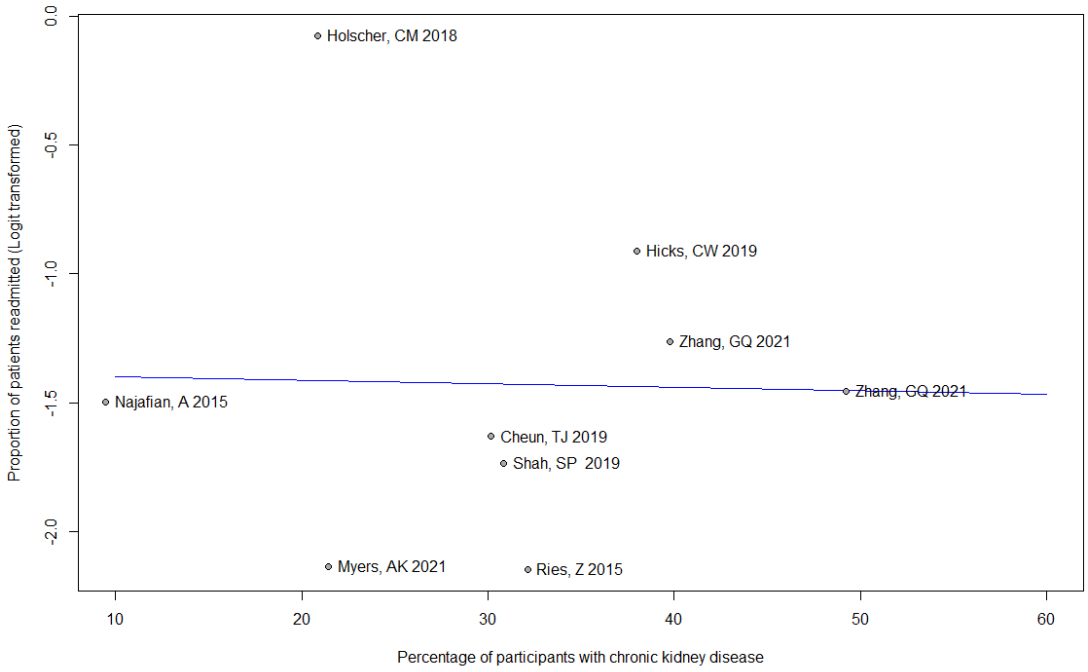
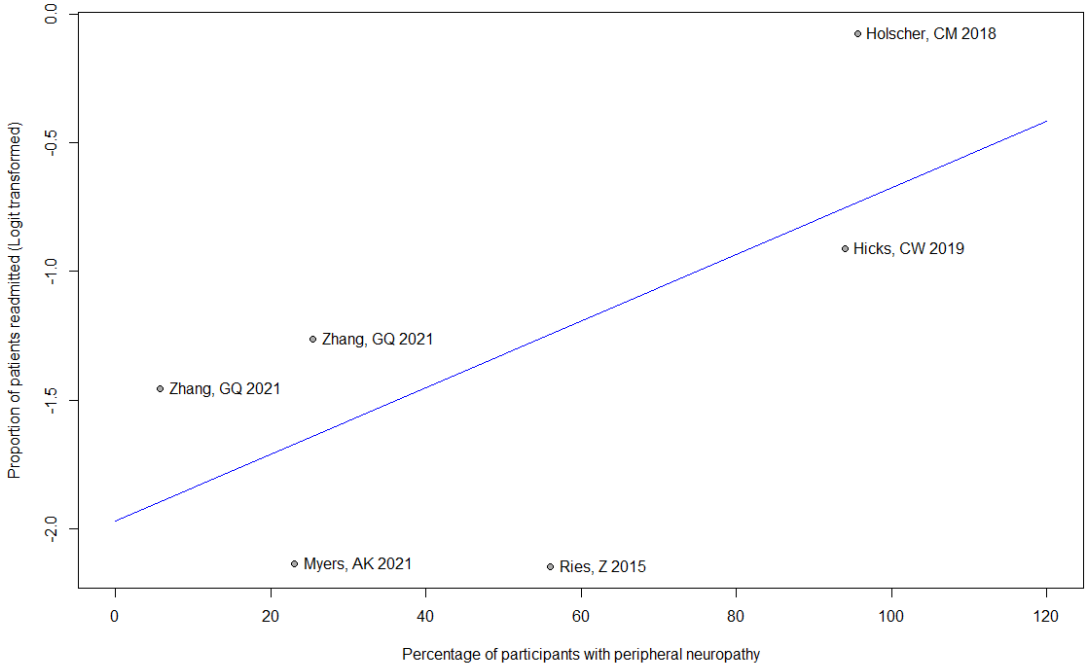
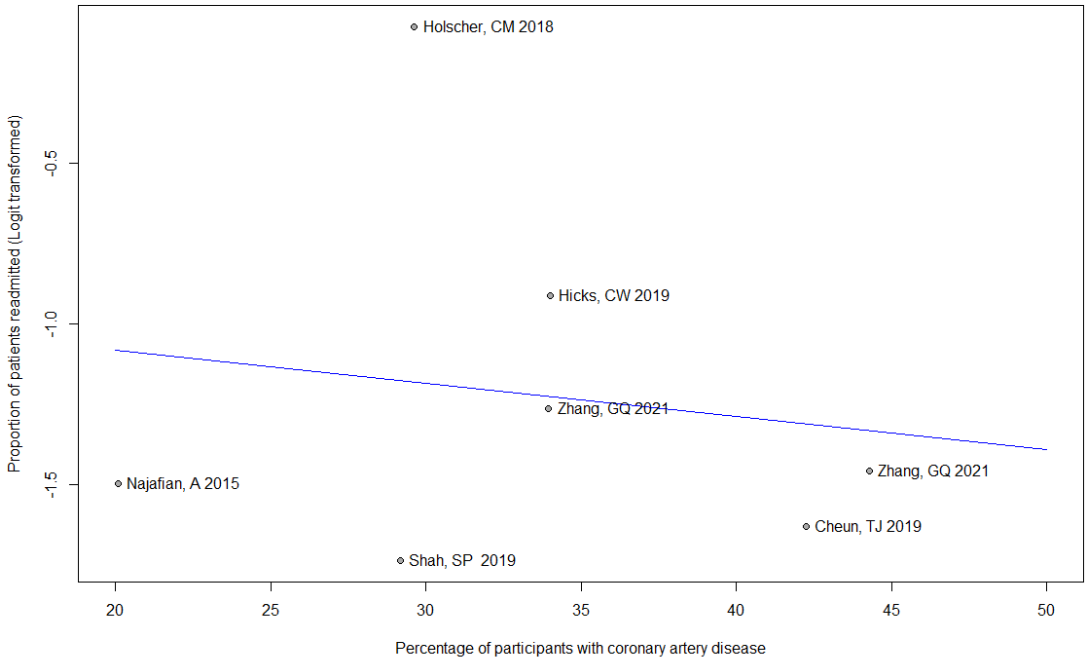
-1.0
-1.5
45
50
55
60
65
70
75
Percentage of participants with dyslipidaemia


Holscher, CM 2018
Hicks, CW 2019
Zhang, GQ 2021
Miller, M 2020
Zhang, GQ 2021
Najafian, A 2015
Myers, AK 2021
Ries, Z 2015
Proportion of patients readmitted (Logit transformed)
0.0
-0.5
-1.0
-1.5
-2.0
10
15
20
25
30
35
40
Percentage of participants currently smoking


Holscher, CM 2018
Hicks, CW 2019
Zhang, GQ 2021
Zhang, GQ 2021
Najafian, A 2015
Cheun, TJ 2019
Shah, SP 2019
Myers, AK 2021
Ries, Z 2015
Proportion of patients readmitted (Logit transformed)
0.0
-0.5
-1.0
-1.5
-2.0
10
20
30
40
50
60
Percentage of participants with chronic kidney disease


Holscher, CM 2018
Hicks, CW 2019
Zhang, GQ 2021
Zhang, GQ 2021
Myers, AK 2021
Ries, Z 2015
Proportion of patients readmitted (Logit transformed)
0.0
-0.5
-1.0
-1.5
-2.0
0
20
40
60
80
100
120
Percentage of participants with peripheral neuropathy


Holscher, CM 2018
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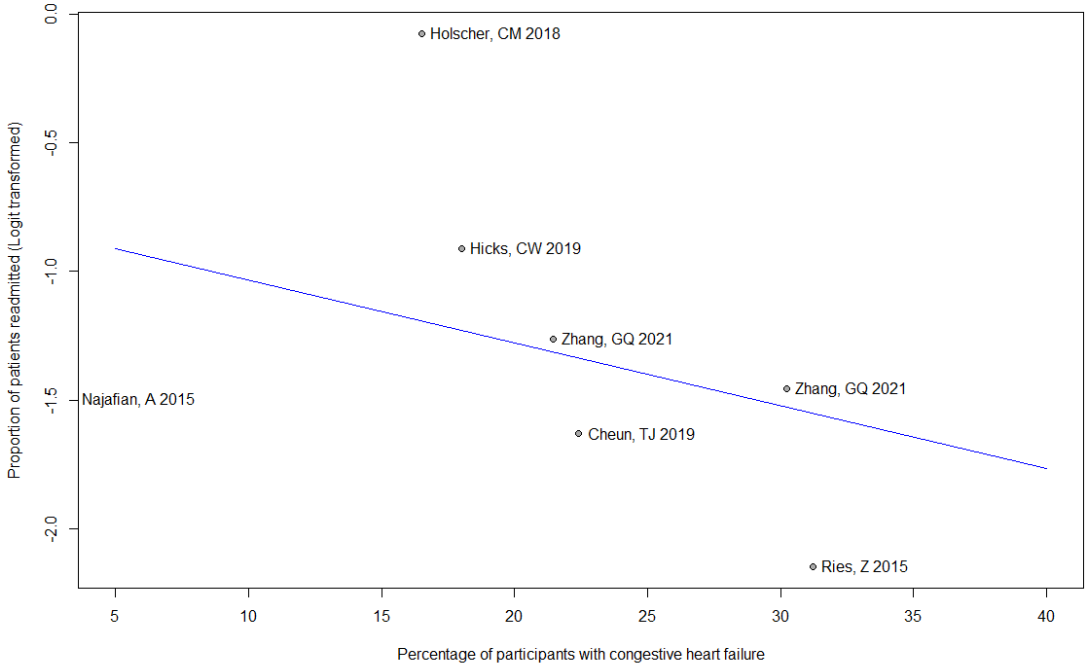
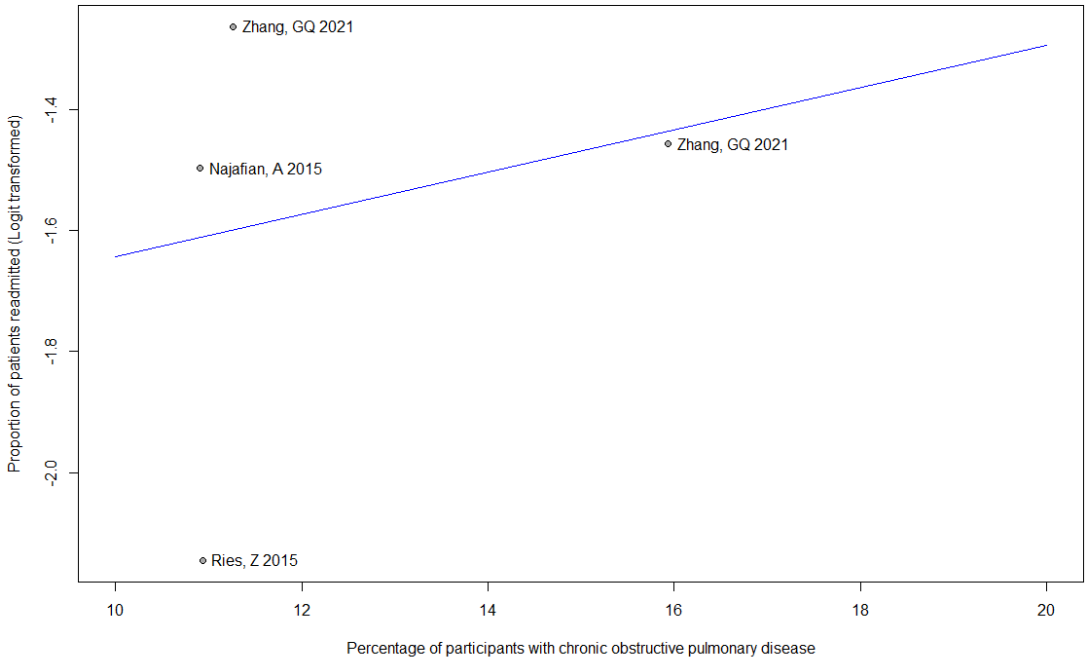
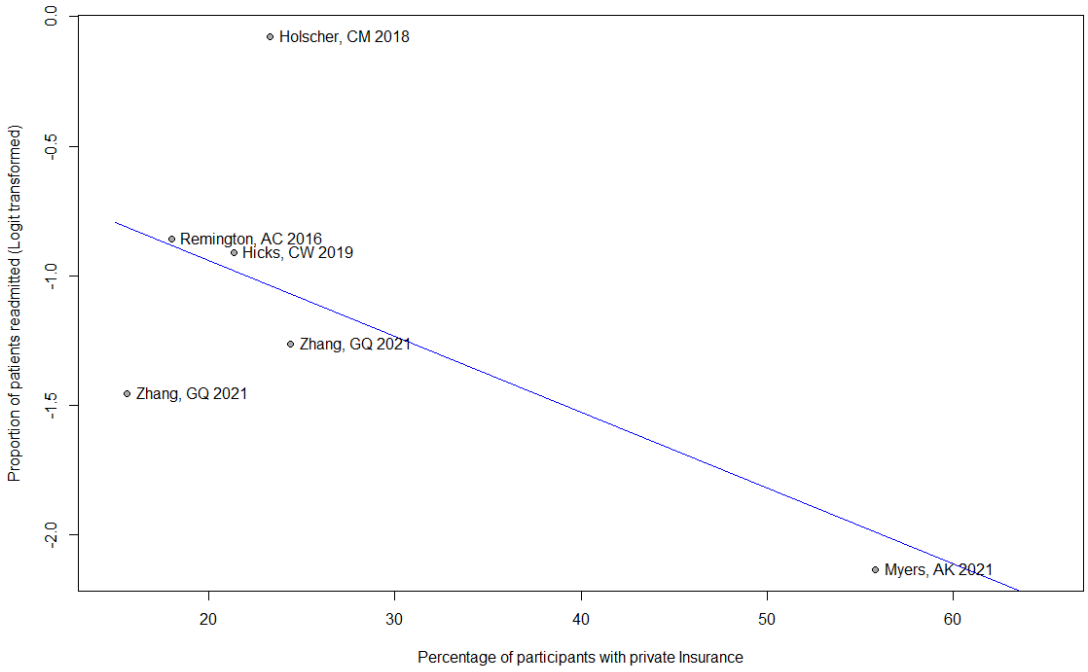
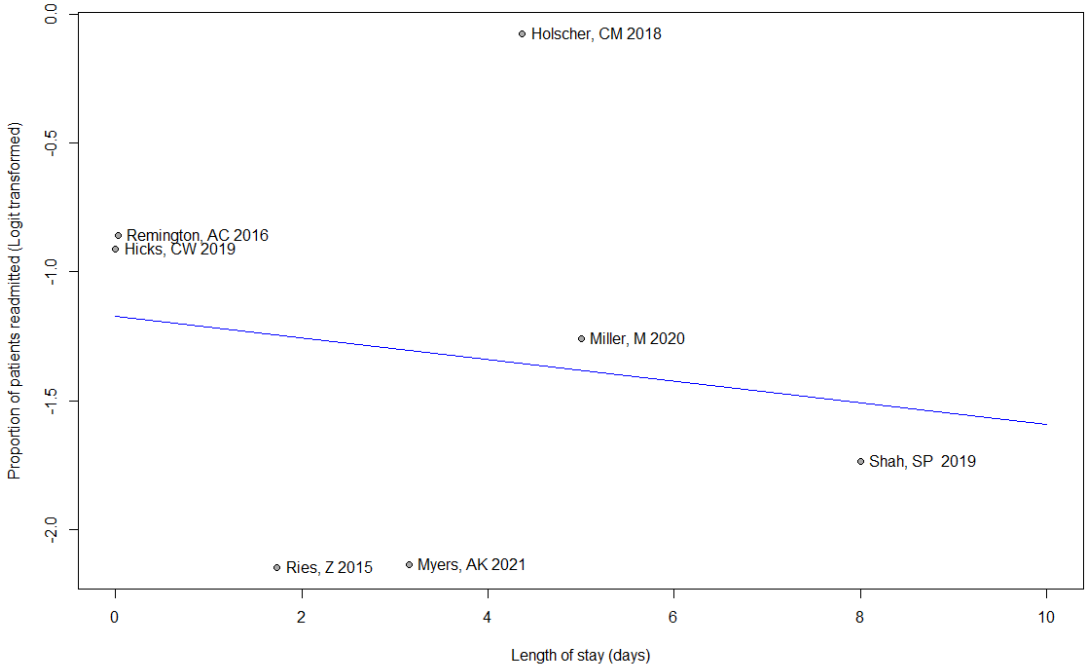
Zhang, GQ 2021
Zhang, GQ 2021
Najafian, A 2015
Cheun, TJ 2019
Shah, SP 2019
Proportion of patients readmitted (Logit transformed)
-0.5
-1.0
-1.5
20
25
30
35
40
45
50
Percentage of participants with coronary artery disease

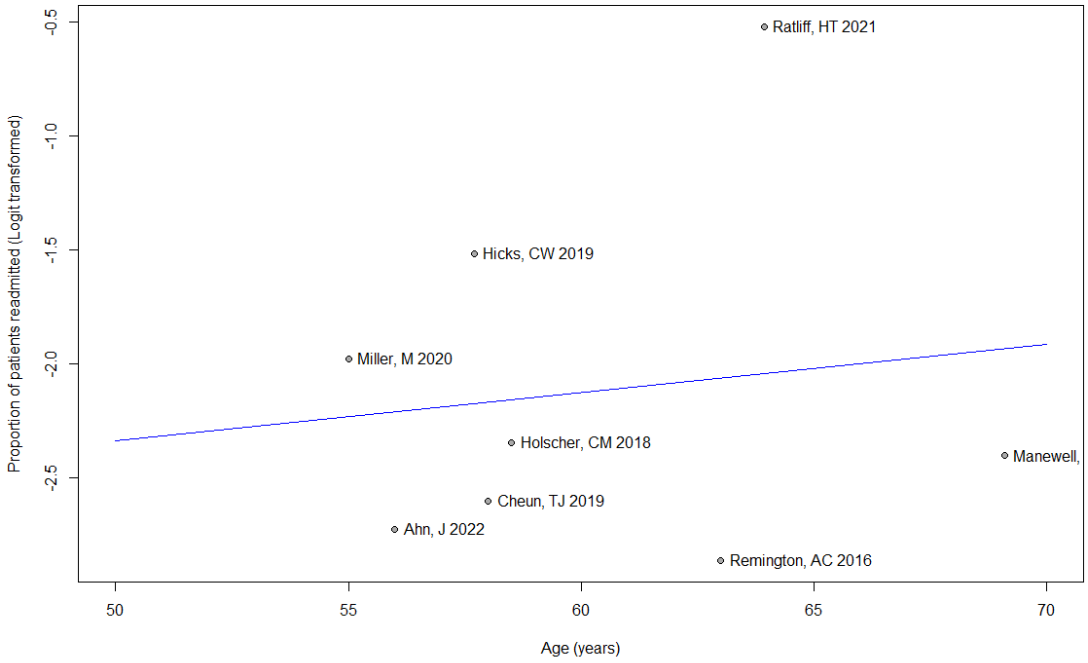

Holscher, CM 2018
Hicks, CW 2019
Zhang, GQ 2021
Zhang, GQ 2021
Najafian, A 2015
Cheun, TJ 2019
Ries, Z 2015
Proportion of patients readmitted (Logit transformed)
0.0
-0.5
-1.0
-1.5
-2.0
5
10
15
20
25
30
35
40
Percentage of participants with congestive heart failure

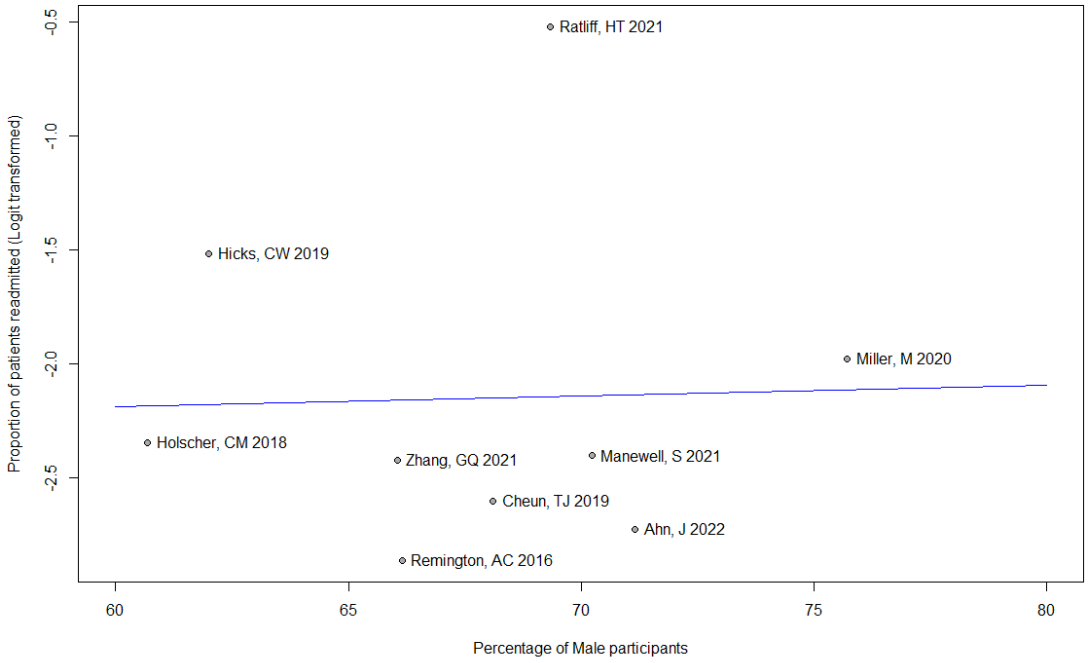

Zhang, GQ 2021
Zhang, GQ 2021
Najafian, A 2015
Ries, Z 2015
Proportion of patients readmitted (Logit transformed)
-1.4
-1.6
-1.8
-2.0
10
12
14
16
18
20
Percentage of participants with chronic obstructive pulmonary disease

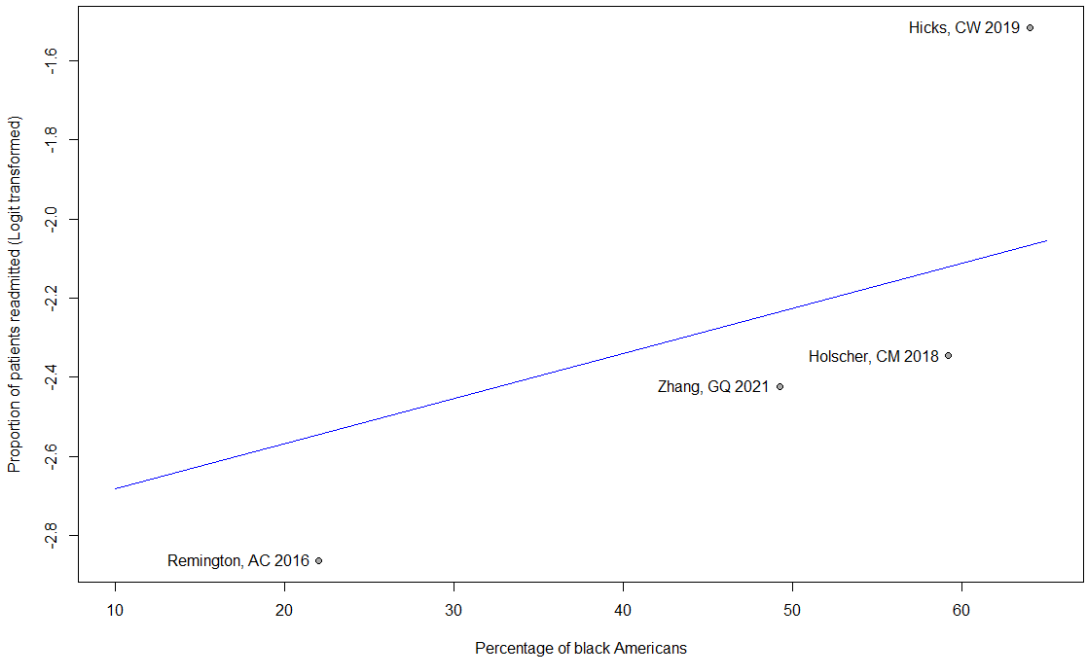

Holscher, CM 2018
Remington, AC 2016
Hicks, CW 2019
Zhang, GQ 2021
Zhang, GQ 2021
Myers, AK 2021
Proportion of patients readmitted (Logit transformed)
0.0
-0.5
-1.0
-1.5
-2.0
20
30
40
50
60
Percentage of participants with private Insurance

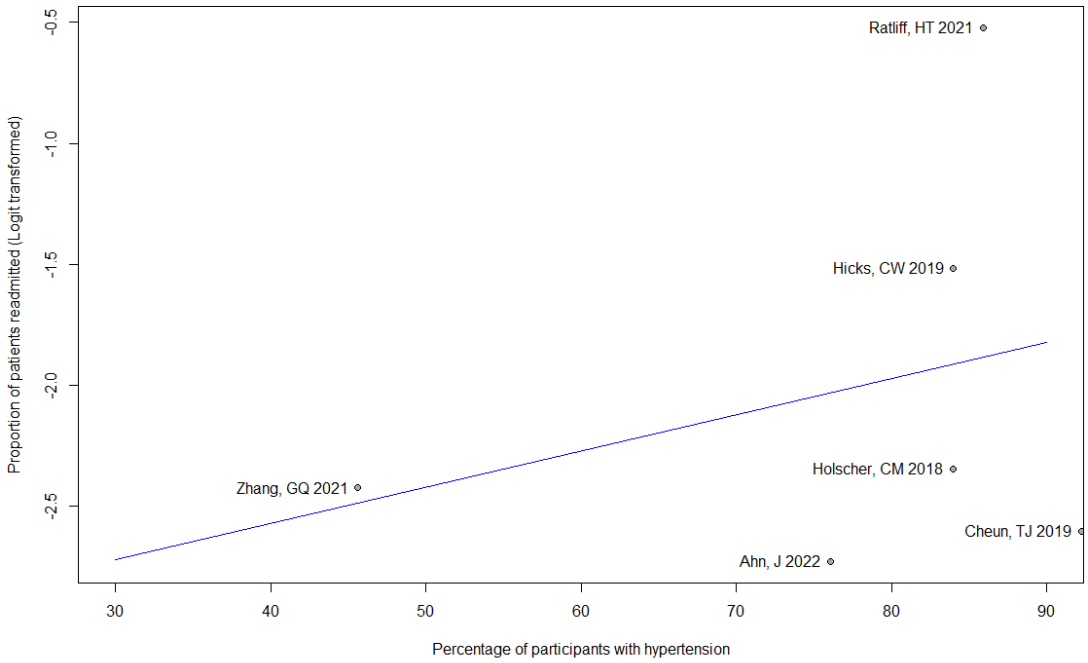

Holscher, CM 2018
Remington, AC 2016
Hicks, CW 2019
Miller, M 2020
Shah, SP 2019
Ries, Z 2015
Myers, AK 2021
Proportion of patients readmitted (Logit transformed)
0.0
-0.5
-1.0
-1.5
-2.0
0
2
4
6
8
10
Length of stay (days)

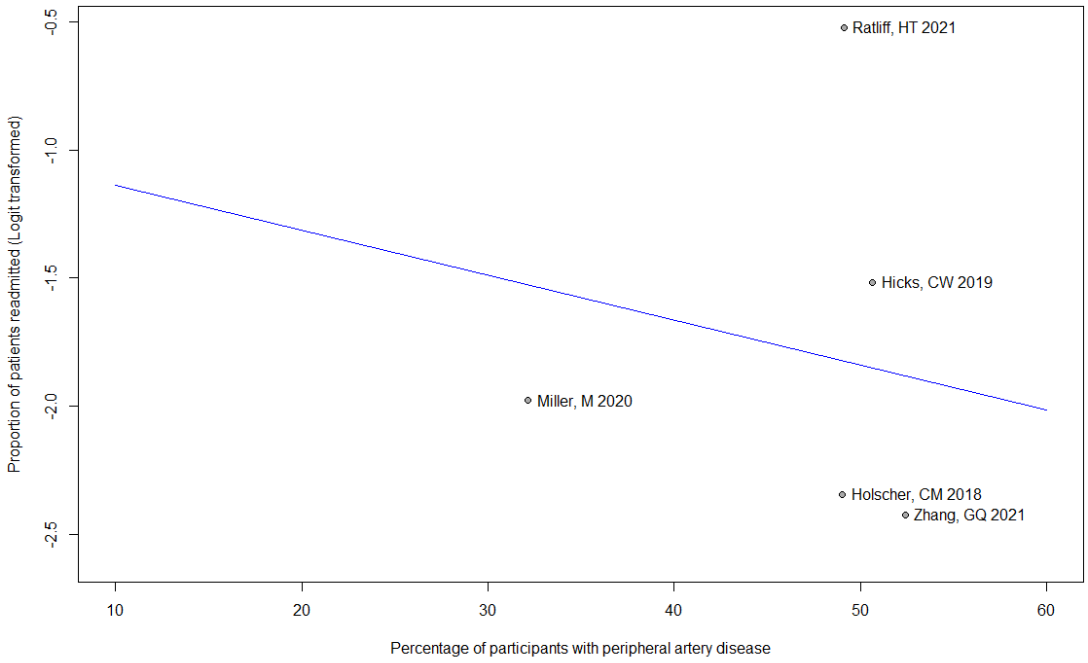
Supplementary Figure 2: Scatter plots of meta regression analysis for risk factors: age, male sex, Black American ethnicity, hypertension, peripheral artery disease, dyslipidaemia, current smoking, chronic kidney disease, peripheral neuropathy, coronary artery disease, chronic cardiac failure, chronic obstructive pulmonary disease, private insurance and length of stay in the hospital during index admission for DFD related readmissions.

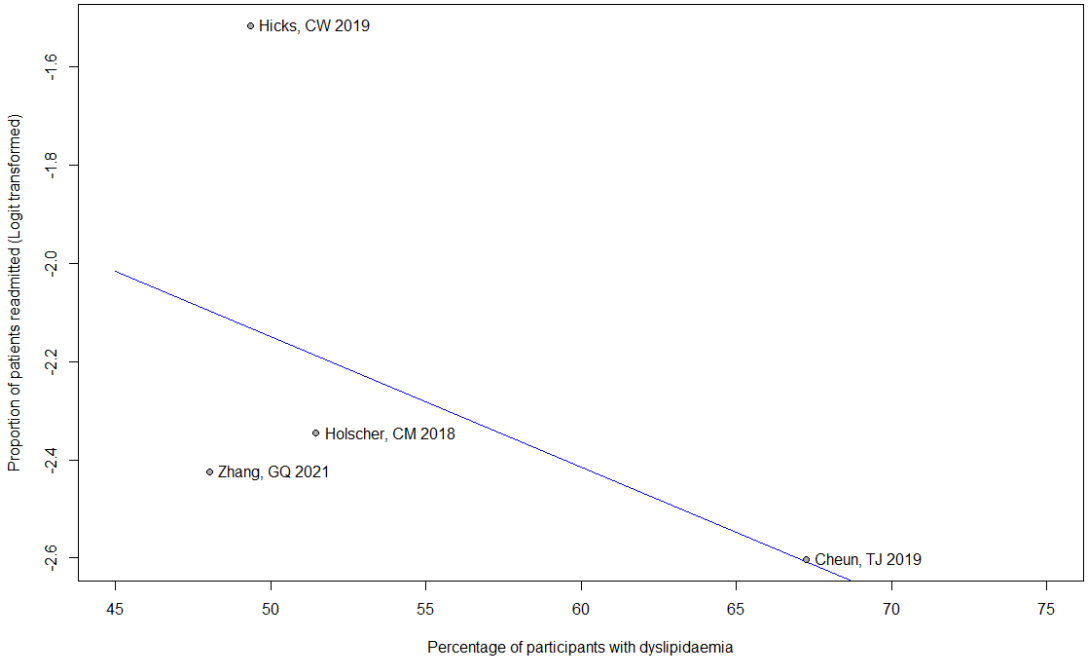


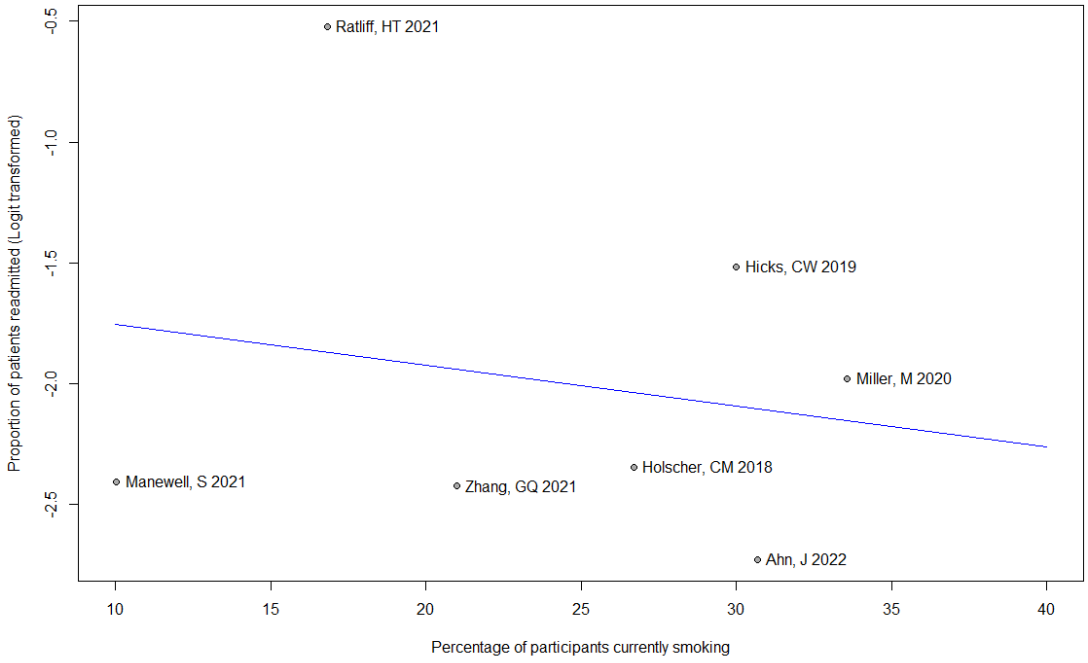


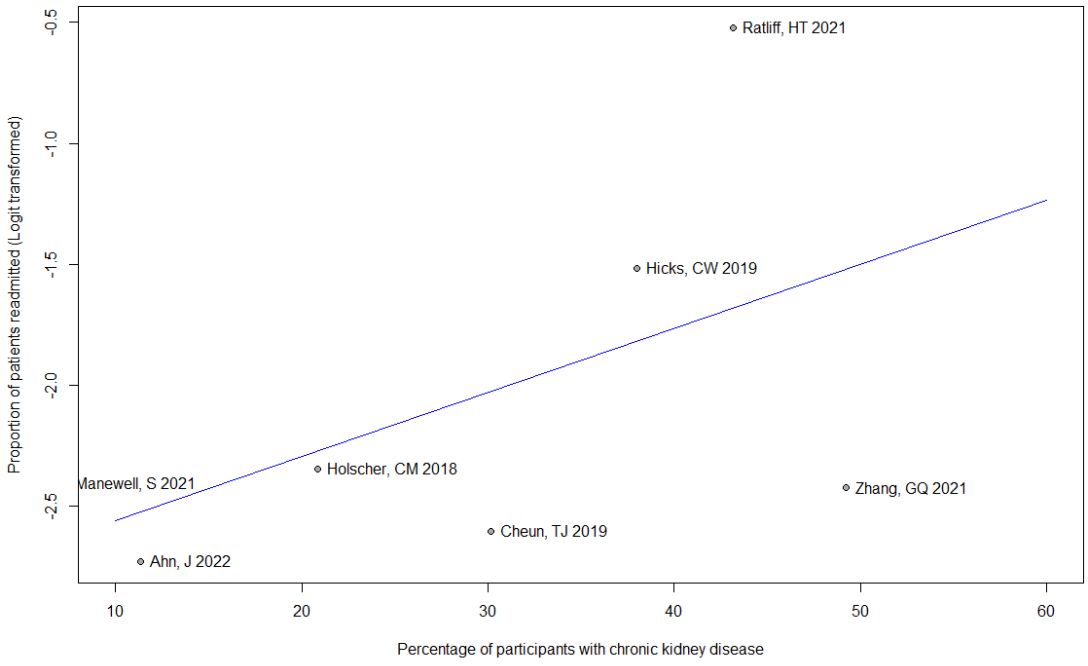

Hicks, CW 2019
Holscher, CM 2018
Zhang, GQ 2021
Remington, AC 2016
Proportion of patients readmitted (Logit transformed)
-1.6
-1.8
-2.0
-2.2
-2.4
-2.6
-2.8
10
20
30
40
50
60
Percentage of black Americans

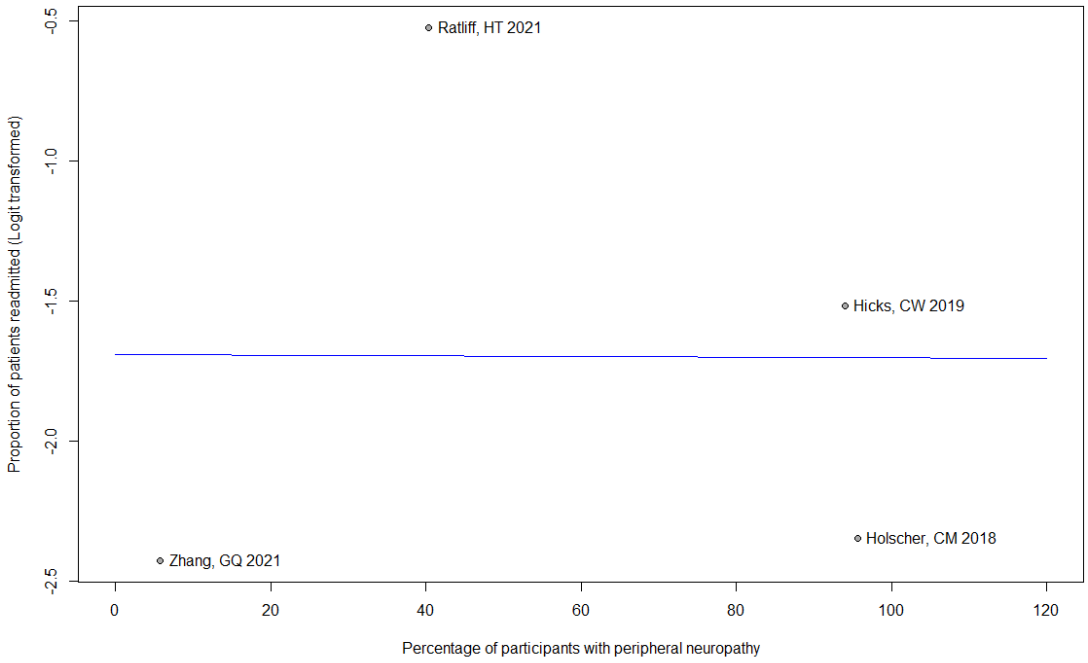

Ratliff, HT 2021
Hicks, CW 2019
Holscher, CM 2018
Zhang, GQ 2021
Cheun, TJ 2019
Ahn, J 2022
Proportion of patients readmitted (Logit transformed)
-0.5
-1.0
-1.5
-2.0
-2.5
30
40
50
60
70
80
90
Percentage of participants with hypertension

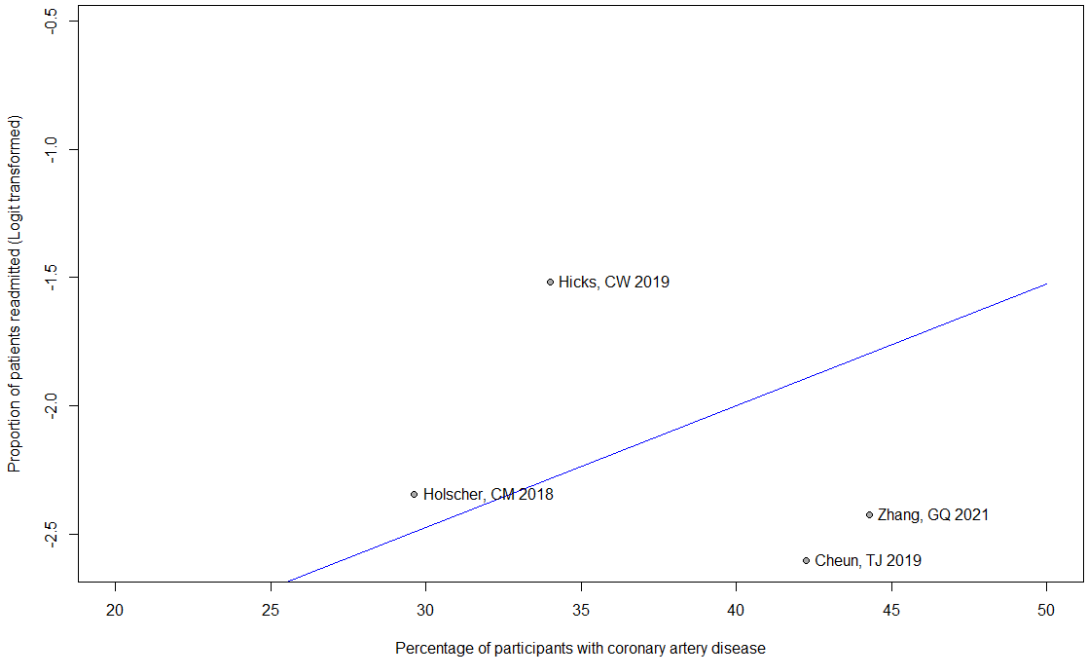

Ratliff, HT 2021
Hicks, CW 2019
Miller, M 2020
Holscher, CM 2018
Zhang, GQ 2021
Proportion of patients readmitted (Logit transformed)
-0.5
-1.0
-1.5
-2.0
-2.5
10
20
30
40
50
60
Percentage of participants with peripheral artery disease

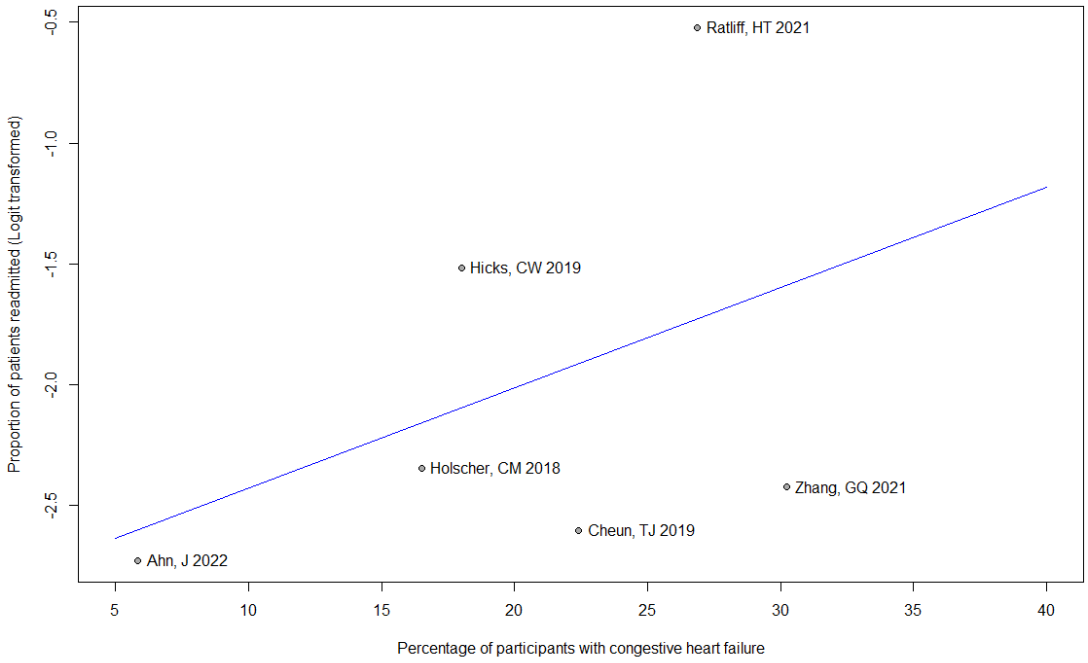

Hicks, CW 2019
Holscher, CM 2018
Zhang, GQ 2021
Cheun, TJ 2019
Proportion of patients readmitted (Logit transformed)
-1.6
-1.8
-2.0
-2.2
-2.4
-2.6
45
50
55
60
65
70
75
Percentage of participants with dyslipidaemia

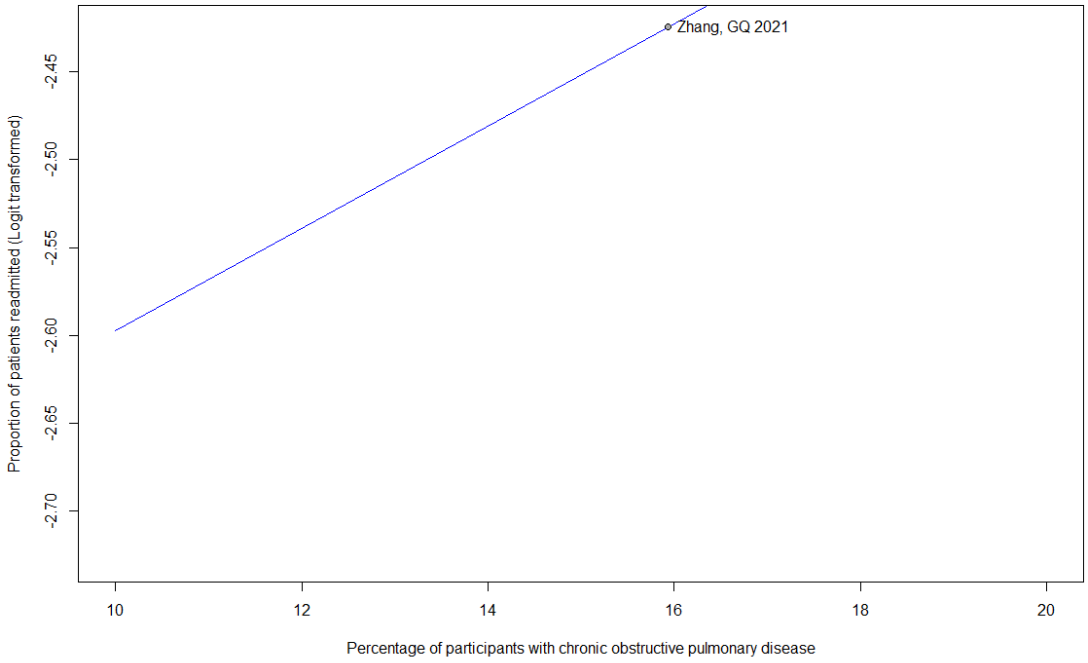

Ratliff, HT 2021
Hicks, CW 2019
Miller, M 2020
Holscher, CM 2018
Manewell, S 2021
Zhang, GQ 2021
Ahn, J 2022
Proportion of patients readmitted (Logit transformed)
-0.5
-1.0
-1.5
-2.0
-2.5
10
15
20
25
30
35
40
Percentage of participants currently smoking

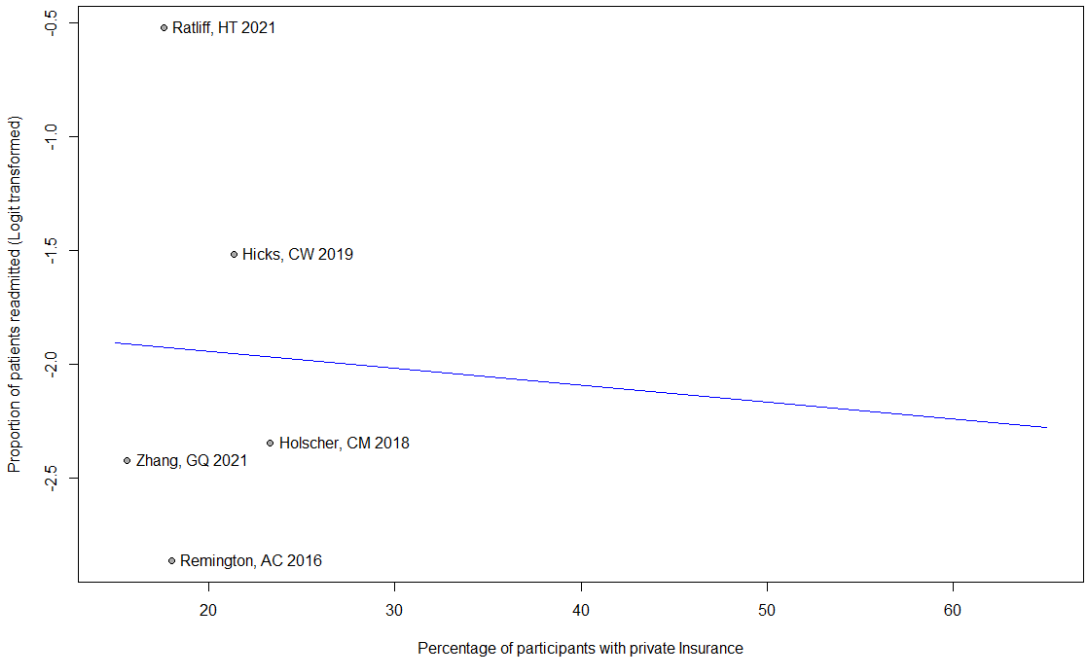

Ratliff, HT 2021
Hicks, CW 2019
Holscher, CM 2018
Manewell, S 2021
Zhang, GQ 2021
Cheun, TJ 2019
Ahn, J 2022
Proportion of patients readmitted (Logit transformed)
-0.5
-1.0
-1.5
-2.0
-2.5
10
20
30
40
50
60
Percentage of participants with chronic kidney disease

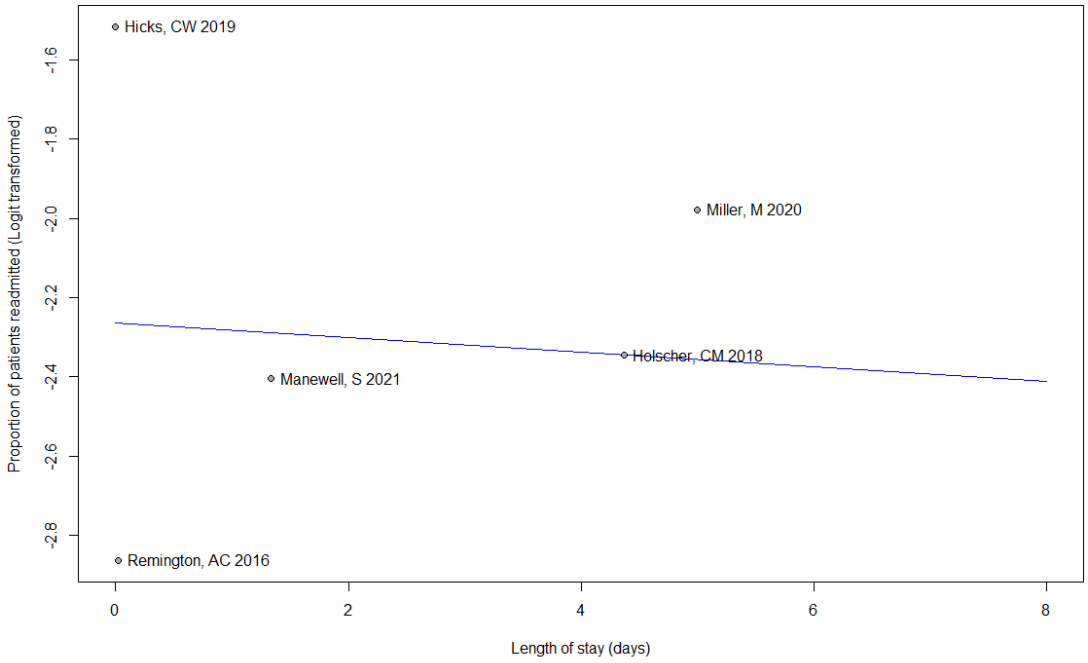

Ratliff, HT 2021
Hicks, CW 2019
Holscher, CM 2018
Zhang, GQ 2021
Proportion of patients readmitted (Logit transformed)
-0.5
-1.0
-1.5
-2.0
-2.5
0
20
40
60
80
100
120
Percentage of participants with peripheral neuropathy


Hicks, CW 2019
Holscher, CM 2018
Zhang, GQ 2021
Cheun, TJ 2019
Proportion of patients readmitted (Logit transformed)
-0.5
-1.0
-1.5
-2.0
-2.5
20
25
30
35
40
45
50
Percentage of participants with coronary artery disease


Ratliff, HT 2021
Hicks, CW 2019
Holscher, CM 2018
Zhang, GQ 2021
Cheun, TJ 2019
Ahn, J 2022
Proportion of patients readmitted (Logit transformed)
-0.5
-1.0
-1.5
-2.0
-2.5
5
10
15
20
25
30
35
40
Percentage of participants with congestive heart failure


Zhang, GQ 2021
Proportion of patients readmitted (Logit transformed)
-2.45
-2.50
-2.55
-2.60
-2.65
-2.70
10
12
14
16
18
20
Percentage of participants with chronic obstructive pulmonary disease


Ratliff, HT 2021
Hicks, CW 2019
Holscher, CM 2018
Zhang, GQ 2021
Remington, AC 2016
Proportion of patients readmitted (Logit transformed)
-0.5
-1.0
-1.5
-2.0
-2.5
20
30
40
50
60
Percentage of participants with private Insurance


Hicks, CW 2019
Miller, M 2020
Holscher, CM 2018
Manewell, S 2021
Remington, AC 2016
Proportion of patients readmitted (Logit transformed)
-1.6
-1.8
-2.0
-2.2
-2.4
-2.6
-2.8
0
2
4
6
8
Length of stay (days)

3. Repeatability, completion time and predictive ability of four diabetes-related foot ulcer classification systems

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Conflicts of Interest Disclosure: The authors declare that there are no conflicts of interests.

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3.1 Abstract

Introduction: The inter and intra-observer reproducibility of measuring the Wound Ischaemia foot Infection (WIFI) score is unknown. The aims of this study were to compare the reproducibility, completion times and ability to predict 30-day amputation of the WIFI, University of Texas Wound Classification System (UTWCS), Site, Ischaemia, Neuropathy, Bacterial Infection and Depth (SINBAD) and Wagner classifications systems using photographs of diabetes-related foot ulcers.

Methods: Three trained observers independently scored the diabetes-related foot ulcers of 45 participants on two separate occasions using photographs. The inter- and intra-observer reproducibility was calculated using Krippendorff's alpha. The completion times were compared with Kruskal-Wallis and Dunn's post-hoc tests. The ability of the scores to predict 30-day amputation rates was assessed using receiver operator characteristic curves and area under the curves.

Results: There was excellent intra-observer agreement (α>0.900) and substantial agreement between observers (α=0.788) in WIFI scoring. There was moderate, substantial or excellent agreement within the three observers (α >0.599 in all instances except one) and fair or moderate agreement between observers (α of UTWCS=0.306, α of SINBAD=0.516, α of Wagner=0.374) for the other three classification systems. The WIFI score took significantly longer ($p<0.001$) to complete compared to the other three scores (medians and inter quartile ranges of the WIFI, UTWCS, SINBAD and Wagner being 1.00 [0.88-1.00], 0.75 [0.50-0.75], 0.50 [0.50-0.50], and 0.25 [0.25-0.50] minutes). None of the classifications were predictive of 30-day amputation ($p>0.05$ in all instances).

Conclusion: The WIFI score can be completed with substantial agreement between trained observers but was not predictive of 30-day amputation.

3.2 Background

People with diabetes-related foot ulcers (DFU) are at high risk of major complications such as minor and major amputation (1). DFU is a leading cause of global disability and requirement for hospital admission (1-3). Grading the severity of DFUs using a classification system is of potential value for predicting the risk of these complications (4). Commonly used DFU classification systems include the Wagner (5), University of Texas Wound Classification System (UTWCS) (6), the Site, Ischemia, Neuropathy, Bacterial Infection, and Depth (SINBAD) score (7) and the Wound Ischaemia foot Infection (WIFI) score (8). These systems are typically designed to aid treatment decisions, communication between health professionals, in conducting audits, benchmarking between services and predicting outcomes (9, 10). It is important that any DFU classification system can be repeated by different clinicians in a rapid time frame and the findings predict outcome (11).

The International Working Group on Diabetic Foot (IWGDF) guideline recommends the use of the WIFI classification system (10) Whilst, the reproducibility of a number of other different DFU classification systems, such as the UTWCS, SINBAD and Wagner, have been previously reported (12-15), to our knowledge the reproducibility of the WIFI score has not been assessed or compared to other systems (16). Furthermore, whilst studies have compared the ability of these different classification systems to predict one-year risk of amputation, none to our knowledge, have investigated their ability to predict 30-day amputation risk (9, 17-19).

The primary aim of this study was to compare the inter- and intra-observer reproducibility of the WIFI, UTWCS, SINBAD and Wagner classifications using photographs of diabetes-related foot ulcers. Secondary aims were to compare completion times and the ability of these scoring systems to predict 30-day risk of amputation.

3.3 Methods

This was a prospective single centre observational cohort study of patients who were admitted to the Townsville University Hospital (TUH) in North Queensland, Australia, for inpatient treatment of a DFU. Recruitment occurred from 1st January 2020 to 30th June 2020. Inclusion criteria were diagnosis with type I or II diabetes, an active DFU, age over 18 years and written informed consent. Patients who presented with gangrene or who had wound debridement or amputations before they could be recruited to the study were excluded. Ethical approval for the study was granted by the Townsville Hospital and Health Services Ethics Committee (HREC/12/QTHS/202 and HREC/12/QTHS/203) and all participants provided written informed consent.

The following data were collected on study entry which were self-reported by the patients and later verified with the medical records: age, time since diagnosis of diabetes, height, weight, smoking history, previous history of hospital admission for the treatment of DFU or amputation. Examination was performed to assess DFU location and the presence of peripheral neuropathy using a 10 g Semmes-Weinstein monofilament and 128Hz tuning fork. Peripheral neuropathy was defined when one of more of 4 sites in the foot (plantar surfaces of the great toe, the 1st, the Participant's heart rate, temperature and respiratory rate were also recorded by the 2nd and the 3rd metatarsal head areas) were insensitive to the monofilament or tuning fork (20). admitting doctors and were obtained from the medical records. Signs of systemic infection were defined to

include high pulse rate [>90 beats per minute], high respiratory rate [> 20 per minute] and abnormal temperature [>38°C or <36°C). White blood cell count and circulating concentrations of C-reactive protein and fasting sugar were also measured at admission. Ankle brachial pressure index (ABPI) was measured in all participants as previously described (21) and the toe pressure (TP) was measured in participants who did not have an ulcer or prior amputation of the hallux using a Huntleigh Dopplex® S/W-V1.6 kit according to the manufacturer's instructions (Huntleigh Healthcare Ltd, UK). Ischaemia (ABPI <0.8 or TP < 60mmHg) was defined as per definitions given in the WIFI classification (6). ABPI was also categorised as high (>1.40), normal (0.90-1.40) and low (<0.9). The ABPI measurements were performed by a single investigator (first author) and were comparable with those measured by vascular sonographers (intraclass correlation coefficient=0.883, n=16) (22).

In order to standardise the assessment of DFUs, photographs were taken of the affected foot and these were used for grading using previously described methods (23, 24). All three assessors classified all ulcers based on one system and then with the next system. The photographs were taken using both a Silhouette star camera (The SilhouetteStar™, Aranz Medical Ltd.) and an i-phone XR (iOS 12.0 software, Apple inc). These photographs along with clinical data and information on ischemia were used to classify ulcers according to the different grading systems [5-8]. This allowed for the remote assessment of DFUs while following appropriate infection control protocols during the COVID-19 pandemic and minimising patient-clinician contact (25).

Three assessors (a vascular surgeon (CG), a podiatrist (MF), and a medical physician (CA)) independently graded the DFUs. All had extensive prior experience in assessing DFUs in clinical practice. Prior to starting the study, each assessor attended a two-hour training session focused on a standardised method of using the classification systems and grading wounds aimed to

optimise consistency in grading. This session involved independent evaluation and grading of three examples of DFUs using each system by each assessor. This was followed by a discussion of scores. Once training was completed, the three observers independently undertook the grading of each DFU using each classification system and then repeated the scoring a second time at least 7 days later (using the same image) to assess the intra-observer agreement. The time taken to complete each score for each participant was recorded using a stopwatch.

The main outcome measure was the reproducibility of the different classification systems and the secondary outcome was requirement for any lower limb amputation, defined to include amputation of the toes or forefoot, or below or above knee amputation (either minor or major amputations) within 30 days of hospital admission. The patients were followed up while they were in hospital and then via out-patient review for 30 days (26).

The sample size was calculated based on the assumption that three observers scoring the ulcer photographs independently would have a substantial inter-observer agreement (80%), with a relative error of 10% (11). The required sample size (80% power; alpha 0.05) was 45 patients (27).

The continuous variables were not normally distributed, as evidenced by the Shapiro-Wilk test and therefore were presented as median and inter-quartile range (IQR). Nominal and ordinal data were summarised as percentages. The inter-observer and intra-observer reproducibility of the different classification systems were measured using Krippendorff's alpha for ordinal data (28). Values were interpreted as: ≤ 0 = no agreement; 0.01–0.20 = slight agreement; 0.21–0.40 = fair agreement; 0.41– 0.60 = moderate agreement; 0.61–0.80 substantial agreement; and 0.81–1.00 = excellent agreement (28) and calculated using R software [(R Core Team (2020). R: A language

and environment for statistical computing. R Foundation for Statistical Computing, Vienna, Austria. Version: 4.02 using rel: Reliability Coefficients. R package, version 1.4.2 and irr: Various Coefficients of Interrater Reliability and Agreement. R package version 0.84.1)]. The time taken to grade each ulcer was compared between the different scoring systems using the Kruskal-Wallis test and post hoc comparisons were performed using Dunn's test. The median of the six scores of each DFU were compared between participants that did and did not subsequently undergo amputation within 30 days of admission using Mann Whitney U test. The scores were also used to construct receiver operating characteristic (ROC) curves to assess the predictive ability of each classification system for amputation (29). Area under the curve (AUC) was calculated and interpreted as: >0.9= excellent, ≥ 0.8 = good, ≥ 0.7 = fair and ≥ 0.6= poor (29). Analyses were performed using SPSS (released 2020, IBM SPSS statistics for Windows, Version 26.0. Armonk, NY, IB Corp). ROC curves were drawn using GraphPad PRISM software, version 7.03 (GraphPad software, Inc, La Jolla, CA).

3.4 Results

A total of forty-five patients were recruited. The baseline demographic characteristics and risk factors of the participants are summarised in Table 1. The median (IQR) age of the participants were 68.1 (56.1-74.1) years and 80% were males. The median (IQR) duration of diabetes was (19.0 10.5-25.0) years.

Table 3-1 Demographic characteristics of included studies

Characteristic	**Summary (n=45)**
Age (years)	68.1 [56.1-74.1]

Male (%)	36 (80.0%)
Height (m)	1.74 [1.68-1.80]
Weight (kg)	90.0 [77.0-113.5]
Body mass index (kgm^{-2})	30.9 [25.9-36.7]
Duration of diabetes (years)	19.0 [10.5-25.0]
Smoking status (%) Current Ex-smokers Non-smokers	 6 (13.3%) 26 (57.8%) 13 (28.9%)
Previous history of hospital admissions for diabetes-related foot disease Single Multiple No previous admissions	 17 (37.8%) 12 (26.7%) 16 (35.6%)
Previous history of minor amputation	19 (42.2%)
Previous history of major amputation	1 (2.2%)
Ankle brachial pressure index in the affected foot	

>1.40 (Non compressible vessels/ High) 0.91-1.40 (Normal) <0.90 (Low)	13 (28.9%) 19 (42.2%) 13 (28.9%)
Presence of systemic features of infection on admission (%)	14 (31.1%)
White cell count ($10^3/\mu L^{-1}$)	10.0 [8.25-11.7]
C reactive protein level (mg/dL^{-1}) [n=34]	39.0 [15.7-99.7]
Location of DFU Forefoot [n=36] Midfoot [n=2] Hindfoot [n=7]	 80.0% 4.4% 15.6%
Type of ulcer Neuropathic [n=34] Neuro-ischemic [n=11]	 75.6% 24.4%

Legend: Shown are numbers (percentage) or median (inter-quartile range).

3.4.1 Time to complete DFU grading

The median time taken to classify each ulcer varied significantly between all four grading systems ($p<0.001$; Table 2). The Wagner score had the lowest median time for completion, and this progressively increased for the SINBAD, Wagner and WIFI scores (P values for bivariate comparisons shown in Table 2).

Table 3-2 Median time taken to assess the severity of the diabetes-assocaited foot ulcers using different classification systems

Scoring System	**Completion time (mins)**	**P value for post-hoc bivariate comparisons**			
		WIFI	**UTWCS**	**SINBAD**	**Wagner**
WIFI	1.00 [0.88-1.00]	NA	<0.001	<0.001	<0.001
UTWCS	0.75 [0.50-0.75]	<0.001	NA	<0.001	<0.001
SINBAD	0.50 [0.50-0.50]	<0.001	<0.001	NA	0.042
Wagner	0.25 [0.25-0.50]	<0.001	<0.001	0.042	NA

Legend: Completion time shown as median (inter-quartile range); NA= Not applicable. P values were obtained from Dunn's test in post hoc comparisons following Kruskal-Wallis test.

3.4.2 Reproducibility

The WIFI classification had substantial inter-observer agreement (α=0.788) and excellent intra-observer agreement (α>0.900) between assessors based on Krippendorff's alpha values (Table 3). Inter-observer agreement for SINBAD scores was moderate (α=0.516). Inter-observer agreements for Wagner and UTWCS scores were fair (α= 0.374 and 0.306 respectively). Intra-observer agreement for all classification systems was moderate (α>0.599) except on one occasion where the agreement was fair related to the UTWCS score (Table 3).

Table 3-3 Krippendorff's alpha values for the intra-observer agreement of different classification systems

	WIFI score agreement	**UTWCS score agreement**	**SINBAD score agreement**	**Wagner Classification agreement**
Inter-observer				
All three observers	0.788	0.306	0.516	0.374
Observer 1 vs. Observer 3	0.805	0.347	0.441	0.526
Observer 1 vs. Observer 2	0.780	0.270	0.536	0.238
Observer 2 vs. Observer 3	0.776	0.214	0.559	0.327
Intra-observer				
Observer 1	0.902	0.791	0.903	0.925
Observer 2	0.908	0.922	0.993	0.873
Observer 3	0.965	0.599	0.911	0.766

Legend: Shown are the Krippendorff's alpha values for agreement between two different observers (as listed), all three observers or within observers.

Observer 1: General practitioner/ physician: Chanika Alahakoon(CA)

Observer 2: Podiatrist: Malindu Fernando (MF)

Observer 3: Vascular Surgeon: Charith Galappaththy (CG)

3.4.3 Prediction of amputations within 30 days

Eighteen (40.0%) participants had a minor amputation and one (2.2%) had a major amputation within 30 days of hospital admission. The median scores for the different classification system of participants who required an amputation and those who did not have an amputation are summarised in Table 4. The median scores for the Wagner (p=0.041), but not UTWCS, SINBAD and WIFI, classifications were significantly more severe for participants who had an amputation compared to those who did not (Table 4). However, based on the area under the curve, none of the classifications were significantly predictive of the requirement for amputation (Table 4).

Table 3-4 Median scores and area under the curve for different classifications of the severity of foot ulcers in patients that did and did not require an amputation

Wound Classification System	Median scores of those who had amputation (n=19)	Median scores of those who did not have amputation (n=26)	P value Mann Whitney U test	AUC [95% CI]	P value of ROC curves
WIFI	2 [2-3]	2 [1-3]	0.342	0.582 [0.415-0.748]	0.352
UTWCS	9 [9-13]	9 [5-11]	0.079	0.653 [0.492-0.813]	0.083
SINBAD	4 [3-4]	3 [3-5]	0.791	0.523 [0.354-0.692]	0.792
Wagner	3 [2-3]	2 [1-3]	**0.041**	0.671 [0.515-0.826]	0.052

Shown are median (inter-quartile range) of scores. Bold indicates statistical significance. 95% CI: 95% confidence intervals

3.5 Discussion

Many classification systems are available for grading the severity of a DFU (5-7, 30). The ideal clinical grading system for DFUs would be rapid to complete, reproducible within and between different health professionals and reliably predict important clinical outcomes. In the current study the reproducibility, completion time and ability of four commonly used grading systems to predict 30-day amputation were assessed. In this study, photographs of DFUs were examined which simulates assessments that are commonly needed in clinical practice due to the increasing use of telehealth to access DFUs (25). It was found the WIFI system had substantial inter-observer and excellent intra-observer reproducibility. The SINBAD system had moderate inter-observer and excellent intra-observer reproducibility. The UTWCS and Wagner classifications had only fair inter-observer and moderate intra-observer reproducibility. None of these scoring systems were able to reliably predict 30-day amputation rates. The median time to complete all of the four ulcer grading systems was one minute or less, making them highly feasible to use in routine clinical practice by busy clinicians.

A number of previous studies have examined the reproducibility of DFU classifications systems. The Wagner, SINBAD and UTWCS classifications have previously been reported to have moderate agreement (12-14). These findings are similar to those of the current study. The current study is the first to report the reproducibility of the WIFI classification system which had substantial agreement between different observers and almost perfect intra-observer agreement (10). Although prior studies have reported the reproducibility and external validity of DFU grading systems, they were not good at predicting the likelihood of amputation within 30 days in the current study (31). The WIFI classification system has however been previously reported to predict the risk of major amputation within one year for both people with and without

diabetes (32-35). The WIFI score has been predominantly used in people with peripheral arterial disease previously (10, 36-38). No prior reports of any of the scoring systems predicting early requirement for any amputation were identified.

A recent retrospective study that classified ulcers based on photographs using five ulcer classification systems reported that the Wagner and UTWCS classifications were better predictors of amputation over an unspecified follow-up time (39). In the current study it was found that the Wagner classification had significantly different median scores between those participants who did and did not require any amputation within 30 days. Based on area under the curve, however, the Wagner classification was not a good predictor of 30-day amputation likelihood. Ankle brachial pressure index < 0.5, toe pressure < 30 mmHg and transcutaneous oxygen pressure < 25 mmHg have been reported to be associated with a risk of major amputation of greater than 25% (40). It is noteworthy that WIFI is the only scoring system which objectively assesses ischaemia, but it was not predictive of 30-day amputation rate in the current study.

A number of limitations of the current study should be noted, including the inability of the observers to assess DFUs in-person during a global pandemic, the use of two types of cameras to photograph the foot, the small sample size and the limited number of assessors. Given the increasing role of remote assessment of DFUs, the results of this study are highly relevant and topical within the field (25). The study was not designed to test whether the classification systems were predictive of 30-day major amputation alone. Furthermore, the outcomes of patients were only assessed up to 30 days and none of the classification systems have been previously validated for the prediction of 30-day amputation incidence. It is therefore possible that the grading systems may have had better predictive ability for outcomes assessed over a longer period as has been previously reported (32-35) and should be the focus of future studies.

3.6 Conclusion

This study suggests that of the four classification systems examined, the WIFI score has the best inter-observer agreement. The time taken to complete the WIFI score was slightly longer than the other classification systems and WIFI did not predict immediate requirement for any amputation.

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4. Risk factors for hospital readmission for diabetes-related foot disease: A prospective cohort study

Risk factors for readmissions for diabetes-related foot disease

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What does this study add to the existing literature and how will it influence future clinical practices?

This is the largest prospective cohort study conducted in Australia looking at predictive factors for readmissions for diabetes-related foot disease incorporating a substantial proportion of Aboriginal and Torres Strait Islander patients. The study found that absence of pedal pulses and loss of protective sensation in the feet are the two most important factors for readmission.

4.1 Abstract

Introduction: Diabetes-related foot disease (DFD) is a common reason for admission to hospital but the predictive factors for repeat admission are poorly defined. The primary aim of this study was to identify rates and predictive factors for DFD related hospital readmission.

Methods: 190 patients admitted to hospital for treatment of DFD at a single regional centre were prospectively recruited between January 2020 and December 2020. Participants were followed for 12 months to evaluate the primary outcome of unplanned hospital readmission. The relationships between predictive factors and readmission were examined using non-parametric statistical tests and Cox proportional hazard analyses.

Results: The median age of the 190 participants was 64.9 (standard deviation 13.30) years and 68.4% were male. Forty-one participants (21.6%) identified themselves as Aboriginal or Torres Strait Islander Peoples. One hundred participants (52.6%) were readmitted to hospital at least once over 12 months. The commonest reason for readmission was for treatment of foot infection (84.0% of first readmission). Absent pedal pulses (unadjusted hazard ratio [HR], 1.90; 95% confidence interval [95% CI], 1.26, 2.85), loss of protective sensation (LOPS) (unadjusted HR, 1.98; 95% CI, 1.08, 3.62) and male sex (unadjusted HR, 1.62; 95% CI, 1.03, 2.54) were predictive factors of readmission. After risk adjustment, only absence of pedal pulses (HR 1.92, 95% CI 1.27-2.91) and LOPS (HR 2.02, 95% CI 1.09-3.74) were significantly associated with higher risk of readmissions.

Conclusion: Over 50% of patients admitted to hospital for treatment of DFD are readmitted within one year. Patients with absent pedal pulses and those with LOPS are twice as likely to be readmitted.

Key words: Diabetic foot, Readmissions, Aboriginal and Torres Strait Islanders

4.2 Introduction

The global burden from diabetes-related foot disease (DFD), including foot ulcers, infections and gangrene, is substantial (1). It was estimated that 4 million years lived with disability were caused by DFD worldwide in 2016 (2).An important burden related to DFD is hospital admission, with a previous study suggesting that one in every thirteen hospital admissions were caused by foot disease (3). Due to the difficulty in treating DFD and its frequent recurrence, repeated admission to hospital is very common and causes substantial healthcare expenditure (4).

A retrospective study examining data from 25,911 participants reported that thirty percent of DFD participants who were discharged from hospitals in Florida and New York were readmitted within 30 days (5). Predictive factors for readmission included greater number of comorbidities, failure to perform any amputation during the index admission and African American and Hispanic ethnicities (5). The authors concluded that more aggressive surgical management of DFD may lead to a reduced risk of readmission in those populations. Another single centre study in Baltimore reported a 30-day readmission rate of 21.5% for DFD, and patents with hypertension and those who were current smokers being at great risk of readmission (6). There is little available data on readmissions for DFD from outside of the United States despite the varying ethnicities and hospital systems throughout the world.

In Australia, the Aboriginal and Torres Strait Islander population have substantially higher rates of DFD and major amputations than non-Indigenous Australians (7-9). Aboriginal and Torres Strait Islander participants are 1.3 times more likely to be readmitted to a hospital to treat chronic diseases in general but data on DFD related readmission are limited (10). A study from Northern Territory, Australia reported that compared to non-Indigenous people, Aboriginal and Torres Strait Islander People had a five times greater incidence of admission, were admitted at a younger age and were more likely to undergo major and minor

amputations (11). However, it is currently unclear whether Aboriginal and Torres Strait Islander People treated in hospital for DFD are more likely to be readmitted (12).

The main aim of this study was to prospectively examine the rate and predictive factors for DFD related readmission to hospital at a regional tertiary care hospital facility in North Queensland, Australia. A secondary aim was to examine if readmission was more common in Aboriginal and Torres Strait Islander People than non-Indigenous Australians.

4.3 Methods

4.3.1 Study design

This study was designed as a prospective cohort study of patients admitted to the vascular surgery ward of Townsville University Hospital (TUH) with DFD including ulceration, infection, or gangrene between the 1st of January 2020 and 31st of December 2020. All participants were followed up for 12 months from the date of recruitment. All follow-up visits were completed by December 31st, 2021. Ethics approval was obtained from the Townsville Hospital and Health Service Human Research Ethics Committee (HREC/12/QTHS/202, HREC/14/QTHS/203). A five-member Aboriginal and Torres Strait Islander reference committee was consulted as previously described (13).

For inclusion, participants had to be admitted to hospital for treatment of DFD, provide written informed consent and have been:

- Aged 18 years or older at the time of index hospital admission;
- previously diagnosed with either type 1 or 2 diabetes;
- have a foot ulcer defined as a full thickness discontinuation of the epithelium (14) or ;
- have a foot infection (14) diagnosed by the treating physician according to previously described methods or;

- have a gangrenous foot lesion defined as the presence of necrotic tissue in the foot (14).

4.3.2 Definitions of predictive factors

Participants' predictive factors were obtained from history and health records at the time of entry into the study. The predictive factors collected included age, sex, Aboriginal and Torres Strait Islander heritage, smoking history, hypertension, ischaemic heart disease (IHD), transient ischemic attack (TIA) or stroke, end stage renal failure (ESRD) and height and weight. Participants who self-identified themselves as Aboriginal and/or Torres Strait Islander People were considered to have Aboriginal and Torres Strait Islander ethnicity (15). Participants who did not self-identify as Aboriginal and Torres Strait Islander People were considered non-Indigenous people for this study. Current smoking was defined as active cigarette smoking within the month prior to admission and previous smoking was defined as history of previously smoking regularly but not in the month prior to admission (16). Never smoking was defined as no history of regularly smoking. Diabetes, stroke, TIA and hypertension were defined by a documented past history of diagnosis (16). IHD was defined as documented history of prior myocardial infarction, angina or previous treatment of IHD (16). ESRF was defined as requirement for dialysis (16).

Previous history of DFD-related hospital admission, history of previous major or minor amputations, presenting problem, duration of symptoms, previous visits to a podiatrist within the last year, and regular use of prescribed therapeutic offloading footwear within the last month were recorded during a participant interview. Fasting blood glucose levels were obtained on admission and HbA1C levels measured within 6 months of the current hospital admission were obtained from medical records.

DFD was assessed using the Wound Ischemia Foot Infection (WIFI) (17) and Site, Ischemia, Neuropathy, Bacterial infection, Area of the ulcer and Depth of the ulcer (SINBAD) (18) classifications through clinical examination of the participant according to previously described methods (19). In assigning SINBAD score to those participants with gangrene, the necrotic tissue area was measured as the area of the gangrene and was categorised under the variable "area of the ulcer" and depth was only measured if there was both ulceration and gangrenous tissue were present in the lesion and the depth could be measured objectively. Ulcer/gangrenous area and depth were measured using a Silhouette Star camera (The SilhouetteStar™, Aranz Medical Ltd.). Peripheral arterial disease (PAD) was defined based on the criteria given by the WIFI classification (17). Ankle brachial pressure index (ABPI) was measured in all participants as previously described (16) and the toe pressure (TP) was measured in participants who did not have an ulcer or prior amputation of the hallux using a Huntleigh Dopplex® S/W-V1.6 kit according to manufacturer's instructions (Huntleigh Healthcare Ltd, UK). For the SINBAD classification absence of peripheral pulses were defined as absence of both pedal pulses (posterior tibial and dorsalis pedis) in the affected limb. For the WIFI classification, foot infection was defined as presence of local infection; presence of signs of inflammation in the surrounding tissues or systemic infection; signs of systemic infection were defined to include high pulse rate (>90 beats per minute), high respiratory rate (> 20 per minute) and abnormal temperature (>38°C or <36°C). For SINBAD classification we assessed presence or absence of infection. Loss of protective sensation (LOPS) was assessed with the 10-g mono-filament test. The plantar surfaces of the first toe, 1st, 3rd and 5th metatarsal heads were examined and if the sensation was not felt in at least one area, it was considered the participant had LOPS (20). Osteomyelitis was defined as ability to probe to the bone through the ulcer or confirmatory radiological evidence from X-rays or Magnetic Resonance Imaging (14).

Timing of the discharge was at the discretion of the treating consultant who considered the healing of the foot wound, the patient's ability to perform tasks of daily living and social suppoort at home. Patients were followed up as a part of standard clinical care which typically involved an out-patient review within 1 week of discharge and then the frequency of follow-up was determinded by the progress of the foot wound. All patients were reviewed by a podiatrist who provided access to offlaoding footwear and regular follow-up according to Australian guidelines (12).

4.3.3 Definitions and assessment of outcomes

The primary outcome was the requirement for a subsequent planned or unplanned readmission into any health care facility for any DFD condition in either leg (referred to as readmission) within a period of one year. Such conditions include any admission for wound infections, wound debridement, amputations, or antibiotic treatment, non-healing ulcers, or ischemia/ gangrene. Participant records were accessed through the hospital system to identify any readmission and were confirmed with three monthly phone calls to participants.

4.3.4 Statistical analysis

Histograms, skewness and kurtosis tests suggested that continuous data were not normally distributed except in the variable age which was reported as mean and standard deviation. Other continuous data were presented as median and inter-quartile range and compared between groups using the Mann-Whitney U test (unless otherwise stated). Nominal data were presented as count and percent (unless otherwise stated) and compared using the chi-squared test. Categorical variables were compared using Pearson's chi square test. The association of predictive factors with readmissions, were examined using Cox proportion hazard analysis and Kaplan-Meier analysis. Cox proportional hazard analyses included adjustment for predictive factors; Aboriginal and Torres Strait Islander ethnicity, sex, smoking status, hypertension, absence of pedal pulses and presence of LOPS. These were identified to have

bivariate association with relevant outcome with a p value <0.05 (13) or were predictive factors that were previously identified to be associated with readmission (4,6). Participants were censored at the time of event or their death or the date of last follow-up if no event was experienced. Hazard ratios and 95% confidence intervals were presented. All Cox regression models presented were found to conform to the proportional hazard's assumption if a global p value of > 0.05 was observed (21). Data were analysed using SPSS v25 (IBM, Armonk, NY) software package.

4.4 Results

4.4.1 Characteristics of the cohort

One hundred and ninety participants were recruited. Baseline characteristics of these participants are shown in Table 1. The mean age of the cohort was 64.0 years (standard deviation, 13.3), with 68.4% being male (Table 1). Forty-one participants (21.6%) self-identified as either Aboriginal or Torres Strait Islander. Of the 100 participants who were readmitted at least once, 38 (38%) had absent pedal pulses and 88 (88%) had LOPS in their feet. Thirty-four (34%) patients had both absent pedal pulses and LOPS. WIFI grade of the 1st readmission are given in Supplementary Table S1.

Table 4-1 Baseline characteristics of the patients

Characteristic	All patients (n=190)
Age (mean and SD)*	64.0 (13.3)
Sex (males %)	130 (68.4%)
Aboriginal And Torres Strait Islander Peoples	41 (21.6%)

Smoking status Never-smokers Current smokers Ex-smokers	 55 (28.9%) 43 (22.6%) 92 (48.2%)
Duration of diabetes in years [median and IQR]	15.00 [8.00-25.00]
Fasting blood glucose levels mmol/l	11.45 [8.98-15.13]
HbA1C %	8.00 [6.80-9.80] (n=134)
Hypertension	143 (75.3%)
Ischemic heart disease	72 (37.9%)
Transient ischemic attack	11 (5.8%)
Stroke	23 (12.1%)
ESRF	10 (5.3%)
Body mass index(kgm-2)	31.5 [26.5-35.7]
ABPI <0.9 0.9-1.4 >1.4	 58 (30.5%) 62 (32.7%) 70 (36.8%)
TP (mmHg)	85.0 [51.5-110.0] (n=109)
Duration of symptoms in days before the index admission	38.0 [11.0-152.3]
Previous hospital admission for DFD	123 (64.7%)
Previous major amputation	8 (4.2%)
Previous minor amputation	78 (41.1%)

Previous podiatry review within one year	119 (62.6%)
Regular use of prescribed therapeutic offloading footwear within the previous month	69 (36.3%)
Variables in Wound Ischemia Foot Infection (WIFI) classification	
Ulcer/gangrene	
No ulcer or gangrene	6 (3.2%)
Shallow ulcer/no gangrene	58 (30.5%)
Deeper ulcer/digital gangrene	106 (55.8%)
Extensive ulcer or gangrene	20 (10.5%)
Ischemia grade	
ABPI>0.8/TP>60mmHg	130 (68.4%)
ABPI 0.6-0.8/TP 40-60mmHg	30 (15.8%)
ABPI 0.4-0.6/TP 30-40mmHg	14 (7.4%)
ABPI <0.4/TP <30mmHg	6 (8.4%)
Infection grade	
No infection	40 (21.1%)
Mild infection	36 (18.9%)
Moderate infection	76 (40.0%)
Severe infection	38 (20.0%)
Risk category	
Very low	33 (17.4%)
Low	36 (18.9%)
Moderate	58 (30.5%)
High	63 (33.2%)
Variables from Site, ischemia, neuropathy, bacterial infection, area of the ulcer and depth of the ulcer (SINBAD) classification	

Site	
Forefoot	137 (72.1%)
Midfoot/hindfoot	53 (27.9%)
Ischemia	
Pedal pulse palpable	132 (69.5%)
Pedal pulse impalpable	58 (30.5%)
Bacterial infection	
No infection	42 (22.1%)
Infection	148 (77.9%)
Neuropathy	
No LOPS	34 (17.9%)
Presence of LOPS	156 (82.1%)
Area of the ulcer	
Area <1cm2	51 (26.8%0
Area>1cm2	139 (73.2%)
Depth of the ulcer	
Superficial ulcer	63 (33.2%)
Ulcer reaches muscle, tendon or bone	127 (66.8%)
Total SINBAD score	
0	2 (1.1%)
1	17 (8.9%)
2	20 (10.5%)
3	30 (15.8%)
4	80 (42.1%)
5	32 (16.8%)
6	9 (4.7%)

Composite variable: presence of LOPS and absent distal pulses	48 (25.3%)

Foot note: Data are presented as n (%) unless specified. *In this instance, the variable "age" was normally distributed and is given as mean (standard deviation, SD)

Those with absent pedal pulses, LOPS and those who had both absent pedal pulses and LOPS in their feet were more likely to be readmitted (Table 2). Male participants were also significantly more likely to be readmitted (Table 2).

Table 4-2 Baseline characteristics of patients who were readmitted for treatment of DFD in comparison to those who were not readmitted

Characteristic	Patients with readmissions following recurrence of diabetes-related foot disease following index admission (n=100)	Patients who were not readmitted following a diabetes-related foot disease index admission (n=90)	P value
Age (mean and SD)*	64.5 (13.3)	63.5 (13.3)	0.607
Sex (males %)	75 (75.0%)	55 (61.1%)	**0.040**
Aboriginal And Torres Strait Islander Peoples	19 (19.0%)	22 (24.4%)	0.362
Smoking status			0.413
Never-smokers	25 (25.0%)	30 (33.3%)	
Current smokers	25.0 (25.0%)	18 (20.0%)	
Ex-smokers	50 (50.0%)	42 (46.7%)	
Duration of diabetes in years [median and IQR]	15.5 [8.00-22.00]	15.0 [10.0-27.0]	0.432
Fasting blood glucose levels mmol/l	11.7 [8.7-15.9]	11.2 [9.2-15.0]	0.688

HbA1C %	8.4 [6.8-9.9] (n=69)	7.7 [6.7-9.7] (n=65)	0.244
Hypertension	77 (77.0%)	66 (73.2%)	0.559
Ischemic heart disease	39 (39.0%)	33 (36.7%)	0.741
Transient ischemic attack	5 (5.0%)	6 (6.7%)	0.623
Stroke	16 (16.0%)	7 (7.8%)	0.083
ESRF	5 (5.0%)	5 (5.6%)	0.864
Body mass index(kgm-2)	31.1 [25.4-36.1]	32.3 [27.0-35.6]	0.368
ABPI <0.9 0.9-1.4 >1.4	 33 (33.0%) 30 (30.0%) 37 (37.0%)	 25 (27.8%) 32 (35.5%) 33 (36.7%)	0.469
TP (mmHg)	81.0 [50.0-107.0] (n=63)	90.0 [54.3-120.0] (n=46)	0.449
Duration of symptom in days before the index admission	52.0 [13.0-148.8]	32.5 [7.0-156.8]	0.333
Previous hospital admission for DFD	67 (67.0%)	56 (62.2%)	0.865
Previous major amputation	4 (4.0%)	4 (5.4%)	0.879
Previous minor amputation	44 (44.0%)	34 (37.8%)	0.571
Previous podiatry review within one year	67 (67.0%)	52 (57.8%)	0.190
Regular use of prescribed therapeutic offloading footwear within the previous month	37 (37.0%)	32 (35.6%)	0.836
Variables in Wound Ischemia Foot Infection (WIFI) classification			

Ulcer/gangrene			0.223
No ulcer or gangrene	1 (1.0%)	5 (5.6%)	
Shallow ulcer/no gangrene	31 (31.0%)	27 (30.0%)	
Deeper ulcer/digital gangrene	55 (55.0%)	51 (56.7%)	
Extensive ulcer or gangrene	13 (13.0%)	7 (7.8%)	
Ischemia grade			0.551
ABPI>0.8/TP>60mmHg	64 (64.0%)	66 (73.3%)	
ABPI 0.6-0.8/TP 40-60mmHg	18 (18.0%)	12 (13.3%)	
ABPI 0.4-0.6/TP 30-40mmHg	9 (9.0%)	5 (5.6%)	
ABPI <0.4/TP <30mmHg	9 (9.0%)	7 (7.8%)	
Infection grade			0.590
No infection	21 (21.0%)	19 (21.1%)	
Mild infection	20 (20.0%)	16 (17.8%)	
Moderate infection	36 (36.0%)	40 (44.4%)	
Severe infection	23 (23.0%)	15 (16.7%)	
Risk category			0.368
Very low	15 (15.0%)	18 (20.0%)	
Low	20 (20.0%)	16 (17.8%)	
Moderate	27 (27.0%)	31 (34.4%)	
High	38 (38.0%)	25 (27.8%)	
Variables from Site, ischemia, neuropathy, bacterial infection, area of the ulcer and depth of the ulcer (SINBAD) classification			
Site			0.184
Forefoot	68 (68.0%)	69 (76.7%)	

Midfoot/hindfoot	32 (32.0%)	21 (23.3%)	
Ischemia			**0.018**
Pedal pulse palpable	62 (62.0%)	70 (77.8%)	
Pedal pulse impalpable	38 (38.0%)	20 (22.2%)	
Bacterial infection			0.507
No infection	24 (24.0%)	18 (20.0%)	
Infection	76 (76.0%)	72 (80.0%)	
Neuropathy			**0.025**
No LOPS	12 (12.0%)	22 (24.4%)	
Presence of LOPS	88 (88.0%)	68 (75.6%)	
Area of the ulcer			0.208
Area <1cm2	23 (23.0%)	28 (31.1%)	
Area>1cm2	77 (77.0%)	62 (69.9%)	
Depth of the ulcer			0.721
Superficial ulcer	32 (32.0%)	31 (34.4%)	
Ulcer reaches muscle, tendon or bone	68 (68.0%)	59 (65.6%)	
Total SINBAD score			0.081
0	1 (1.0%)	1 (1.1%)	
1	5 (5.0%)	12 (13.3%)	
2	10 (10.0%)	10 (11.1%)	
3	18 (18.0%)	12 (13.3%)	
4	38 (38.0%)	42 (46.7%)	
5	20 (20.0%)	12 (13.3%)	
6	8 (8.0%)	1 (1.1%)	

Composite variable: presence of LOPS and absent distal pulses	34 (34%)	14 (15.6%)	**0.003**

Foot note: Data are presented as n (%) unless specified

*In this instance, the variable "age" was normally distributed and was compared between the two groups using Independent Sample *t* test.

95% CI; 95% Confidence interval, DFD; Diabetes-related foot disease, HbA1C; Glycosylated haemoglobin level, ABPI; Ankle brachial pressure index, TP; Toe pressure, LOPS; Loss of protective sensation

4.4.2 Readmission

Of the 190 participants, seventeen patients (8.9%) died during the study period. The causes of deaths are shown in Supplementary Table S2. All the other participants were followed for one year. A total of 100 (52.6%) participants were readmitted a total of 230 times for treatment of DFD (median readmission episodes per participant 1 [IQR 0 to 2]). The median time to readmission was 0.53 [Inter quartile range, IQR 0.11 to 0.99] years.

Ninety-five participants were readmitted to treat foot disease on the same side as the original admission while five participants were readmitted to treat contralateral foot disease. Table 3 shows the reasons for the first readmission, which was most commonly foot infection. Reasons for all DFD-related readmissions, including multiple re-admission occurring over the 12 months follow-up are shown in Supplementary Table S3.

High fasting blood glucose levels and HbA1C during the index admission were associated with multiple readmissions (Supplementary Table S4, $p<0.05$).

Table 4-3 Cause and treatment given for first episode of DFD-related hospital readmission

Presenting problem and treatment for DFD related readmission to hospital	Total number of readmissions with DFD (in=100 patients)	Aboriginal and Torres Strait Islanders (n=19)	Non-Indigenous patients (n=81)
Foot infections/Cellulitis/Sepsis	**84 (84.0%)**	**18 (94.7%)**	**66 (81.5%)**
Treatment			
Intravenous antibiotic administration alone	41 (41.0%)	6 (31.6%)	35 (43.2%)
Minor amputation	18 (18.0%)	5 (26.3%)	13 (16.0%)
Major amputation	1 (1.0%)	0 (0.0%)	1 (1.2%)
Wound debridement	24 (24.0%)	7 (36.8%)	17 (21.0%)
Ischemia or gangrene	**14 (14.0%)**	**1 (5.3%)**	**13 (16.0%)**
Treatment			
Peripheral endovascular revascularisation	11 (11.0%)	1 (5.3%)	10 (12.3%)
Open revascularisation	1 (1.0%)	0 (0.0%)	1 (1.2%)
Diagnostic angiogram only	2 (2.0%)	0 (0.0%)	2 (2.5%)
Non-healing ulcers	**2 (2.0%)**	**0 (0.0%)**	**2 (2.5%)**
Treatment			
Wound pain management	1 (1.0%)	0 (0.0%)	1 (1.0%)
Skin graft	1 (1.0%)	0 (0.0%)	1 (1.0%)

Foot note: Data are presented as n (%) unless specified

4.4.3 Predictive factors of readmission

In unadjusted cox proportional hazard analysis male participants were significantly more likely to be readmitted (hazard ratio, HR, 1.62, 95% Confidence Interval 1.03 to 2.54; p=0.038). Those presenting with absent pedal pulses and those with LOPS were also more likely to be readmitted (HR 1.90, 95% CI 1.26 to 2.85; p=0.002 and HR 1.98, 95% CI 1.08 to 3.62; p=0.027). In analysis adjusted for Aboriginal and Torres Strait Islander status, sex, smoking and hypertension, absence of pedal pulses and LOPS were independently associated with readmissions (HR 1.92, 95% CI 1.27 to 2.91 and HR 2.02, 95% CI 1.09 to 3,74, respectively) (Table 4).

Table 4-4 Cox regression model to define predictive factors for DFD-related hospital readmission

Risk Factor	Unadjusted hazard ratio [95% CI]	P value	Adjusted hazard ratio [95%CI]	P value
Aboriginal and Torres Strait Islander status	0.77 [0.47-1.26]	0.297	0.99[0.59-1.68]	0.973
Male sex	1.62 [1.03-2.54]	**0.038**	1.54 [0.95-2.51]	0.083
Smoking status	1.12 [0.89-1.42[	0.330	1.03 [0.81-1.32]	0.806
Hypertension	1.16 [0.73-1.84]	0.545	1.05 [0.66-1.70]	0.813
Absence of pedal pulses	1.90 [1.26-2.85]	**0.002**	1.92 [1.27-2.91]	**0.002**
Presence of LOPS	1.98 [1.08-3.62]	**0.027**	2.02 [1.09-3.74]	**0.025**

Foot note:

Data are given as hazard ratio, HR and [95% confidence interval, CI], LOPS, Loss of protective sensation

4.4.4 Readmissions based on Aboriginal and Torres Strait Islander heritage

Aboriginal and Torres Strait Islander participants were significantly younger, were more likely to be a current smoker, more likely to present to the hospital with a shorter duration of symptoms than non-Indigenous participants with foot infection but with palpable pedal pulses compared to non-Indigenous participants and were less likely to use podiatry services than non-Indigenous Australians. Females accounted for approximately half of the recruited Aboriginal and Torres Strait Islander People whereas most non-Indigenous participants were male (Supplementary Table S5).

The incidence of DFD related readmission at 1 year were 46.3% in Aboriginal and Torres Strait Islander participants and 54.4% in non-Indigenous patients, respectively (Log rank test p value 0.294) (Supplementary Figure S1).

4.5 Discussion

To our knowledge this is the largest prospective cohort study conducted outside the United States to investigate DFD-related readmission to hospital. It is noteworthy that 21.6% of the recruited cohort were Aboriginal and Torres Strait Islander People. Given Aboriginal and Torres Strait Islander People make up approximately 8% of the total population of North Queensland where the study was based, this demonstrates a substantial burden of DFD in Aboriginal and Torres Strait Islander People in the region (22). Over 50% of the participants were readmitted within one year illustrating the substantial hospital burden caused by DFD (23). Absence of pedal pulses and LOPS were independent predictive factors of readmission. Rates of readmission were similar in Aboriginal and Torres Strait Islander People and non-Indigenous participants.

Previous studies from the United States have reported male gender, presence of multiple comorbidities, smoking (6), and ethnicity (5) are predictive factors of DFD related

readmission. Predictive factors for readmissions in the Australian patients have not been reported. A study from New South Wales reported that older age (75 years or more), male sex, those who were never married, background of presenting from English speaking countries, and coming from lower-income households (less than AUD 20,000 per year) were predictive factors for developing DFD (24). In our study the only independent predictive factors for readmission to hospital were absent pedal pulses and LOPS. Similar results have previously been shown in studies looking at predictive factors for hospital admissions for DFD (25). Current Australian guidelines recommend appropriate offloading footwear and regular follow-up at the discretion of the treating physician, for an active foot ulcer following discharge from hospital (12). For healed foot ulcers the follow-up interval varies depending on the risk of developing a subsequent foot ulcer. More intensive follow-up may be beneficial in patients with absent pedal pulses and LOPS in order to provide more rapid treatment of infection (12).

When a patient is admitted to the hospital with DFD it is important to stage any foot wound, assess the foot blood supply and extent of the foot infection. This will enable effective communication between health professionals, and it will also give a baseline score which can be used to predict the outcome (17). Treatment may include debridement, antibiotic therapy and revascularisation. Effective discharge planning can help prevent readmission (26). Secondary prevention measures including regular foot care by a podiatrist, offloading footwear, control of blood glucose and dyslipidaemia help prevent recurrent DFD and reduce readmission but are challenging to implement widely (28). It is important to note that the use of offloading footwear was poor in this cohort and that may have contributed to the high readmissions rates. The current guidelines recommned offloading footwear to be used by those patients especially if they have LOPS (12).

The overall cost of managing patients with DFD in hospital has increased overtime despite the apparent static nature of the length of stay of the patient in the hospital and the proportion of emergency admissions. This change is attributed to admission of more unwell patients and attempts at limb salvage (29). In the United States, presence of diabetes increases the likelihood of being admitted with a foot ulcer by 11-fold accounting for over 80% of all amputations increasing the hospital costs over 10-fold every five years (30). Patient education and implementation of early prevention strategies such as early referral to multidisciplinary care and referral to limb salvage teams that address prevention, surveillance and management of foot disease can reduce the burden associated with DFD and hospital admissions (31). A study from the United States reported that after implementation of a DFD management program the number of foot-related hospital admissions decreased by 37.8% over a year (28) Such DFD management programs needs to be developed in culturally safe ways to be implemented successfully in high-risk populations (32).

This study has both strengths and limitations. To our knowledge this is the first study outside the United States investigating DFD-related hospital readmission. Limitations of the study include single center design, short follow up and small sample size. It is possible that some of the predictive factors not associated with readmission could have been confounded by limited statistical power. Future studies with larger sample sizes and longer follow-up are needed.

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4.7 Conflict of interest statement/Funding

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4.9 Supplementary Material

Supplementary Table S1: WIFI Classification of the foot lesion at 1st readmission

	Overall WIFI grade	Ulcer/gangrene grade	Ischemia grade	Infection grade
Very Low	1 (1.0%)	0 (0.0%)	61 (61.0%)	3 (3.0%)
Low/mild	8 (8.0%)	33 (33.0%)	22 (22.0%)	14 (14.0%)
Moderate	33 (33.0%)	59 (59.0%)	8 (8.0%)	36 (36.0%)
High	58 (58.0%)	8 (8.0%)	9 (9.0%)	47 (47.0%)

Note:

95 (95.0%) of the patients were readmitted for the treatment of a complication on the ipsilateral foot while 5 patients (5.0%) were readmitted for the treatment of a complication on the contra-lateral foot

Supplementary Table S2: Cause of death

Cause of death	Frequency
Myocardial infarction/ischemia to the myocardium	5
Sepsis following diabetes-related foot disease	**3***
Refusal of dialysis	2
Stroke	1
Carcinoma	1
Decline in general health due to old age	1
Respiratory failure following interstitial lung disease	1
Subdural haematoma following a fall	1
Adrenal adenoma	1
Suicide	1

Note:

**These patients had palliative treatment of foot gangrene and infection as they were deemed unfit for revascularisation due to multiple co-morbidities and frailty.

Supplementary Table S3: Cause and treatment given for DFD-related hospital readmissions

Presenting problem and treatment for DFD related readmission to hospital	Total number of readmissions with DFD (in=100 patients)	Aboriginal and Torres Strait Islanders (n=19)	Non-Indigenous patients (n=81)
Foot infections/Cellulitis/Sepsis	**165 (71.7%)**	**30 (65.2%)**	**135 (73.3%)**
Treatment			
Intravenous antibiotic administration alone	73 (31.7%)	13 (28.3%)	60 (58.3%)
Minor amputation	46 (20.0%)	8 (17.4%)	38 (36.9%)
Major amputation	6 (2.6%)	1 (2.2%)	5 (2.7%)
Wound debridement	40 (17.4%)	8 (17.4%)	32 (17.4%)
Ischemia or gangrene	**53 (23.1%)**	**10 (21.7%)**	**43 (23.4%)**
Treatment			
Peripheral endovascular revascularisation	28 (12.2%)	7 (15.2%)	21 (11.4%)
Open revascularisation	4(3.9%)	0 (0.0%)	4 (2.2%)
Diagnostic angiogram only	4 (1.7%)	0 (0.0%)	4 (2.2%)
Conservative management	17(7.4%)		

		3 (6.5%)	14 (7.6%)
Non-healing ulcers	**12 (5.2%)**	**6 (13.1%)**	**6 (3.3%)**
Treatment			
Dressing change	8 (7.8%)	4 (8.7%)	4 (2.2%)
Skin graft	3 (1.3%)	1 (2.2%)	2 (1.1%)
Bleeding from surgical site and conservative management	1 (0.4%)	1 (2.2%)	0 (0.0%)
Total number of readmissions	**230**	**46**	**184**

Supplementary Table S4: Baseline characteristics by number of DFD related readmissions

Risk Factors	Patients with no readmissions (n=90)	Patients with a single admission (n=39)	Patients with two or more admissions (n=61)	P value
Age	64.96[53.24-70.64]	66.15[54.22-75.07]	59.27[50.95-70.92]	0.457
Aboriginal and Torres Strait Islander status	22(24.4%)	6(15.4%)	13(21.3%)	0.516
Sex (male %)	55(61.1%)	33(84.6%)	42(68.9%)	**0.031**
Smoking				
Non-smokers	30(33.3%)	12(30.8%)	13(21.3%)	0.591
Current smokers	18(20.0%)	9(23.1%)	16(26.2%)	
Ex-smokers	42(46.7%)	18(46.2%)	32(52.5%)	

Duration of diabetes	15.00[9.50-25.50]	17.00[8.00-26.00]	16.00[8.00-21.00]	0.522
Fasting blood sugar	11.80[9.10-15.35]	9.90[8.30-13.13]	14.30[11.20-18.90]	**0.029**
HbA1c*	7.70[6.70-9.65]	7.65[6.15-8.93]	8.80[7.60-10.40]	**0.008**
Hypertension	66(73.3%)	31(79.5%)	46(75.4%)	0.758
Ischemic heart disease	33(36.7%)	15(38.5%)	24(39.3%)	0.943
Transient Ischemic Attack	6(6.7%)	1(2.6%)	4(6.6%)	0.626
Stroke	7(7.8%)	4(10.3%)	12(19.7%)	0.082
ESRF	5(5.6%)	2(5.1%)	3(4.9%)	0.984
Body mass index	32.30(27.01-35.64)	30.18(23.29-33.77)	31.64(25.61-37.96)	0.171
Presentations Gangrene Osteomyelitis Soft tissue infections Ulcer	 7(7.8%) 1(1.1%) 29(32.2%) 53(58.9%)	 6(15.4%) 2(5.1%) 10(25.6%) 21(53.8%)	 5(8.2%) 2(3.3%) 16(26.2%) 38(62.3%)	0.602
Duration of the problem in days	30.00[6.00-168.00]	59.00[12.25-127.75]	30.00[11.00-66.00]	0.573
Previous admissions None One or more	 34(37.8%) 54(62.1%)	 13(33.3%) 28(68.3%)	 20(32.8%) 41(66.1%)	0.908
Past history of major amputations	4 (4.4%)	3(7.7%)	1(1.6%)	0.335

Past history of minor amputations	34(37.8%)	17(43.6%)	27(44.3%)	0.539
Utilisation of podiatry services	52(57.8%)	24(61.5%)	43(70.5%)	0.136
Offloading percentage	0.00[0.00-91.67]	0.00[0.00-87.50]	0.00[0.00-100.0]	0.813
WIFI score Ulcer/gangrene grade None Superficial ulcer or no gangrene Deep ulcer or gangrenous toes Extensive ulcer or extensive gangrene	 5(5.6%) 27(30.0%) 51(56.7%) 7(7.8%)	 0(0.0%) 11(28.2%) 24(61.5%) 4(10.3%)	 1(1.6%) 20(32.8%) 31(50.8%) 9(14.8%)	0.459
WIFI score ischemia grade None Mild Moderate Severe	 66(73.3%) 12(13.3%) 5(5.6%) 7(7.8%)	 21(53.8%) 8(17.9%) 6(15.4%) 5(12.8%)	 43(70.5%) 11(18.0%) 3(4.9%) 4(6.6%)	0.260
WIFI score infection grade None Mild Moderate Severe	 19(21.1%) 16(17.8%) 40(44.4%) 15(16.7%)	 8(20.5%) 11(28.2%) 10(25.6%) 10(25.6%)	 13(21.3%) 9(14.8%) 26(42.6%) 13(21.3%)	0.408

WIFI score				
Very low risk	18(20.0%)	7(17.9%)	8(13.1%)	0.229
Low risk	16(17.8%)	6(15.4%)	14(23.0%)	
Moderate risk	31(34.4%)	7(17.9%)	20(32.8%)	
High risk	25(27.8%)	19(48.7%)	19(31.1%)	
SINBAD score				
Site				
Forefoot	69(76.7%)	27(69.2%)	41(67.2%)	0.403
Midfoot/hindfoot	21(23.3%)	12(30.8%)	20(32.8%)	
Ischemia				
Palpable pulse	70(77.8%)	20(51.3%)	42(68.9%)	**0.011**
Pulse impalpable	20(22.2%)	19(48.7%)	19(31.1%)	
Infection				
Present	72(80.0%)	29(74.4%)	47(77.0%)	0.763
Absent	18(20.0%)	10(25.6%)	14(23.0%)	
Peripheral neuropathy				
Present	68(75.6%)	33(84.6%)	55(90.2%)	0.064
Absent	22(24.4%)	6(15.4%)	6(9.8%)	
Area				
<1cm2	28(31.1%)	10(25.6%)	13(21.3%)	0.404
>1cm2	62(68.9%)	29(74.4%)	48(78.7%)	
Depth				
Superficial	31(34.4%)	10(25.6%)	22(36.1%)	0.524
Deep				

	59(65.6%)	29(74.4%)	39(63.9%)	
SINBAD score				
0	1(1.1%)	1(2.6%)	0(0.0%)	0.271
1	12(13.3%)	1(2.6%)	4(6.6%)	
2	10(11.1%)	3(7.7%)	7(11.5%)	
3	12(13.3%)	8(20.5%)	10(16.4%)	
4	42(46.7%)	14(35.9%)	24(39.3%)	
5	12(13.3%)	8(20.5%)	12(19.7%)	
6	1(1.1%)	4(10.3%)	4(6.6%)	

Foot note:

IQR; Inter-quartile range, HbA1C; Glycosylated haemoglobin level, ABPI; Ankle brachial pressure index, TP; Toe pressure

Supplementary Table S5: Baseline characteristics of all patients by Aboriginal and Torres Strait Islander status (n=190)

Characteristic	Non-Indigenous (n=149)	Aboriginal and Torres Strait Islanders (n=41)	P value
Age (median and IQR)	67.61[59.03-75.00]	55.10[49.61-60.84]	**<0.001**
Sex (males %)	110(73.8%)	20(48.8%)	**0.002**
Smoking status			**0.037**
Non-smokers	41(27.5%)	14(34.1%)	
Current smokers	29(19.5%)	14(34.1%)	
Ex-smokers	79(53.0%)	13(31.7%)	
Duration of diabetes	18.00[8.00-26.00]	15.00[10.00-20.00]	0.304

Fasting blood glucose levels mmol/l	11.20[8.95-14.90]	13.40[8.90-18.15]	0.169
HbA1C	8.05[6.80-9.60] (n=98)	7.80[6.90-10.50] (n=36)	0.908
Hypertension	113(75.8%)	30(73.2%)	0.726
Ischemic heart disease	60(40.3%)	12(29.3%)	0.199
Transient ischemic attack	9(6.0%)	2(4.9%)	0.778
Stroke	18(12.1%)	5(12.2%)	0.984
ESRF	6(4.0%)	4(9.8%)	0.145
Body mass index	31.35[25.08-35.35]	33.42[28.35-37.22]	0.303
Presenting complication Ulcer Gangrene Osteomyelitis Soft tissue infection	 94(63.1%) 12(8.1%) 3(2.0%) 40(26.8%)	 18(43.9%) 6(14.6%) 2(4.9%) 15(36.6%)	0.137
Duration of the current symptom in days before the index admission	57.0(13.0-181.0)	27.0(5.5-61.0)	**0.013**
Previous hospital admissions for DFD	96(64.4%)	27(65.9%)	0.695
Previous major amputations	8(5.4%)	0(0.0%)	0.137
Previous minor amputations	61(40.9%)	17(41.5%)	0.485
Previous podiatry reviews within one year	100(67.1%)	19(46.3%)	**0.015**
Regular use of prescribed therapeutic offloading footwear within the previous month	58(38.9%)	11(26.8%)	0.154

Variables in Wound Ischemia Foot Infection (WIFI) classification			
Ulcer/gangrene			
No ulcer or gangrene	3(2.0%)	3(7.3%)	0.070
Shallow ulcer/no gangrene	51(34.2%)	7(17.1%)	
Deeper ulcer/digital gangrene	81(54.4%)	25(61.0%)	
Extensive ulcer or gangrene	14(9.4%)	6(14.6%)	
Ischemia grade			
ABPI>0.8/TP>60mmHg	98(65.8%)	32(78.0%)	0.402
ABPI 0.6-0.8/TP 40-60mmHg	25(16.8%)	5(12.2%)	
ABPI 0.4-0.6/TP 30-40mmHg	13(8.7%)	1(2.4%)	
ABPI <0.4/TP <30mmHg	13(8.7%)	3(7.3%)	
Infection grade			
No infection	36(24.2%)	4(9.8%)	0.198
Mild infection	27(18.1%)	9(22.0%)	
Moderate infection	59(39.6%)	17(41.5%)	
Severe infection	27(18.1%)	11(26.8%)	
Risk category			
Very low	28(18.8%)	5(12.2%)	0.545
Low	30(20.1%)	6(14.6%)	
Moderate	43(28.9%)	15(36.6%)	

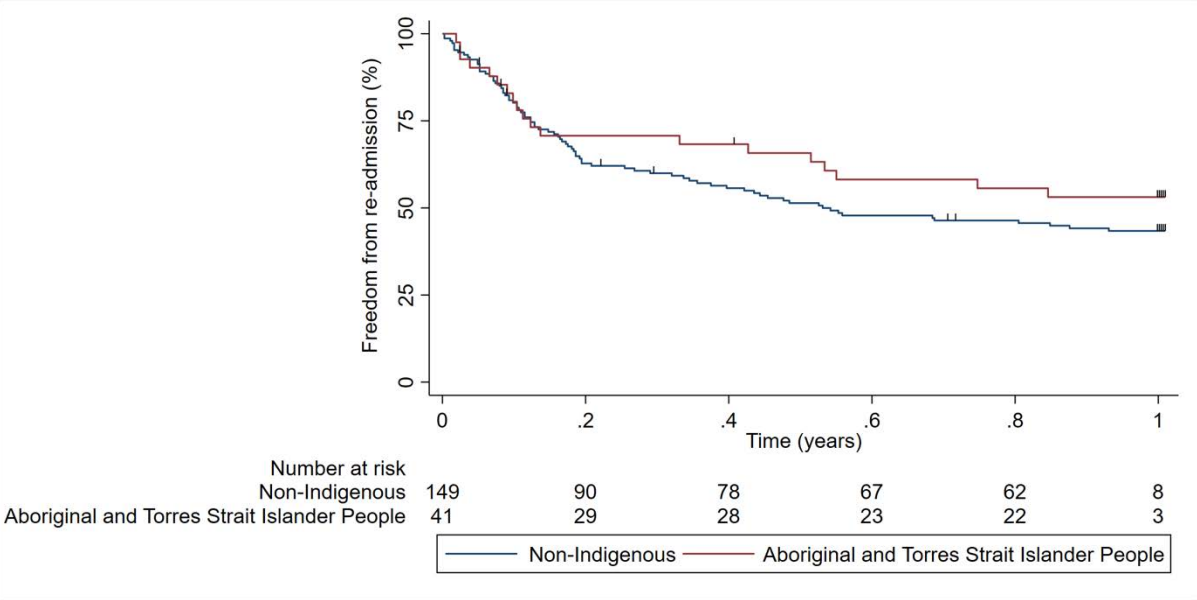
High	48(32.2%)	15(36.6%)	
Variables from Site, ischemia, neuropathy, bacterial infection, area of the ulcer and depth of the ulcer (SINBAD) classification			
Site Forefoot Midfoot/hindfoot	 108(72.5%) 41(27.5%)	 29(70.7%) 12(29.3%)	 0.825
Ischemia Pulse palpable Pulse impalpable	 98(65.8%) 51(34.2%)	 34(82.9%) 7(17.1%)	 **0.035**
Infection No infection Infection	 38(25.5%) 111(74.5%)	 4(9.8%) 37(90.2%)	 **0.031**
Neuropathy No neuropathy Presence of neuropathy	 26(17.4%) 123(82.6%)	 8(19.5%) 33(80.5%)	 0.760
Area of the ulcer Area <1cm2 Area>1cm2	 44(29.5%) 105(70.5%)	 7(17.1%) 34(82.9%)	 0.111
Depth of the ulcer Superficial ulcer Ulcer reaches muscle, tendon or bone	 53(35.6%) 96(64.4%)	 10(24.4%) 31(75.6%)	 0.178
Total SINBAD score 0 1 2	 2(1.3%) 16(10.7%) 14(9.4%)	 0(0.0%) 1(2.4%) 6(14.6%)	 0.293

3	26(17.4%)	4(9.8%)	
4	58(38.9%)	22(53.7%)	
5	25(16.8%)	7(17.1%)	
6	8(5.4%)	1(2.4%)	

Foot note:

IQR; Inter-quartile range, HbA1C; Glycosylated haemoglobin level, ABPI; Ankle brachial pressure index, TP; Toe pressure

Supplementary Figure S1: Kaplan-Meier curve illustrating the freedom from readmissions in Aboriginal and Torres Strait Islander and non-Indigenous participants



5. Cohort study examining the presentation, distribution, and outcome of peripheral artery disease in Aboriginal and Torres Strait Islander Australians and non-Indigenous Australians

Short Title: Peripheral artery disease in Indigenous Australians

Disclosure: This chapter has been published in the European Journal of Vascular and Endovascular Surgery.

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Declarations of interest: none

What does this paper add?

This is the first study to conduct a detailed imaging assessment of the distribution and severity of peripheral artery disease in Aboriginal and Torres Strait Islander Australians presenting to a vascular department. Aboriginal and Torres Strait Islander participants had more severe tibial artery disease compared to non-Indigenous participants. This difference may contribute to the high incidence of major amputation in Aboriginal and Torres Strait Islander People.

5.1 Abstract

Objective: This study investigated the anatomical distribution, severity, and outcomes of peripheral artery disease (PAD) in Aboriginal and Torres Strait Islander Australians compared with non-Indigenous Australians.

Design: Retrospective cohort study.

Materials and Methods: The distribution, severity and outcome of PAD were assessed using a validated angiographic scoring system and reviews of medical records in a cohort of Aboriginal and Torres Strait Islander and non-Indigenous Australians. The relationship between ethnicity and PAD severity, distribution and outcome were examined using non-parametric statistical tests, Kaplan-Meier and Cox-proportional hazard analyses.

Results: Seventy-three Aboriginal and Torres Strait Islander and 242 non-Indigenous Australians were included and followed for a median [inter-quartile range; IQR] of 6.7 [2.7-9.3] years. Aboriginal and Torres Strait Islander patients were more likely to present with symptoms of chronic limb threatening ischemia (81% versus 25%, $p<0.001$), had greater median (IQR) angiographic scores for the symptomatic limb (7 [5-10] vs 4 [2-7]) and tibial arteries (5 [2-6] versus 2 [0-4]) and had higher risks of major amputation (hazard ratio, HR, 6.1, 95% CI 3.6 to 10.5; $p<0.001$) and major adverse cardiovascular events (MACE; HR 1.5, 95% CI 1.0 to 2.3], $p=0.036$), but not revascularisation (HR 0.8, 95% CI 0.5 to 1.3; $p=0.37$), compared to non-Indigenous Australians. The associations with major amputation and MACE were no longer significant when adjusted for limb angiographic score.

Conclusion: Compared with non-Indigenous Australians, Aboriginal and Torres Strait Islander Australians had more severe tibial artery disease and higher risk of major amputation and MACE.

Key words: Aboriginal and Torres Strait Islander Australians; Peripheral artery disease; Diabetes related foot disease; Chronic limb threatening ischemia

5.2 Introduction

Aboriginal and Torres Strait Islander Australians have an excess burden of foot ulcers and amputations (1-3). Previous studies have reported that major amputation rates are 3 to 38-fold greater in Aboriginal and Torres Strait Islander Australians than in non-Indigenous Australians (1, 3, 4). Previously identified causes of the excess burden of foot disease include high prevalence and early onset of diabetes and high rates of peripheral neuropathy and peripheral artery disease (PAD) (1, 5, 6).

PAD is a key risk factor for foot disease and major amputation (7-9) There has, however, been limited study of PAD in Aboriginal and Torres Strait Islander Australians (1). A small study reported that Aboriginal and Torres Strait Islander patients (n=16) with PAD presented at a younger age, were more likely to have diabetes and had a 5-fold greater risk of major adverse cardiovascular events (MACE) compared to the non-Indigenous patients (n=385) (10). Aboriginal and Torres Strait Islander Australians with type 2 diabetes in Western Australia have been reported to have a prevalence of PAD of between 16% and 31% in different phases of the Fremantle diabetes study (5, 11) and a prevalence rate of 49% in a study from North Queensland (12). No previous study has examined the severity or distribution of PAD in Aboriginal and Torres Strait Islander Australians. The high rate of major amputation in Aboriginal and Torres Strait Islander Australians could be explained by a greater risk of developing severe PAD which presents as ischaemic rest pain or tissue loss (defined as chronic limb threatening ischemia; CLTI) and/ or more severe lower extremity artery occlusive disease (10). It is also possible that Aboriginal and Torres Strait Islander Australians are more prone to tibial artery occlusive disease, given the high prevalence of diabetes in this population which could contribute to a higher risk of major amputation (13, 14). This study had number of aims. The primary aim was to compare the severity and distribution of PAD between Aboriginal and Torres Strait Islander and non-Indigenous

Australians presenting with symptomatic PAD (15). The secondary aims were to compare the incidence of major amputations, MACE, all-cause mortality and lower extremity revascularization and examine if any differences in PAD severity and distribution might explain differences in outcome. Sub-analyses were restricted to participants presenting with diabetes or CLTI alone.

5.3 Materials and Methods

5.3.1 Design

This was a retrospective study of patients presenting to the Townsville University Hospital Vascular and Endovascular Surgery Department, Queensland, Australia. Patients were eligible for inclusion if they presented between February 2005 and December 2020 with symptoms of PAD including intermittent claudication or CLTI diagnosed as previously reported (16, 17). PAD was defined by a ≥50% stenosis or occlusion in at least one lower limb artery using previously published criteria (5, 18). Only patients who had ultrasound, digital subtraction angiography (DSA) and/or computed tomography angiography (CTA) imaging of the abdominal aorta, iliac, femoral and tibial arteries in the symptomatic leg were eligible for inclusion. Patients were excluded if they were asymptomatic, had undergone a major amputation of the symptomatic leg, if they presented with acute limb ischemia or if they did not have relevant high-quality imaging available, e.g. due to artefacts imposed by metal implants. The study was approved by the Townsville Hospital and health Service Human Research Ethics Committee (HREC/13/QTHS/125) and James Cook University (H4947). Public Health Act approval was obtained for a consent waiver and access to data from the Queensland death register (RD004829; RD005150).

5.3.2 Aboriginal and Torres Strait Islander ethnicity

Aboriginal and Torres Strait Islander ethnicity was based on self-identification by patients at the time of presentation to the hospital. These data were extracted from hospital medical records.

5.3.3 Presentation and risk factors

Presenting symptoms and risk factors were collected from hospital medical records and a prospective database (19), which were completed at the time of the patients' first presentation to the hospital. Data collected included age, sex, smoking history, diabetes, hypertension, coronary heart disease (CHD), stroke, end stage renal failure (ESRF), prior peripheral revascularisation (endovascular or open surgical revascularisation) and medications (19). Intermittent claudication was defined as leg pain on exertion relieved by rest related to PAD (20). CLTI was defined based on a history of ischemic rest pain, ischemic ulceration or gangrene secondary to PAD (17). Diabetes, hypertension, CHD, stroke and ESRF were based on prior diagnosis documented in medical records (19). ESRF was defined by requirement for dialysis (19). Smoking history was classified as ever or never smoking (19). All prescribed medications including antiplatelet agents (aspirin and clopidogrel), angiotensin converting enzyme inhibitors (ACEI) and angiotensin receptor blockers (ARBs), other anti-hypertensive and hypoglycaemic medications were collected.

5.3.4 Image acquisition

Computed tomographic angiography (CTA) performed using a 64 slice multi-scanner (Philips, North Ryde, New South Wales, Australia) as described previously, was used during the study period (15). Arterial duplex was performed using a Canon Aplio i800 (model: TUS-A1800/5W) machine by an experienced sonographer. Digital subtraction angiography (DSA) was performed by a board-certified vascular surgeon using a Siemens Artis Zeego Q (model: 116990) imaging system.

5.3.5 Assessment of PAD severity and distribution

PAD severity was assessed from the CTA, DSA or ultrasound images using a previously validated angiographic scoring system (called the ANGIO score) (15). This scoring system was used because it was specifically developed to be used in CTA and DSA and because we have found it to have excellent inter-observer reproducibility (15). The aorta, common iliac, external iliac, common femoral, profunda femoris, superficial femoral and popliteal arteries were scored 0, 1 or 2 according to the degree of stenosis or occlusion (15). A score of 0 was assigned if there was no stenosis or the stenosis was <50%, a score of 1 was assigned if there was a non-occlusive stenosis of >50% and a score of 2 was assigned if there was complete occlusion (15). Due to reduced resolution of imaging for the distal arteries, the three tibial arteries were scored as 2 for an occlusion and 0 if there was no occlusion as previously reported (15). Criteria for grading stenosis severity on CTA and DSA followed the method we have previously shown to be reproducible (15). For ultrasound, a velocity ratio of 2 was used to define ≥50% stenosis (21). Scores for all ten arteries supplying one limb were summed to provide the total limb ANGIO score which was reported out of 20 with higher scores representative of more severe PAD. ANGIO scores were also reported related to the following artery segments: a) aorto-iliac (infra-renal aorta, common iliac artery and external iliac artery); b) femoro-popliteal (common femoral, profunda femoris, superficial femoral and popliteal arteries) and c) the tibial arteries (anterior tibial, posterior tibial and peroneal arteries). ANGIO scoring was restricted to the most symptomatic leg in each patient.

5.3.6 Reproducibility assessment

For this study, the inter-observer and intra-observer reproducibility of the ANGIO scoring were examined by two trained assessors. The agreements between ANGIO scores performed from CTA versus DSA (n=14 limbs) and CTA versus ultrasound (n= 11 limbs) performed by

one observer were also examined. Observers were blinded to the patient information at the time of assessment. Images from 20 randomly selected patients who were representative of the sample and who had undergone both CTA (n=40 limbs) and either DSA (n=14 limbs) and/or ultrasound (n=11 limbs) on the symptomatic leg at entry were assessed. ANGIO score on CTA scans were conducted first. ANGIO score was performed independently by both assessors twice one week apart. Reproducibility and agreement between ANGIO scores were measured with weighted kappa (κ) statistics with quadratic weights as previously described. [22] The agreement within and between observers for assessment of ANGIO score from CTA (κ 0.871 and 0.713; p<0.001 in both instances), DSA (κ 0.741 and 0.744; p<0.001 in both instances) and ultrasound (κ0.673 and 0.768; p<0.001 in both instances) were substantial (22). The agreement between ANGIO scores measured from CTA vs DSA (κ=0.741; p<0.001) and CTA vs ultrasound (κ=0.673; p<0.001) were also substantial (Supplementary Table S1).

5.3.7 Outcome assessment

Patients were followed up after recruitment and outcome data were obtained from both a review of hospital medical records and using linked hospital admission records from the Queensland Hospital Admitted Patient Data Collection which is regularly audited to minimize inaccuracies (19). Outcomes included major amputation, MACE, all-cause mortality and requirement for lower extremity revascularisation. Major amputation was defined as a lower extremity amputation at or proximal to the ankle (23). MACE was defined as myocardial infarction, stroke or cardiovascular death. All-cause mortality was defined as death from all causes (10). Lower extremity revascularisation included any open surgical or endovascular lower extremity revascularisation procedure as previously described (23).

Decisions about requirement for operative interventions were at the discretion of the treating consultant surgeon but were in line with current international guidelines, including lifestyle limiting intermittent claudication failing to respond to conservative therapy and CLTI (17,24).

5.3.8 Sample size

The required sample size was estimated according to the planned Cox regression analysis focused on major amputation. Based on prior studies, the incidence of major amputation was estimated to be 40% over minimum of 2 years (25). The regression analysis was planned to include up to ten variables including age, sex, smoking, diabetes, hypertension, ESRF, past history of revascularisation, presentation with CLTI and total ANGIO score. Monte Carlo simulations suggest that a multivariate regression model is powered sufficiently when ten outcome events per degree of freedom of the predictor variables are observed (26). Based on these estimates a sample size of approximately 250 participants were adequate.

5.3.9 Statistical Analysis

Histograms, skewness and kurtosis tests suggested that continuous data were not normally distributed, and they were summarised using median values and inter-quartile ranges and compared between groups using Mann Whitney U test. Categorical data were presented as percentages and were compared between groups using chi square test. Time to events were estimated using Kaplan-Meier analyses, with differences between groups compared using log rank tests if the proportion of events occurred evenly over time or Breslow test if there was an apparent initial disparity between the two groups. Multivariable Cox proportional hazard analyses were performed to assess the association between Aboriginal and Torres Strait Islander ethnicity and major amputations, MACE or lower extremity revascularisation adjusting for age, sex, smoking, diabetes, hypertension, ESRF, past history of revascularisation, presentation with CLTI and total ANGIO score. The selection of variables

for adjustment was based on those that have been established as risk factors for events or were found to be significantly different ($p<0.05$) between the comparator groups (10). Examination of the residuals for the final multivariate models with Schoenfeld's test suggested that the assumptions of proportional hazards were met. Two sub-analyses were performed limiting the analyses to patients: a) presenting with CLTI; and b) who had a diagnosis of diabetes. $P < 0.05$ was considered significant for all analyses. All statistical analyses were conducted using SPSS v25 (IBM SPSS Inc., Armonk, NY, USA) and STATA version 14.1 (Stata Corp, College Station, Texas, USA) software packages.

5.4 Results

5.4.1 Characteristics of the cohort

Three hundred and fifteen patients were included, of whom 73 (23%) identified as being Aboriginal and Torres-Strait Islander people. The number of patients that were included, and their outcomes are given in Supplementary Figure 1. Aboriginal or Torres-Strait Islander patients were significantly younger, more likely to be female and have a prior diagnosis of diabetes, hypertension and ESRF, but significantly less likely to be a smoker than non-Indigenous patients (Table 1). Aboriginal or Torres-Strait Islander patients were also significantly more likely to be prescribed with anti-hypertensive medications, statins and diabetes medications than non-Indigenous patients. Non-Indigenous patients were significantly more likely to be prescribed with aspirin.

Table 5-1 Characteristics of the included participants in relation to Aboriginal and Torres Strait Islander ethnicity

Characteristics	Aboriginal or Torres Strait	Non-Indigenous Australians (n=242)	p-value

	Islander Australians (n=73)		
Age (years)	60.0 [52.8-67.5]	68.9 [61.4-74.5]	**<0.001**
Male sex	43 (59%)	185 (77%)	**0.003**
BMI	28.7 [25.6-34.6]	26.7 [23.9-30.5]	**0.035**
Diabetes Fasting glucose	64 (88%) 6.2 [5.4-12.7]	84 (35%) 5.7 [5.1-7.2]	**<0.001** **0.028**
Smoking Ever smoking Never smoking	 53 (73%) 20 (27%)	 206 (85%) 36 (15%)	**0.014**
Dyslipidaemia	60 (82%)	166 (67%)	**0.024**
Hypertension	64 (88%)	176 (73%)	**0.009**
CHD	40 (55%)	118 (49%)	0.366
Previous TIA	4 (6%)	19 (8%)	0.348
Previous stroke	10 (14%)	28 (12%)	0.625
ESRF eGFR	19 (26%) 69.5 [20.8-83.8]	17 (7%) 75.0 [64.0-91.0]	**<0.001** **0.001**
Medications			

Aspirin	43 (58.9%)	182 (75.2%)	**0.007**
Other antiplatelet drugs	11 (15.1%)	40 (16.5%)	0.767
Warfarin	6 (8.2%)	31 (12.8%)	0.197
ACEI	41 (56%)	98 (41%)	**0.018**
Beta-blockers	33 (45%)	79 (33%)	**0.049**
Calcium channel blocker	24 (33%)	71 (29%)	0.546
Metformin	33 (45%)	41 (17%)	**<0.001**
Insulin	31 (43%)	27 (11%)	**<0.001**
Statin	60 (82%)	166 (67%)	**0.024**
Presentation:			
Intermittent claudication	14 (19%)	181 (75%)	**<0.001**
CLTI	59 (81%)	61 (25%)	
Previous revascularisation*	18 (25%)	52 (22%)	0.568
Endovascular revascularisation	17 (23%)	30 (12%)	**0.023**
Open revascularisation	7 (10%)	33 (14%)	0.357

Data shown as median (inter-quartile range) or number (percentage). BMI, body mass index; ESRF, end stage renal failure; ACEI, Angiotensin converting enzyme inhibitors; TIA, transient ischemic attack; CHD, Coronary heart disease; CLTI, Chronic limb threatening ischemia. eGFR, estimated glomerular filtration rate; CCB, Calcium channel blocker.

*Some participants in the study have had both previous endovascular and open revascularisation procedures. BMI and fasting glucose values were missing in 53 non-Indigenous participants and in 40 Aboriginal and Torres Strait Islander participants. eGFR was missing in 84 non-Indigenous participants and 59 Aboriginal and Torres Strait Islander participants.

5.4.2 Comparison of PAD severity in Aboriginal and Torres Strait Islander and non-Indigenous patients

A substantially higher proportion of Aboriginal and Torres Strait Islander patients presented with CLTI (81%) compared to non-Indigenous patients (25%) ($p<0.001$; Table 1). The total limb and tibial ANGIO scores were also significantly higher in the Aboriginal and Torres Strait Islander patients compared to the non-Indigenous patients (Table 2).

Table 5-2 Comparison of ANGIO Scores in Aboriginal and Torres Strait Islander participants and non-Indigenous participants presenting with peripheral artery disease, chronic limb threatening ischemia and diabetes

Artery segment	Aboriginal and Torres Strait Islander Australians	Non-Indigenous Australians	P-value
Whole cohort (n=315)			
	n=242	n=73	

Femoro-popliteal	2 [0-4]	2 [0-3]	0.13
Tibial artery	5 [2-6]	2 [0-4]	**<0.001**
Total limb	7 [5-10]	4 [2-7]	**<0.001**
Participants with diabetes (n=148)			
	n=64	n=84	
Femoro-popliteal	2 [0-4]	2 [0-3]	0.096
Tibial artery	5 [2-6]	2 [0-4]	**0.004**
Total limb	7 [5-10]	4 [2-7]	**0.003**
Participants with chronic limb threatening ischemia (n=120)			
	n=59	n=61	
Femoro-popliteal	2 [0-4]	2 [0-3]	0.420
Tibial artery	6 [2-6]	4 [2-4]	**0.004**
Total limb	8 [4-10]	6 [4-8]	**0.022**

Shown are median (inter-quartile range; IQR). Median ANGIO score of the Aorto-iliac section continued to be 0.00 [0.00-1.00] in all instances and was not significantly different between the two groups hence not reported in the table.

5.4.3 Association between Aboriginal or Torres Strait islander ethnicity and events

Participants were followed for a median [IQR] of 6.7 [2.7-9.3] years. By Kaplan Meir analysis the incidence of major amputation, MACE, all-cause mortality and lower extremity

revascularisation at 5 years were 35%, 40%, 41% and 37% in Aboriginal and Torres Strait Islander patients and 10%, 31%, 32% and 47% in non-Indigenous patients, respectively. The incidences of major amputation and MACE but not all-cause mortality and lower extremity revascularisation were significantly higher in Aboriginal and Torres Strait Islander patients than non-Indigenous patients (p values of log rank tests <0.001, 0.035, 0.137, 0.365 respectively) (Figure 1). Additional analysis confirmed that the incidence of major amputation was significantly greater in Aboriginal and Torres Strait Islander patients than non-Indigenous patients in the initial period of follow up (p value of Breslow test <0.001).

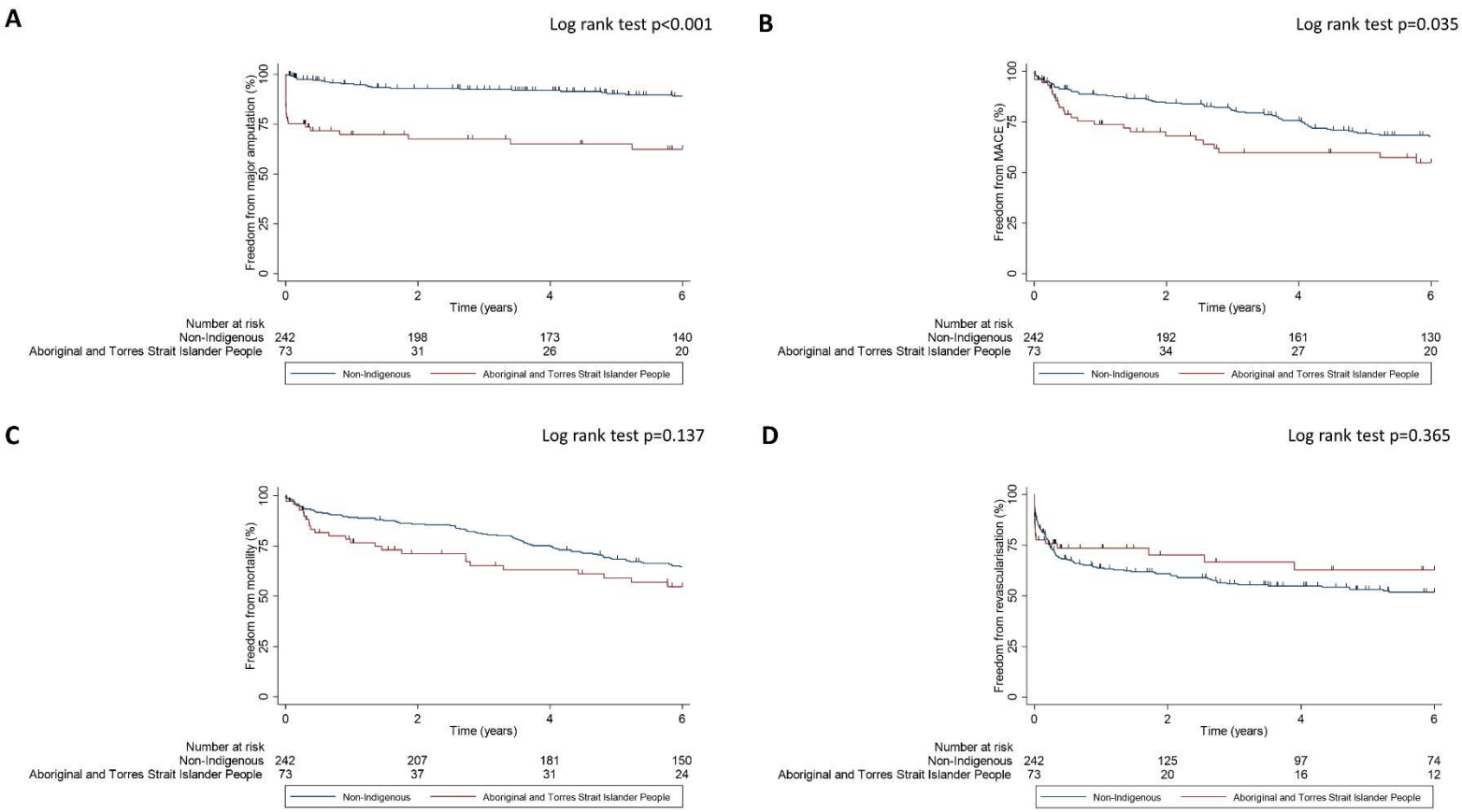

Figure 5-1 Kaplan-Meier curve illustrating the freedom of events by ethnicity in participants with peripheral artery disease, A; Major amputation, B: Major adverse cardiovascular event, C: All-cause mortality, D; Lower extremity revascularisation

In unadjusted Cox proportional hazard analyses, Aboriginal and Torres Strait Islander patients were at a greater risk of major amputation (hazard ratio, HR, 6.1, 95% CI 3.6, 10.5; p<0.001) and MACE (HR 1.5, 95% CI 1.0, 2.3; p=0.036) but not all-cause mortality (HR 1.3, 95% CI 0.9, 1.9; p=0.14) and lower extremity revascularisation (HR 0.8, 95% CI 0.5 to 1.3; p=0.37) (Table 3). In an analysis adjusted for age, sex, smoking, ESRF, diabetes, hypertension, past history of revascularisation and CLTI, Aboriginal and Torres Strait Islander ethnicity was associated with a significantly higher risk of major amputation (HR 2.5, 95% CI 1.2 to 5.0; p=0.012) but not MACE, all-cause mortality or lower extremity revascularisation (Table 3). In analyses adjusted for age, sex, smoking, ESRF, diabetes, hypertension, past history of revascularisation, CTLI and limb ANGIO score, Aboriginal and Torres Strait Islander ethnicity was no longer significantly associated with the risk of major amputation (HR 1.7, 95% CI 0.8, 3.6; p=0.17) (Table 3). Independent risk factors for major amputation included ESRF, CLTI and ANGIO score (Supplementary Table S2). Age, ESRF, diabetes and limb ANGIO score were independently associated with MACE (Supplementary Table S3) while age, ESRF, CLTI and limb ANGIO score were independently associated with all-cause mortality (Supplementary Table S4). None of the risk factors were independently associated with the risk of lower extremity revascularisation (Supplementary Table S5).

Table 5-3 Cox proportional hazard analyses for the association between Aboriginal and Torres Strait Islander status and major amputation, major adverse cardiovascular events, all-cause mortality and revascularization

Adverse event	Unadjusted HR [95% CI]	p-value	Adjusted model 1	p-value	Adjusted model 2	p-value
Whole cohort (n=315)						

Major amputation	6.1 (3.6, 10.5)	<0.001	2.5 (1.2, 5.0)*	0.012	1.7 [0.8, 3.6]†	0.17
MACE	1.5 (1.0, 2.3)	0.036	1.2 (0.7-2.0)*	0.56	0.9 (0.6, 1.6)†	0.82
Mortality	1.3 (0.9, 1.9)	0.14	0.8 (0.5, 1.3)*	0.35	0.7 (0.4, 1.1)†	0.10
Revascularisation	0.8 (0.5, 1.3)	0.37	0.8 (0.4, 1.3)*	0.32	0.8 (0.4, 1.4)†	0.37
Participants with diabetes (n=148)						
Major amputation	3.9 (2.0, 7.8)	<0.001	2.3 (1.0-5.1)‡	0.049	1.9 (0.8, 4.5)§	0.18
MACE	1.1 (0.7, 1.7)	0.85	1.3 (0.7, 2.2)‡	0.45	1.1 (0.6, 1.9)§	0.88
Mortality	0.9 (0.6, 1.4)	0.59	0.9 (0.6, 1.5)‡	0.73	0.8 (0.5, 1.4)§	0.48
Revascularisation	1.2 (0.7, 2.0)	0.57	1.4 (0.8, 2.8)‡	0.28	1.5 (0.7, 3.0)§	0.27
Participants with chronic limb threatening ischemia (n=120)						
Major amputation	2.3 (1.2, 4.2)	0.011	1.9 (0.9, 4.1)‖	0.96	1.5 (0.7, 3.5)¶	0.31

MACE	1.0 (0.6, 1.8)	0.91	1.5 (0.8, 3.0)‖	0.22	1.2 (0.8, 3.0)¶	0.71
Mortality	0.8 (0.5, 1.2)	0.28	1.1 (0.6, 1.9)‖	0.85	0.9 (0.5, 1.6)¶	0.70
Revascularisation	0.7 (0.4, 1.4)	0.33	1.0 (0.5, 2.2)‖	0.96	1.1 (0.5, 2.4)¶	0.83

Shown are hazard ratios (95% confidence intervals). CLTI, Chronic limb threatening ischemia. MACE, major adverse cardiovascular event; All-cause mortality is reported.

Adjusted for *age, sex, smoking, ESRF, diabetes, hypertension, past history of revascularisation and CLTI; †age, sex, smoking, ESRF, diabetes, hypertension, past history of revascularisation, CLTI and limb ANGIO score; ‡age and CLTI; §age, CLTI and limb ANGIO score; ‖age, diabetes and CLTI; ¶age, diabetes, CLTI and limb ANGIO score.

5.4.4 Sub-analyses restricted to participants with diabetes or CTLI

Median follow up of patients with diabetes was 4.8 [1.0-8.2] years and that of participants with CLTI was 3.1 [0.4-6.9] years. The findings in sub-analyses restricted to participants with diabetes (n=148, Aboriginal and Torres Strait Islander patients= 64 and non-Indigenous patients= 84) and CTLI (n=120, Aboriginal and Torres Strait Islander patients= 59 and non-Indigenous patients= 61) are summarised in Table 2 to 3, Supplementary Figure 2 to 3 and Supplementary Tables S6 to S15. In general, they showed similar findings to the main analysis with Aboriginal and Torres Strait Islander ethnicity being associated with significantly greater total limb and tibial ANGIO scores (Table 2) and greater risk of major amputation which was no longer significant after adjusting for ANGIO score (Table 3).

5.5 Discussion

To our knowledge this is the first objective comparison of the distribution and severity of PAD in Aboriginal and Torres Strait Islander Australians compared to non-Indigenous Australians. Aboriginal and Torres Strait Islander Australians were significantly more likely to present with CLTI and had significantly higher total limb and tibial ANGIO scores, by comparison to non-Indigenous Australians. These differences remained significant in analyses restricted to patients with diabetes or CLTI alone. These findings may in part explain the higher risk of major amputation in Aboriginal and Torres Strait Islander Australians compared to non-Indigenous Australians since tibial artery disease is a prognostic marker for amputation (27). This theory was supported by our finding that after adjustment for ANGIO score Aboriginal and Torres Strait Islander ethnicity was no longer significantly associated with greater risk of major amputation.

A recent systematic review found that Hispanic and Black American patients were significantly more likely to present with CLTI as compared to White American patients (28). Hispanic and Black American patients were also significantly more likely to require a lower extremity amputation than White American patients (28). The current study, while conducted in a total different population had comparable findings. The majority of the Aboriginal and Torres Strait Islander participants presented with CLTI, while the non-Indigenous patients most commonly presented with intermittent claudication. A recent review identified that there have been very few studies of PAD in First Nation populations (29). Prior studies of Australian Aboriginal and Torres Strait Islander People have focused on assessing cardiovascular risk factors and their relationship with the incidence of amputation without objective assessment of the peripheral arteries (3, 5, 10, 11, 30). Limited reports have also suggested that PAD prevalence is greater in Aboriginal and Torres Strait Islander Australians and that presentation occurs at an earlier age than in non-Indigenous Australians (10,12). For

example, in the largest previous prospective study, the Fremantle Diabetes Study group found that the prevalence of PAD was significantly higher in Aboriginal and Torres Strait Islander participants as compared to non-Indigenous Australians (31% versus 22%, $p<0.05$) (11). Yet, none of these prior studies had examined the distribution and severity of PAD in Aboriginal and Torres Strait Islander Australians by examination of imaging of the lower extremity arteries.

Compared to non-Indigenous participants, Aboriginal and Torres Strait Islander Australians included in the current study were significantly younger, more commonly had diabetes and more frequently presented with CLTI and had a higher risk of major amputation and MACE, similar to previous reports (10, 29). Tibial artery disease is an important risk factor for CLTI (31). Detailed assessment of the lower extremity arteries using a reproducible scoring system (15) showed that tibial artery ANGIO score was significantly greater in Aboriginal and Torres Strait Islander than non-Indigenous participants. In contrast, there was no significant difference in ANGIO scores for the more proximal arteries. This finding might have related to the significant imbalance in diagnosis of diabetes between the groups. The results were, however, similar in a sub-analysis restricted to participants with diabetes suggesting that the diabetes imbalance was not the key reason. A recent study found that the high-density lipoprotein-cholesterol (HDL-c) of Aboriginal and Torres Strait Islander Australians with a history of both diabetes and PAD had significantly less ability to stimulate endothelial tube formation *in vitro* compared with the HDL-c from patients with diabetes but no PAD (32). This finding was related to 14-fold higher expression of anti-angiogenic micro-RNA miR 181c-5p within the HDL-c of patients with PAD compared to those without PAD (32). It was previously suggested that delayed presentation of diabetes and its complications in Aboriginal and Torres Strait Islander Australians resulted from lack of culturally appropriate health services and remoteness from major healthcare centres (33,34). This may have

contributed to the frequent presentation of Aboriginal and Torres Strait Islander patients with CLTI noted in this study.

It is notable that despite the high incidence of CLTI amongst Aboriginal and Torres Strait Islander participants, the rate of lower extremity revascularisation was not significantly different to that in non-Indigenous participants. The increased challenges of revascularisation in patients with distal disease may have contributed to this finding but this requires further investigation. A recent study from Canada reported that despite similar rates of revascularisation procedures conducted in First Nations people compared to non-Indigenous patients, First Nations people had higher rates of lower extremity amputations and greater mortality than non-Indigenous patients (35). Future research is needed to understand what barriers First Nations people face in receiving adequate PAD care and what interventions are necessary to achieve equitable outcomes. Development of culturally acceptable awareness and multidisciplinary treatment programs targeting First Nations people who present from unique cultural, socioeconomic and geographic backgrounds may help to improve outcomes (29).

The current study has several strengths and limitations. Strengths included the use of a validated and reproducible method to assess the distribution and severity of PAD and the study of a unique population. Weaknesses included the single centre recruitment, the relatively small sample size, the heterogeneity of the patients included and the retrospective design which prohibited collection of some data such as the severity of peripheral neuropathy, size and location of the foot ulcer, presence of osteomyelitis and degree of infection. The sample size calculation was based on a rate of major amputation of 40% which was higher than found and thus comparisons between groups were likely underpowered. The ANGIO scoring system was used to assess PAD severity and distribution as it was validated for scoring different imaging modalities with an excellent inter-observer reliability. There

were significant differences between the two groups of patients related to the presence of diabetes as a risk factor and presentation to the hospital with CLTI. Sub-group analyses restricted to those with diabetes or CLTI were conducted to address this which did not alter the main findings.

Future directions

Future research is needed to examine the mechanisms responsible for the high prevalence of distal artery disease in Aboriginal and Torres Strait Islander People and to develop culturally appropriate PAD awareness and treatment programs to facilitate earlier presentation and improved care.

5.6 Conclusion

This study found that Aboriginal and Torres Strait Islander Australians were significantly more likely to present with CLTI, had more severe tibial artery disease and were at a higher risk of major amputation and MACE than non-Indigenous Australians. Further research is needed to better understand the reasons for these findings and to develop interventions to improve outcomes in Aboriginal and Torres Strait Islander Australians.

5.7 Acknowledgments

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5.10 Supplementary Material:

Supplementary Table S1: Reproducibility of ANGIO Score between two observers and between the same observer for different imaging types

Imaging Modality	Kappa Value	Significance
Inter Observer Agreement		
CTA (n=35)	0.713	<0.001
DSA (n=14)	0.744	<0.001
USS (n=11)	0.768	<0.001
Intra-Observer Agreement		
CTA (n=35)	0.871	<0.001
DSA (n=14)	0.741	<0.001
USS (n=11)	0.673	<0.001
CTA vs DSA (n=14)	0.741	<0.001

CTA vs USS (n=15)	0.673	<0.001

Supplementary Table S2: Cox proportional hazard analyses for the association between risk factors and **major amputations** in participants with **peripheral arterial disease**

Risk factor	Unadjusted hazard ratio [95% CI]	p-value	Adjusted hazard ratio [95% CI] [a]	p-value	Adjusted hazard ratio [95% CI] [b]	p-value
Aboriginal and Torres Strait Islander status	6.11[3.55-10.52]	**<0.001**	2.46 [1.22-4.97]	**0.012**	1.70 [0.80-3.62]	0.169
Age	0.97 [0.95-0.99]	**<0.036**	1.00 [0.97-1.03]	0.914	0.99 [0.96-1.02]	0.566
Sex	1.65 [0.94-2.89]	0.079	1.24 [0.68-2.27]	0.476	1.42 [0.77-2.62]	0.266
Smoking	0.51 [0.27-0.94]	**0.031**	1.45 [0.74-2.82]	0.279	1.48 [0.74-2.93]	0.267
ESRF	5.40[2.93-9.96]	**<0.001**	2.34 [1.19-4.58]	**0.014**	2.69 [1.37-5.27]	**0.004**

Diabetes	3.21 [1.80-5.72]	**<0.001**	0.79 [0.38-1.63]	0.522	0.73[0.35-1.53]	0.402
Hypertension	2.17 [1.02-4.60]	**0.044**	1.65 [0.74-3.66]	0.222	1.44[0.63-3.27]	0.387
Past history of revascularisation	2.09 [1.20-3.66]	**0.010**	1.93 [1.09-3.41]	**0.023**	1.46 [0.80-2.66]	0.212
CLTI	9.70 [5.05-18.64]	**<0.001**	6.86 [3.20-14.71]	**<0.001**	6.36 [2.96-13.78]	**<0.001**
Limb ANGIO score	1.23 [1.15-1.31]	**<0.001**	NA	NA	1.13[1.05-1.23]	**0.002**

Foot note: Bold indicates significant results. 95% CI, 95% confidence intervals, ESRF, end stage renal failure; CLTI, chronic limb threatening ischemia; NA, not applicable

[a] Risk factors in the model included Aboriginal or Torres Strait Islander status, age, sex, smoking, ESRF, diabetes, hypertension, past history of revascularisation and CLTI.

[b] Risk factors in the model included Aboriginal or Torres Strait Islander status, age, sex, smoking, ESRF, diabetes, hypertension, past history of revascularisation, CLTI and limb ANGIO score.

Supplementary Table S3: Cox proportional hazard analyses for the association between risk factors and **major adverse cardiovascular events** in participants with **peripheral arterial disease**

Risk factor	Unadjusted hazard ratio [95% CI]	p-value	Adjusted hazard ratio [95% CI] [a]	p-value	Adjusted hazard ratio [95% CI] [b]	p-value
Aboriginal and Torres Strait Islander status	1.53 [1.03-2.29]	**0.036**	1.17 [0.70-1.95]	0.561	0.94 [0.55-1.61]	0.824
Age	1.03[1.02-1.05]	**<0.001**	1.04 [1.02-1.06]	**<0.001**	1.04 [1.02-1.06]	**<0.001**
Sex	1.30[0.91-1.86]	0.157	1.05 [0.71-1.56]	0.796	1.09 [0.74-1.61]	0.654
Smoking	0.79 [0.52-1.22]	0.286	1.43 [0.87-2.36]	0.159	1.43 [0.87-2.36]	0.161
ESRF	2.65 [1.67-4.22]	**<0.001**	2.12 [1.27-3.57]	**0.004**	2.36 [1.40-3.97]	**0.001**
Diabetes	1.96 [1.40-2.74]	**<0.001**	1.54 [1.04-2.29]	**0.030**	1.51 [1.02-2.23]	**0.040**
Hypertension	2.37 [1.49-3.78]	**<0.001**	1.69 [1.04-2.76]	**0.034**	1.54 [0.94-2.53]	0.085

Past history of revascularisation	1.13 [0.75-1.69]	0.543	1.08 [0.72-1.62]	0.702	0.97 [0.64-1.46]	0.867
CLTI	1.55 [1.09-2.18]	**0.013**	1.27 [0.82-1.98]	0.284	1.20 [0.77-1.87]	0.422
Limb ANGIO score	1.11[1.06-1.17]	**<0.001**	NA	NA	1.08 [1.03-1.15]	**0.002**

Foot note: Bold indicates significant results. 95% CI, 95% confidence intervals, ESRF, end stage renal failure; CLTI, chronic limb threatening ischemia; NA, not applicable

[a] Risk factors in the model included Aboriginal or Torres Strait Islander status, age, sex, smoking, ESRF, diabetes, hypertension, past history of revascularisation and CLTI.

[b] Risk factors in the model included Aboriginal or Torres Strait Islander status, age, sex, smoking, ESRF, diabetes, hypertension, past history of revascularisation, CLTI and limb ANGIO score.

Supplementary Table S4: Cox proportional hazard analyses for the association between risk factors and **all-cause mortality** in participants with **peripheral arterial disease**

Risk factor	Unadjusted hazard ratio [95% CI]	p-value	Adjusted hazard ratio [95% CI] [a]	p-value	Adjusted hazard ratio [95% CI] [b]	p-value
Aboriginal and Torres Strait Islander status	1.33 [0.91-1.93]	0.138	0.80 [0.50-1.28]	0.351	0.67 [0.41-1.09]	0.104
Age	1.04 [1.03-1.06]	**<0.001**	1.05 [1.03-1.07]	**<0.001**	1.05 [1.03-1.07]	**<0.001**
Sex	1.26 [0.92-1.73]	0.155	1.00 [0.71-1.42]	0.993	1.04 [0.74-1.48]	0.816
Smoking	0.74 [0.51-1.08]	0.118	1.50 [0.97-2.32]	0.068	1.48 [0.96-2.28]	0.078
ESRF	3.24 [2.17-4.83]	**<0.001**	2.60 [1.64-4.12]	**<0.001**	2.87 [1.80-4.55]	**<0.001**
Diabetes	1.87 [1.39-2.50]	**<0.001**	1.31 [0.93-1.86]	0.128	1.27 [0.89-1.81]	0.178
Hypertension	2.13 [1.45-3.15]	**<0.001**	1.69 [1.04-2.76]	**0.024**	1.49 [0.99-2.25]	0.057

Past history of revascularisation	1.16 [0.82-1.66]	0.398	1.11 [0.77-1.59]	0.581	1.02 [0.71-1.46]	0.928
CLTI	2.19 [1.63-2.94]	**<0.001**	2.22 [1.54-3.20]	**<0.001**	2.12 [1.47-3.60]	**<0.001**
Limb ANGIO score	1.10 [1.06-1.15]	**<0.001**	NA	NA	1.08 [1.03-1.14]	**0.004**

Foot note: Bold indicates significant results. 95% CI, 95% confidence intervals, ESRF, end stage renal failure; CLTI, chronic limb threatening ischemia; NA, not applicable

[a] Risk factors in the model included Aboriginal or Torres Strait Islander status, age, sex, smoking, ESRF, diabetes, hypertension, past history of revascularisation and CLTI.

[b] Risk factors in the model included Aboriginal or Torres Strait Islander status, age, sex, smoking, ESRF, diabetes, hypertension, past history of revascularisation, CLTI and limb ANGIO score.

Supplementary Table S5: Cox proportional hazard analyses for the association between risk factors and **revascularisation** in participants with **peripheral arterial disease**

Risk factor	Unadjusted hazard ratio [95% CI]	p-value	Adjusted hazard ratio [95% CI] [a]	p-value	Adjusted hazard ratio [95% CI] [b]	p-value
Aboriginal and Torres Strait Islander status	0.80 [0.50-1.29]	0.368	0.75 [0.43-1.32]	0.322	0.77 [0.43-1.37]	0.368
Age	0.99 [0.98-1.01]	0.532	0.99 [0.97-1.01]	0.238	0.99 [0.97-1.01]	0.279
Sex	0.99 [0.67-1.48]	0.989	1.12 [0.74-1.69]	0.622	1.11 [0.73-1.68]	0.619
Smoking	1.31 [0.80-2.16]	0.279	1.28 [0.74-1.69]	0.602	1.29 [0.75-2.22]	0.367
ESRF	0.53 [0.26-1.07]	0.077	0.50 [0.23-1.06]	0.069	0.50 [0.23-1.06]	0.070
Diabetes	0.82 [0.58-1.15]	0.247	0.83 [0.56-1.23]	0.341	0.83 [0.56-1.23]	0.355
Hypertension	1.06 [0.71-1.58]	0.765	1.31 [0.85-2.01]	0.219	1.31 [0.86-2.01]	0.213

Past history of revascularisation	0.92 [0.61-1.39]	0.698	0.94 [0.62-1.43]	0.789	0.95 [0.63-1.45]	0.818
CLTI	0.95 [0.66-1.37]	0.801	1.33 [0.86-2.07]	0.202	1.35 [0.86-2.10]	0.189
Limb ANGIO score	0.98 [0.93-1.03]	0.424			0.99 [0.94-1.05]	0.699

Foot note: Bold indicates significant results. 95% CI, 95% confidence intervals, ESRF, end stage renal failure; CLTI, chronic limb threatening ischemia; NA, not applicable

[a] Risk factors in the model included Aboriginal or Torres Strait Islander status, age, sex, smoking, ESRF, diabetes, hypertension, past history of revascularisation and CLTI.

[b] Risk factors in the model included Aboriginal or Torres Strait Islander status, age, sex, smoking, ESRF, diabetes, hypertension, past history of revascularisation, CLTI and limb ANGIO score.

Supplementary Table S6: Characteristics of included participants presenting with **diabetes**

Characteristics	Aboriginal or Torres Strait Islander Australians (n=64) Percentages	Non-Indigenous Australians (n=84) Percentages	p-value
Age (years)	60.00 [52.78-67.53] (59)	69.95 [63.28-74.93] (61)	**<0.001**
Male (sex)	37 (57.8%)	61 (72.6%)	0.059
Smoking Ever smoking No smoking	 44 (68.8%) 20 (31.3%)	 65 (77.4%) 19 (22.6%)	0.238
Hypertension	57 (89.1%)	74 (88.1%)	0.855
Coronary heart disease	33 (51.6%)	53 (63.1%)	0.159
Previous stroke	9 (14.1%)	13 (15.5%)	0.811

ESRF	18 (28.1%)	13 (15.5%)	0.061
Medications			
Aspirin	38 (59.4%)	66 (78.6%)	**0.011**
Other antiplatelet medications	10 (15.6%)	24 (28.6%)	0.064
ACEI	37 (57.8%)	43 (51.2%)	0.423
Beta-blockers	29 (45.3%)	31 (36.9%)	0.302
Calcium channel-blocker	22 (34.4%)	31(36.9%)	0.750
Metformin	33 (51.6%)	41 (48.8%)	0.740
Insulin	31 (48.4%)	27 (32.1%)	**0.044**
Statin	54 (84.4%)	64 (76.2%)	0.220
Presentation:			

Intermittent claudication CLTI	10 (15.6%) 54 (84.4%)	48 (57.1%) 36 (42.9%)	**<0.001**
Previous revascularisation* Endovascular revascularisation Open revascularisation	16 (25.0%) 15 (23.4%) 05 (7.8%)	20 (23.8%) 13 (15.5%) 10 (11.9%)	0.867 0.221 0.414

Data shown as median (inter-quartile range) or number (percentage). Foot note: Bold indicates significant results. Values in parenthesis are number of participants in each group. ESRF, end stage renal failure; ACEI, Angiotensin converting enzyme inhibitors, *Some participants in the study have had both previous endovascular and open revascularisation

Supplementary Table S7: Cox proportional hazard analyses for the association between risk factors and **major amputations** in participants with **diabetes**

Risk factor	Unadjusted hazard ratio [95% CI]	p-value	Adjusted hazard ratio [95% CI] [a]	p-value	Adjusted hazard ratio [95% CI] [b]	p-value
Aboriginal and Torres Strait Islander status	3.90 [1.95-7.81]	**<0.001**	2.27 [1.00-5.12]	**0.049**	1.85 [0.76-4.50]	0.177
Age	0.97 [0.94-0.99]	**0.035**	0.99 [0.96-1.03]	0.695	0.99 [0.95-1.03]	0.548
CLTI	6.62 [2.56-17.16]	**<0.001**	4.83 [1.78-13.09]	**0.002**	4.58 [1.68-12.50]	**0.003**
Limb ANGIO score	1.13 [1.04-1.23]	**0.006**	NA	NA	1.08 [0.99-1.17]	0.220

Foot note: Bold indicates significant results. 95% CI, 95% confidence intervals, CLTI, chronic limb threatening ischemia; NA, not applicable

[a] Risk factors in the model included Aboriginal or Torres Strait Islander status, age and CLTI.

[b] Risk factors in the model included Aboriginal or Torres Strait Islander status, age, CLTI and limb ANGIO score

Supplementary Table S8: Cox proportional hazard analyses for the association between risk factors and **major adverse cardiovascular events** in participants with **diabetes**

Risk factor	Unadjusted hazard ratio [95% CI]	p-value	Adjusted hazard ratio [95% CI] [a]	p-value	Adjusted hazard ratio [95% CI] [b]	p-value
Aboriginal and Torres Strait Islander status	1.05 [0.66-1.66]	0.851	1.25 [0.71-2.19]	0.446	1.05 [0.57-1.92]	0.876
Age	1.03 [1.00-1.05]	**0.029**	1.03 [0.99-1.05]	0.055	1.03 [0.99-1.05]	0.078
CLTI	1.02 [0.66-1.59]	0.927	1.03 [0.63-1.70]	0.901	1.02 [0.62-1.69]	0.944
Limb ANGIO score	1.07 [1.00-1.14]	**0.042**	NA	NA	1.07 [0.99-1.15]	0.064

Foot note: Bold indicates significant results. 95% CI, 95% confidence intervals, CLTI, chronic limb threatening ischemia; NA, not applicable

[a] Risk factors in the model included Aboriginal or Torres Strait Islander status, age and CLTI.

[b] Risk factors in the model included Aboriginal or Torres Strait Islander status, age, CLTI and limb ANGIO score.

Supplementary Table S9: Cox proportional hazard analyses for the association between risk factors and **all-cause mortality** in participants with **diabetes**

Risk factor	Unadjusted hazard ratio [95% CI]	p-value	Adjusted hazard ratio [95% CI] [a]	p-value	Adjusted hazard ratio [95% CI] [b]	p-value
Aboriginal and Torres Strait Islander status	0.89 [0.58-1.37]	0.589	0.92 [0.56-1.50]	0.730	0.83 [0.49-1.39]	0.475
Age	1.03 [1.00-1.05]	0.065	1.02 [1.00-1.05]	**0.038**	1.02 [0.99-1.05]	0.056
CLTI	1.35 [0.90-2.03]	0.146	1.59 [1.03-2.46]	**0.037**	1.57 [1.02-2.44]	**0.043**
Limb ANGIO score	1.05 [0.98-1.11]	0.164	NA	NA	1.05 [0.98-1.12]	0.175

Foot note: Bold indicates significant results. 95% CI, 95% confidence intervals, CLTI, chronic limb threatening ischemia; NA, not applicable

[a] Risk factors in the model included Aboriginal or Torres Strait Islander status, age and CLTI.

[b] Risk factors in the model included Aboriginal or Torres Strait Islander status, age, CLTI and limb ANGIO score.

Supplementary Table S10: Cox proportional hazard analyses for the association between risk factors and **revascularisation** in participants with **diabetes**

Risk factor	Unadjusted hazard ratio [95% CI]	p-value	Adjusted hazard ratio [95% CI] [a]	p-value	Adjusted hazard ratio [95% CI] [b]	p-value
Aboriginal and Torres Strait Islander status	1.18 [0.68-2.04]	0.569	1.43 [0.75-2.75]	0.281	1.48 [0.74-2.96]	0.265
Age	1.00 [0.98-1.03]	0.743	1.01 [0.98-1.04]	0.548	1.01 [0.98-1.04]	0.515
CLTI	0.81 [0.48-1.39]	0.448	0.74 [0.41-1.31]	0.298	0.74 [0.42-1.32]	0.306
Limb ANGIO score	0.99 [0.92-1.08]	0.982			0.99 [0.91-1.07]	0.769

Foot note: Bold indicates significant results. 95% CI, 95% confidence intervals, CLTI, chronic limb threatening ischemia; NA, not applicable

[a] Risk factors in the model included Aboriginal or Torres Strait Islander status, age and CLTI.

[b] Risk factors in the model included Aboriginal or Torres Strait Islander status, age, CLTI and limb ANGIO score.

Supplementary Table S11: Characteristics of included participants presenting with **chronic limb threatening ischemia**

Characteristics	Aboriginal or Torres Strait Islander Australians (n=59) Percentages	Non-Indigenous Australians (n=61) Percentages	p-value
Age (years)	60.00 [52.78-67.53] (59)	72.20 [64.10-77.22] (61)	**<0.001**
Male (sex)	36 (61.0%)	43 (70.5%)	0.274
Diabetes	54 (91.5%)	36 (59.0%)	**<0.001**
Smoking Ever smoking No smoking	 39 (66.1%) 20 (33.9%)	 42 (68.9%) 19 (31.1%)	0.748
Hypertension	50 (84.7%)	45 (73.8%)	0.139
Coronary heart disease	31 (52.5%)	38 (62.3%)	0.280

Previous stroke	9 (15.3%)	7 (11.5%)	0.543
ESRF	17 (28.8%)	10 (16.4%)	0.103
Medications			
Aspirin	35 (59.3%)	48 (78.7%)	**0.022**
Other antiplatelet medications	9 (15.3%)	13 (21.3%)	0.391
ACEI	30 (50.8%)	27 (44.3%)	0.470
Beta-blockers	24 (40.7%)	24 (39.3%)	0.881
Calcium channel-blocker	19 (32.2%)	14 (23.0%)	0.256
Metformin	27 (45.8%)	15 (24.6%)	**0.015**
Insulin	27 (45.8%)	12 (19.7%)	**0.002**
Statin	48 (81.4%)	42 (68.9%)	0.114

Presentation:			
Intermittent claudication	14 (19.2%)	181 (74.8%)	**<0.001**
CLTI	59 (80.8%)	61 (25.2%)	
Previous revascularisation*	15 (25.4%)	18 (29.5%)	0.616
Endovascular revascularisation	15 (25.4%)	11 (18.0%)	0.326
Open revascularisation	05 (8.5%)	11 (18.0%)	0.124

Data shown as median (inter-quartile range) or number (percentage). Foot note: Bold indicates significant results. Values in parenthesis are number of participants in each group. ESRF, end stage renal failure; CLTI, chronic limb threatening ischemia; ACEI, Angiotensin converting enzyme inhibitors, *Some participants in the study have had both previous endovascular and open revascularisation

Supplementary Table S12: Cox proportional hazard analyses for the association between participant characteristics and **major amputations** in participants with **chronic limb threatening ischemia**

Risk factor	Unadjusted hazard ratio [95% CI]	p-value	Adjusted hazard ratio [95% CI] [a]	p-value	Adjusted hazard ratio [95% CI] [b]	p-value
Aboriginal and Torres Strait Islander status	2.26 [1.21-4.22]	**0.011**	1.91 [0.88-4.14]	0.964	1.54 [0.67-3.53]	0.312
Age	0.98 [0.95-1.00]	0.076	1.01 [0.98-1.04]	0.629	0.99 [0.95-1.02]	0.357
Diabetes	1.30 [0.63-2.64]	0.437	0.61 [0.32-1.18]	0.142	0.92 [0.43-1.95]	0.818
CLTI	1.89 [0.74-4.82]	0.185	0.71 [0.34-1.51]	0.378	1.34 [0.49-3.69]	0.570
Limb ANGIO score	1.10 [1.02-1.19]	0.018	NA	NA	1.08 [0.99-1.17]	0.089

Foot note: Bold indicates significant results. 95% CI, 95% confidence intervals, CLTI, chronic limb threatening ischemia; NA, not applicable

[a] Risk factors in the model included Aboriginal or Torres Strait Islander status, age, diabetes and CLTI

[b] Risk factors in the model included Aboriginal or Torres Strait Islander status, age, diabetes, CLTI and limb ANGIO score.

Supplementary Table S13: Cox proportional hazard analyses for the association between participant characteristics and **major cardiovascular adverse events** in participants with **chronic limb threatening ischemia**

Risk factor	Unadjusted hazard ratio [95% CI]	p-value	Adjusted hazard ratio [95% CI] [a]	p-value	Adjusted hazard ratio [95% CI] [b]	p-value
Aboriginal and Torres Strait Islander status	1.03 [0.59-1.79]	0.914	1.53 [0.78-3.03]	0.218	1.16 [0.77-3.03]	0.706
Age	1.03 [1.01-1.06]	**0.009**	1.05 [1.02-1.08]	**0.002**	1.04 [1.01-1.07]	**0.006**
Diabetes	1.41 [0.72-2.76]	0.310	1.65 [0.82-3.34]	0.161	1.66 [0.82-3.34]	0.156
CLTI	0.92 [0.46-1.84]	0.813	0.79 [0.37-1.66]	0.531	0.82 [0.39-1.74]	0.602
Limb ANGIO score	1.09 [1.02-1.17]	**0.016**	NA	NA	1.08 [1.00-1.17]	**0.048**

Foot note: Bold indicates significant results. 95% CI, 95% confidence intervals, CLTI, chronic limb threatening ischemia; NA, not applicable

[a] Risk factors in the model included Aboriginal or Torres Strait Islander status, age, diabetes and CLTI,

[b] Risk factors in the model included Aboriginal or Torres Strait Islander status, age, diabetes, CLTI and limb ANGIO score.

Supplementary Table S14: Cox proportional hazard analyses for the association between participant characteristics and **all-cause mortality** in participants with **chronic limb threatening ischemia**

Risk factor	Unadjusted hazard ratio [95% CI]	p-value	Adjusted hazard ratio [95% CI] [a]	p-value	Adjusted hazard ratio [95% CI] [b]	p-value
Aboriginal and Torres Strait Islander status	0.77 [0.48-1.23]	0.276	1.06 [0.60-1.86]	0.853	0.89 [0.48-1.64]	0.700
Age	1.04 [1.02-1.06]	**<0.001**	1.04 [1.02-1.07]	**0.002**	1.04 [1.01-1.06]	**0.004**
Diabetes	0.93 [0.57-1.53]	0.778	1.10 [0.65-1.87]	0.719	1.09 [0.65-1.85]	0.740
CLTI	1.10 [0.62-1.93]	0.752	1.17 [0.64-2.13]	0.615	1.21 [0.66-2.21]	0.546
Limb ANGIO score	1.05 [0.98-1.12]	0.150	NA	NA	1.06 [0.98-1.14]	0.129

Foot note: Bold indicates significant results. 95% CI, 95% confidence intervals, CLTI, chronic limb threatening ischemia; NA, not applicable

[a] Risk factors in the model included Aboriginal or Torres Strait Islander status, age, diabetes and CLTI

[b] Risk factors in the model included Aboriginal or Torres Strait Islander status, age, diabetes, CLTI and limb ANGIO score.

Supplementary Table S15: Cox proportional hazard analyses for the association between participant characteristics and **revascularisation** in participants with **chronic limb threatening ischemia**

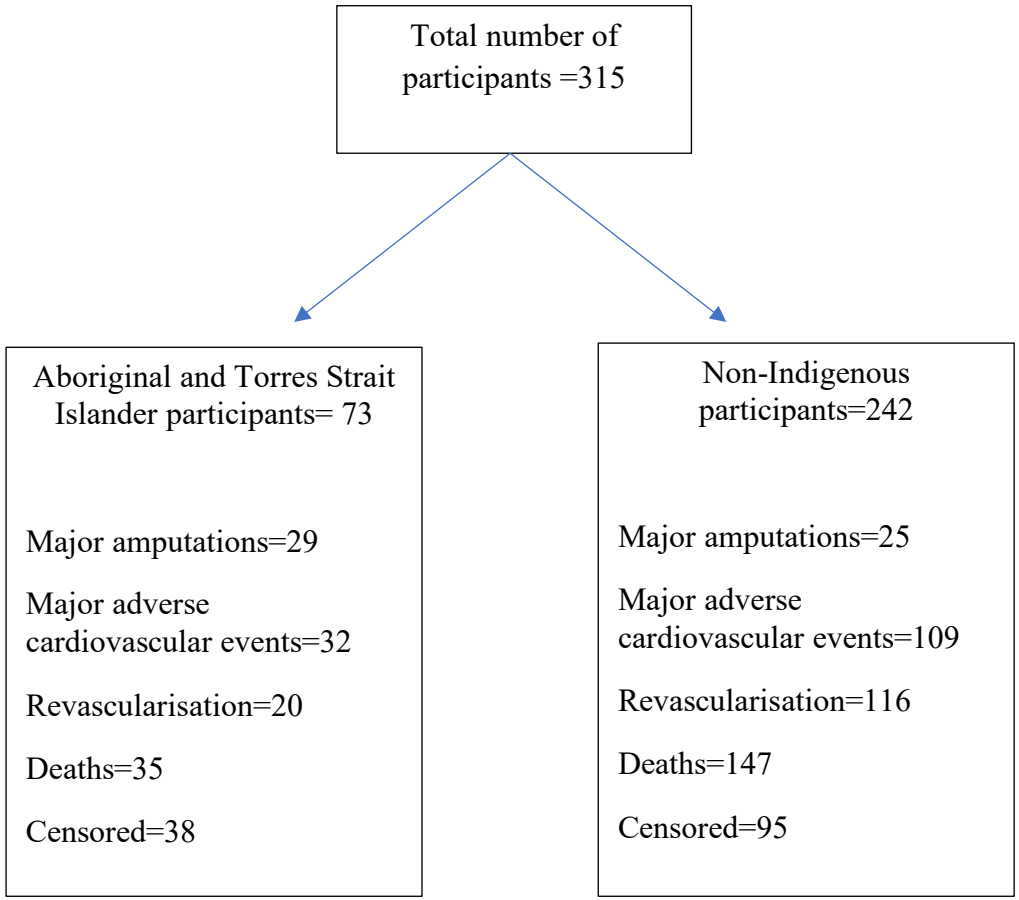
Risk factor	Unadjusted hazard ratio [95% CI]	p-value	Adjusted hazard ratio [95% CI] [a]	p-value	Adjusted hazard ratio [95% CI] [b]	p-value
Aboriginal and Torres Strait Islander status	0.73 [0.39-1.38]	0.332	1.02 [0.47-2.23]	0.964	1.09 [0.49-2.44]	0.826
Age	1.01 [0.99-1.04]	0.324	1.01 [0.98-1.04]	0.629	1.01 [0.98-1.04]	0.526
Diabetes	0.57 [0.31-1.05]	0.072	0.61 [0.32-1.18]	0.142	0.60 [0.31-1.17]	0.136
CLTI	0.66 [0.32-1.33]	0.243	0.71 [0.34-1.51]	0.378	0.71 [0.34-1.50]	0.372
Limb ANGIO score	0.97 [0.89-1.06]	0.540	NA	NA	0.97 [0.88-1.06]	0.475

Foot note: Bold indicates significant results. 95% CI, 95% confidence intervals, CLTI, chronic limb threatening ischemia; NA, not applicable

[a] Risk factors in the model included Aboriginal or Torres Strait Islander status, age, diabetes and CLTI

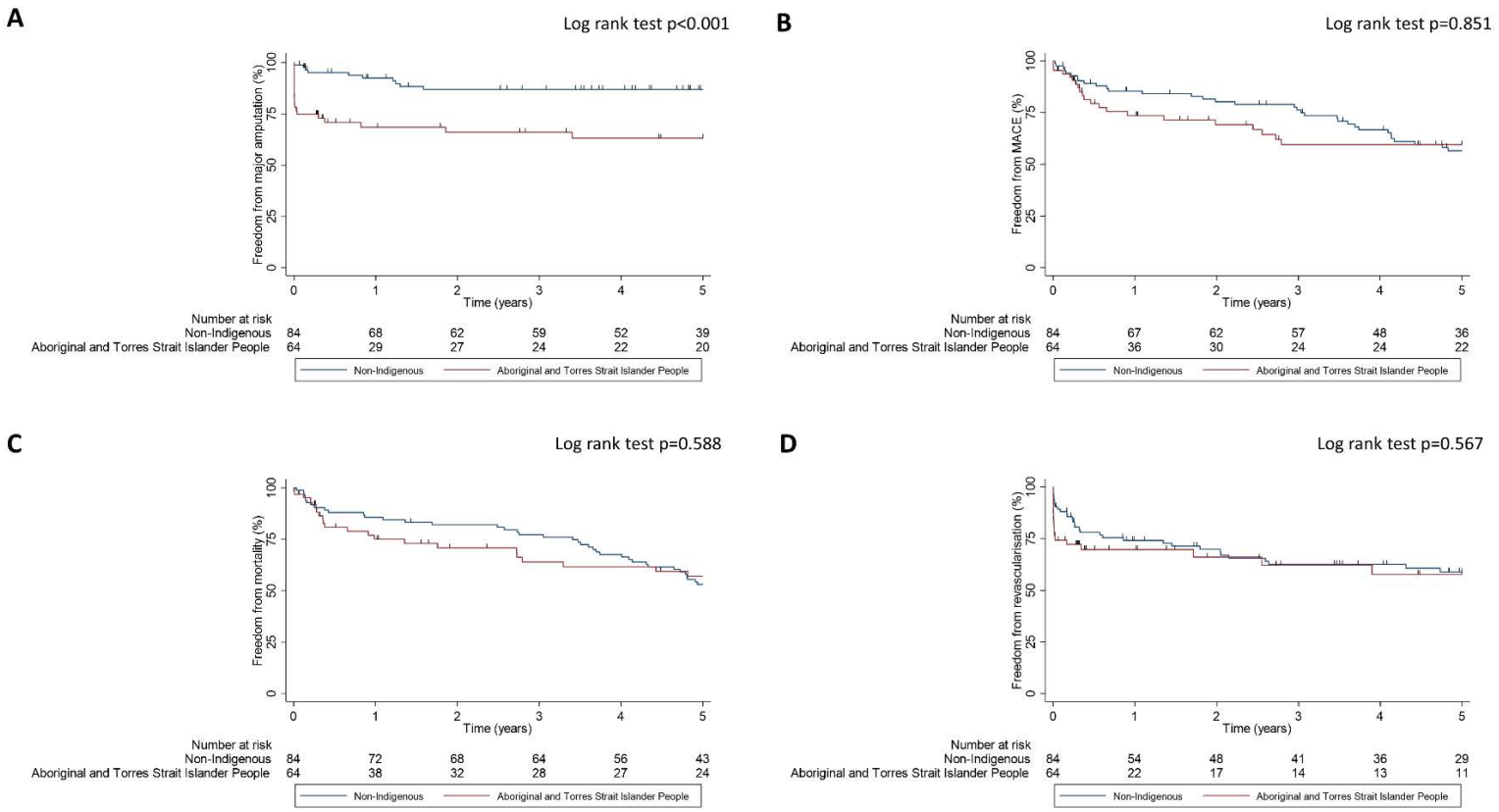
[b] Risk factors in the model included Aboriginal or Torres Strait Islander status, age, diabetes, CLTI and limb ANGIO score.

Supplementary Figure 1



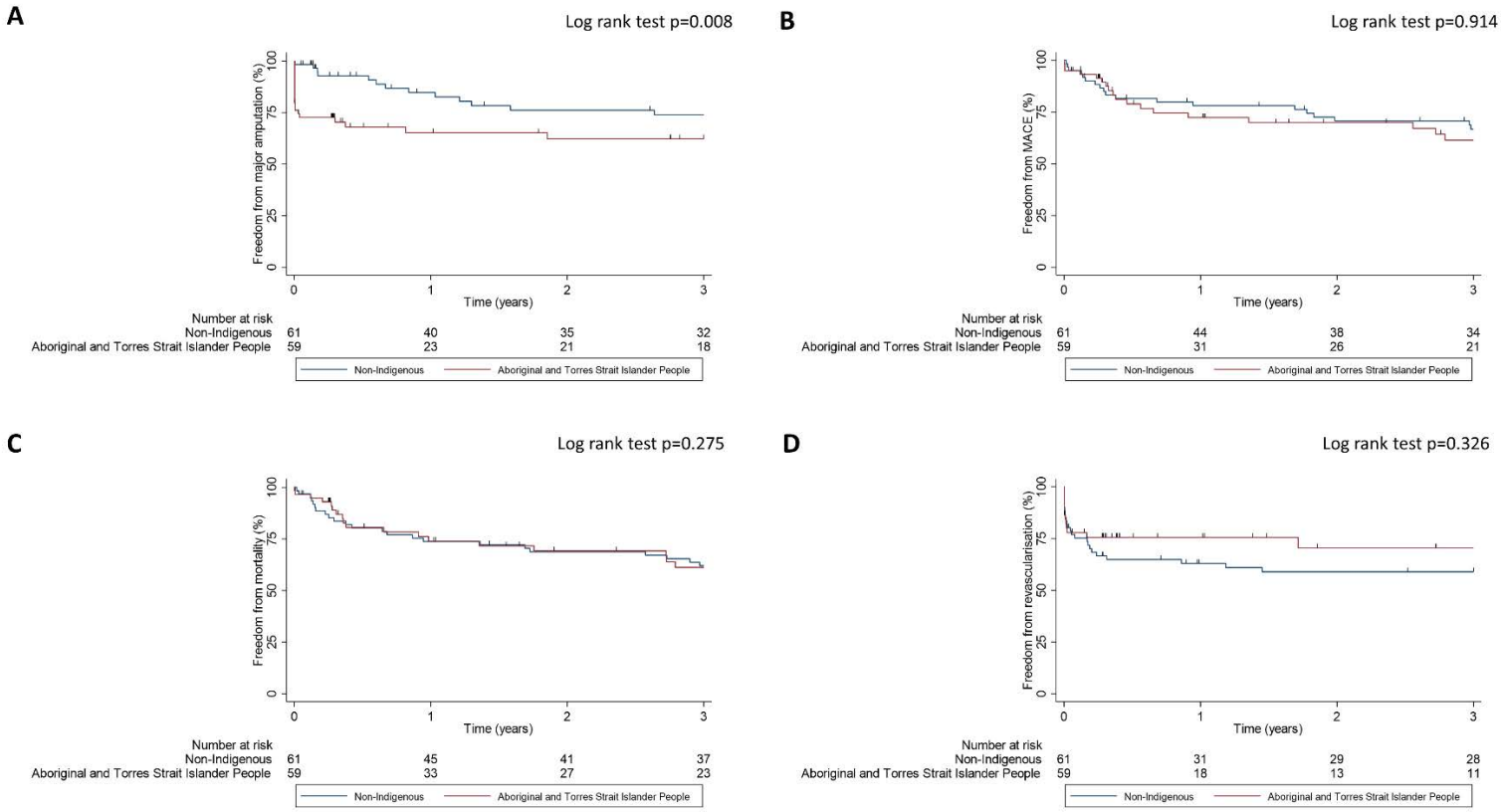
Supplementary Figure 1: Flow diagram of the number of partitionist included in the study and events they experienced over the follow up period by Aboriginal and Torres Strait Islander status

Supplementary Figure 2



Supplementary Figure 2: Kaplan-Meier curve illustrating the cumulative proportion of Aboriginal and Torres Strait Islander participants and non-Indigenous participants with **diabetes**, A; who had a major amputation, B; who had a major adverse cardiovascular event, C; those who had all-cause mortality, D; who had a revascularisation

Supplementary Figure 3



Supplementary Figure 3: Kaplan-Meier curve illustrating the cumulative proportion of Aboriginal and Torres Strait Islander participants and non-Indigenous participants with **chronic limb threatening ischemia,** A; who had a major amputation, B; who had a major adverse cardiovascular event, C; those who had all-cause mortality, D; who had a revascularisation

6. Association between remoteness and ethnicity with major amputation following minor amputation in people with diabetes-related foot disease

Disclosure: This chapter has been submitted to Journal of Vascular Surgery.

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Key words:

Diabetes-related foot disease, peripheral artery disease, remoteness, Aboriginal and Torres Strait Islander ethnicity

Type of Research

Single-centre retrospective cohort study

Key Findings

The study included 534 participants with diabetes following a minor lower limb amputation. One hundred and three participants (19.3%) had major amputation during follow-up. The risk (hazard ratio [95% CI]) of major amputation was not significantly higher in participants from remote areas (0.97, 0.67-1.47) or for Aboriginal and Torres Strait Islander people (HR 1.44, 95% CI 0.96, 2.16). Ischemic heart disease, peripheral artery disease, and osteomyelitis were significant contributors to major amputation.

Take Home Message

Major amputation is very common following minor amputation to treat DFD and the risk of major amputation is increased by ischemic heart disease, peripheral artery disease, and osteomyelitis. People residing in rural and remote locations, and Aboriginal and Torres Strait Islander peoples do not appear to be disproportionately affected compared to those in urban areas and non-Indigenous people respectively.

6.1 Abstract

Introduction

The primary aim was to examine the associations between remoteness and Aboriginal and Torres Strait Islander status with risk of major amputation and death following initial treatment of diabetes-related foot disease (DFD) by a minor amputation. A secondary aim was to identify risk factors for major amputation and death following minor amputation in people with diabetes.

Methods

This study is a retrospective analysis of prospectively collected data of patients who required a minor amputation following DFD at a regional tertiary hospital in Queensland, Australia from 2000 to 2019. Baseline characteristics were collected together with remoteness of residence and ethnicity. Remoteness was classified according to the 2019 Modified Monash Model (MMM) system. Ethnicity was based on self-identification as an Aboriginal and Torres Strait Islander or non-Indigenous person. The outcomes of a major amputation (primary), repeat minor amputation and death were examined using Cox-proportional hazard analyses by remoteness and ethnicity.

Results

A total of 534 participants were included, with 306 (57.3%) residing in metropolitan or regional centres, 228 (42.7%) in rural and remote communities and 144 (27.0%) were Aboriginal or Torres Strait Islander people. During a median (inter quartile range) follow-up of 4.0 (2.1-7.6) years, 103 participants (19.3%) had major amputation, 230 (43.1%) had repeat minor amputation and 250 (46.8%) died. The risk (hazard ratio [95% CI]) of major amputation and death were not significantly higher in participants residing in rural and remote areas (0.97, 0.67-1.47; and 0.98, 0.76-1.26) or those who identified as Aboriginal or Torres Strait Islander people (HR 1.44, 95% CI 0.96, 2.16 and HR 0.89, 95% CI 0.67, 1.18). Ischemic heart disease (IHD) peripheral artery disease (PAD) and osteomyelitis and foot ulceration ($p<0.001$ in all instances) were independent risk factors for major amputation.

Conclusion

Major amputation and death are common following minor amputation to treat DFD and the risk of major amputation is increased by IHD, PAD and osteomyelitis. Remoteness or Aboriginal and Torres Strait Islander ethnicity were not associated with subsequent major amputations.

6.2 Introduction

Diabetes-related foot disease (DFD), such as foot ulcers, infections, and gangrene, affects approximately one-third of patients with diabetes over their lifetime (1, 2). Minor amputation (distal to the ankle joint) is frequently required in the treatment of DFD (3, 4), with individuals that undergo minor amputations reported to have reduced quality of life (5, 6) and frequently develop recurrent DFD requiring further amputation (7).

A UK study found that 46% of patients required a re-amputation (minor or major) within 2 years of their first lower extremity amputation for DFD (7). A recent meta-analysis estimated that the rate of re-amputation was 19% (inter quartile range, IQR, 5% to 32%) at one year and 37% (IQR 27 to 47%) at 5 years following a minor amputation (8). A US study reported a major amputation rate of 10% within one year following an ipsilateral toe amputation following DFD (9) and a recent meta-analysis estimated that 30% (95% CI 24% to 37%) of people undergoing trans-metatarsal amputation for DFD, later required a major amputation during follow up (10). Patients requiring a minor amputation also have a risk of mortality of approximately 10% per year (11, 12). A previous study reported that the possible risk factors for a repeat amputation following an index amputation in dysvascular limb include chronic obstructive pulmonary disease, abnormal ankle brachial pressure index, elevated white cell count and previous revascularisation (13), but specific risk factors for DFD related re-amputations are not clearly understood.

A recent population-based cohort study conducted on patients with diabetes in Italy reported that respective mortality rates at 1 and 4 years were 33% and 65% following major amputations and 18% and 45% following minor amputations. Significant risk factors for mortality were age ≥65, diabetes-related cardiovascular complications, and chronic renal disease for patients with minor LEA, and age ≥75 years, chronic renal disease, and usage of antidepressant for participants with major amputation in patients with diabetes (14). A recent

systematic review investigating re-amputation rates in people with diabetes stresses the unavailability of studies conducted over long periods of time (8). It is noteworthy that burden of DFD is substantially greater in rural and remote, and First Nation's populations (15, 16). It is also noteworthy that Aboriginal and Torres Strait Islander Australians have a 3-6-fold increased likelihood of developing a DFD complication compared to non-Indigenous Australians following uncontrolled diabetes over longer periods, smoking and peripheral artery disease (PAD) (17).

No prior study has investigated whether remoteness or Aboriginal and Torres Strait Islander status were associated with risk of major amputation following a minor amputation. The primary aim of this study was to examine the association between remoteness with risk of major amputation, repeat minor amputation and death following initial treatment of DFD by a minor amputation. The secondary aim was to examine the association of same outcomes with Aboriginal and Torres Strait Islander status. Further, we aimed to identify additional risk factors associated with the above outcomes and the predictive ability of the included risk factors in classifying major amputations in both instances.

6.3 Methods

6.3.1 Study design and data source

This was a retrospective analysis of prospectively collected data of patients who were admitted to a regional tertiary hospital in Queensland Australia (Townsville University Hospital, TUH) for a minor amputation following DFD, between the 1st of January 2000 and 31st of December 2019. Patients were followed-up until 31st of December 2020. Data were obtained from hospital records. Ethics approval was obtained from the Townsville Hospital and Health Service Human Research Ethics Committee [HREC/13/QTHS/125](18, 19). This included approval for a patient consent waiver that was required because of the retrospective

design. A five-member Aboriginal and Torres Strait Islander reference committee was consulted for the approval of the research as previously described (20).

6.3.2 Population

For inclusion, participants had to have undergone a minor amputation following DFD during the study period, been previously diagnosed with diabetes and have data available on place of residence and Aboriginal and Torres Strait Islander status. Patients with previous major amputation (unilateral or bilateral), those who underwent an amputation procedure in the absence of diabetes, those who were <18 years of age and those with missing patient records were excluded. After identification of the participant through ORMIS, the relevant participant's hospital admission record during which the participant had the index minor amputation was accessed to obtain necessary data.

Minor amputation was defined as amputation distal to the ankle joint (3). Toe amputations were defined as amputation of a toe at or distal to the metatarso-phalangeal joint. A trans-metatarsal amputation was defined as an amputation across metatarsal bones. Forefoot amputation was defined as an amputation distal to the ankle joint at or proximal to tarso-metatarsal joints (3). Participants were identified using operating rooms management systems (ORMIS) as previously described (15). All patients undergoing any amputation procedure in the TUH are recorded in this system.

6.3.3 Potential risk factors

Participants' baseline potential risk factors were obtained from hospital admission records at the time of the index minor amputation. These included age, sex, smoking, diabetes, hypertension, ischaemic heart disease (IHD), peripheral artery disease (PAD), end stage renal failure (ESRF), Aboriginal and Torres Strait Islander status and past history of minor amputation. Current smoking was defined as active smoking within the last month as per

documented in the admission record at the time of index admission (21). Diabetes and hypertension were defined by a documented medical diagnosis at the time of hospital admission (21). IHD was defined as a documented history of myocardial infarction, angina or previous treatment of IHD (22). PAD was defined as ankle brachial pressure index (ABPI) <0.9, previous peripheral revascularisation and/ or imaging identified stenosis or occlusion of lower limb arteries as previously described as per participants records during index admission (22). ESRF was defined as requirement for dialysis. Primary diagnosis for hospital admission for index minor amputation was classified as foot ulcer, soft tissue infection, osteomyelitis or gangrene. In the instance where there is a combination of the above presentations all relevant data were included. For example, if a participant had a foot ulcer and soft tissue infection, both data were included in the analysis. Aboriginal and Torres Strait Islander status was based on self-identification by patients at the time index minor amputation for DFD.

6.3.4 Remoteness

Remoteness was classified according to the 2019 Modified Monash Model (MMM) system (23) using the post code of the participants which has previously been associated with the degree of inequality of access to healthcare (24). There were no participants from MMM1 category. Regional areas, such as Townsville and Mackay, were classified as MMM2, and other regional areas, medium-sized towns, small towns, remote and very remote towns were classified as MMM categories 3 to 7 respectively. For analyses MMM categories 1 to 2 and 3 to 7 were separately grouped.

6.3.5 Assessment of outcomes

The primary outcome was a major amputation, defined as proximal to the ankle, in either leg during the follow-up period (25). Other outcomes include requirement of a repeat minor amputation in either leg, or all-cause mortality. Outcome events were obtained through

ORMIS (amputation data) and subsequent review of participants' medical records. The current TUH hospital recording system allows you to access medical records from all the hospitals in the region and we were able to identify all outcomes through this system. Participants were censored at the time of their death, or the date of last follow-up identified through the last hospital record (in-patient or out-patient), if no event was experienced.

6.3.6 Sample size calculation

Since this study was a retrospective observational study, the sample size was informed by the number of participants available rather than a pre-specified sample size estimate. Prior to analysis the available sample size was considered based on the plan to assess the association of remoteness with the requirement for major amputation in an adjusted Cox proportional hazard analysis. The Cox proportional hazard analysis was planned to include up to 10 covariates of which some of the variates such as MMM Classification variable had multiple permutations. Based on a prior study it was estimated that the major amputation rate would be at least 40% during a minimum two-year median follow-up (7). Based on this, at least 250 individuals would lead to a well powered analysis considering the requirement to attain at least 10 outcome events per degree of freedom according to Monte Carlo simulations (26).

6.3.7 Statistical Analysis

Histograms, skewness and kurtosis tests suggested that continuous data were not normally distributed. Thus, continuous data were presented as median and inter-quartile range and compared between groups using the Mann-Whitney U test. Nominal and categorical data were presented as counts and percentage (unless otherwise stated) and compared using the Pearson's chi-squared test. Multivariate Cox proportional hazard analyses were performed to assess the association between MMM categories with major amputation, repeat minor amputations and all cause death after adjusting for age, sex, smoking, IHD, PAD, ESRF and

osteomyelitis. Similar analyses were conducted separately for Aboriginal and Torres Strait Islander status and major amputation, repeat minor amputations and all cause death after adjusting for age, sex, smoking, IHD, PAD, ESRF and osteomyelitis. Selection of variables for adjustment was based on those that have been established as risk factors for events or bivariate comparison of variables that were significantly different between groups ($p<0.05$). All model assumptions were met. Factors that were highly correlated were not included in the same model but in different models. Cox regression model outcomes were reported as hazard ratios (HR) and 95% confidence intervals (CI). The ability of the model to predict the respective outcomes was assessed using concordance index (c-index). Individual contribution of predictor variables was assessed by calculating the Likelihood Ratio Test (LRT) statistic. LRT was calculated as twice the difference of log likelihood values of full cox regression model versus a reduced model where one predictor variable was removed to determine its contribution to the outcome prediction. The significance was determined by comparing the obtained LRT values against the difference in degrees of freedom in the critical value of Chi-squared distribution. In our analyses, since one variable was removed at a time, the change in degrees of freedom was 1 corresponding to critical value of 3.84 in the chi-squared distribution table. LRT values greater than the critical value were considered to be significantly important in predicting the outcomes. Additionally, Kaplan-Meier curves performed to graphically represent the probability of events over time and statistically represented using log rank tests to compare the events between the different population groups assessed. Data were analysed using SPSS v29 (IBM, Armonk, NY) software package.

6.4 Results

6.4.1 Characteristics of participants

A total of 534 participants were included following an index admission for 504 toe amputations (94.4%), 24 trans-metatarsal amputations (4.5%) and 6 mid-tarsal amputations (1.1%). Three hundred and six participants (57.3%) resided in MMM categories 1 or 2, 228 (42.7%) in MMM categories 3-7 locations. One hundred and forty-four (27.0%) participants identified as Aboriginal and Torres Strait Islanders.

Aboriginal and Torres Strait Islanders people were significantly more likely to be residing in MMM categories 3-7 than non-Indigenous participants (Table 1). Other baseline demographic factors or risk factors were not different between those presenting from MMM categories 1, 2 or those presenting from MMM categories 3-7. Aboriginal and Torres Strait Islander participants were also significantly younger, more likely to be male, live in MMM categories 3-7, have ESRF and be admitted with gangrene, ulceration or infection, but less likely to have had previous revascularisation surgery compared to non-Indigenous participants (Table 2).

Median (IQR) follow-up for the cohort was 4.0 (2.1 to 7.6) years. One hundred and three participants (19.3%) had a major amputation and 230 (43.1%) had a repeat minor amputation. A total of 110 major amputations and 340 minor amputations were performed. Eighty-four participants (81.6%) underwent a major amputation on the ipsilateral side while nineteen (18.4%) had a major amputation on the contralateral side. A total of 250 participants (46.8%) died during follow up. There were no significant differences in the rates of major amputation, minor amputation, or mortality between participants from regional cities (MMM categories 1 to 2) and those from more rural localities (MMM categories 3-7), (log rank test $p > 0.05$ in all instances) (Figure 1). Outcomes were similar for Aboriginal and Torres Strait Islander and non-Indigenous Australians (log rank test p values >0.05 in all instances) (Figure 2).

Table 6-1 Risk factors at recruitment in participants who were admitted for an index minor amputation based on remoteness

	MMMC 1&2 Urban or Regional centres (n=306)	MMMC 3-7 Regional, rural and remote towns (n=228)	Significance
Age	61.00 [52.00-71.00]	62.00 [53.00-72.00]	0.406
Male sex	215 (70.3%)	155 (68.0%)	0.572
Aboriginal and Torres Strait Islanders	70 (22.9%)	74 (32.5%)	**0.014****
Smoking	161 (52.6%)	121 (53.1%)	0.917
Hypertension	233 (76.1%)	158 (69.3%)	0.077
IHD	124 (40.5%)	93 (40.8%)	0.951
PAD	102 (33.3%)	88 (38.6%)	0.209
ESRF	31 (10.1%)	23 (10.1%)	0.987
Past history of minor amputation	23 (7.5%)	18 (7.9%)	0.871
Past history of revascularisation			
Endovascular	38 (12.4%)	32 (14.0%)	0.584
Open vascular	34 (11.1%)	36 (15.8%)	0.113

Immediate presenting problem			
Osteomyelitis			
Gangrene	90 (29.4%)	56 (24.6%)	0.214
Ulcer	61 (19.9%)	45 (19.7%)	0.955
Infection	253 (82.7%)	181 (81.6%)	0.335
	260 (85.0%)	186 (81.6%)	0.297

Foot note

MMMC; Modified Monash Model Classification, IHD; ischemic heart disease, PAD; peripheral artery disease, ESRF; end stage renal failure

** More Aboriginal and Torres Strait islander people presented from remote locations.

Bold indicates significant results

Table 6-2 Characteristics of participants by their ethnicity

	Aboriginal and Torres Strait Islanders (n=144)	Non-Indigenous patients (n=390)	Significance
Age	54.17 [52.23-56.11]	64.40 [63.13-65.64]	**<0.001**
Male sex	80 (55.6%)	290 (74.4%)	**<0.001 (FET)**
Rurality			**<0.001**
MMMC 1 and 2	70 (48.6%)	236 (60.5%)	
MMMC 3 to7	74 (51.4%)	154 (39.5%)	
Smoking	80 (55.6%)	202 (51.2%)	0.440
Hypertension	109 (75.7%)	282 (72.3%)	0.433
IHD	51 (35.4%)	166 (42.6%)	0.136
PAD	48 (33.3%)	142 (36.4%)	0.510
ESRF	24 (16.7%)	30 (7.7%)	**0.002**

Past history of minor amputation	13 (9.0%)	28 (7.2%)	0.477
Past history of revascularisation Endovascular Open vascular	 10 (6.9%) 9 (6.3%)	 60 (15.4%) 61 (15.6%)	 **0.010** **0.004**
Immediate presenting problem Osteomyelitis Gangrene Ulcer Infection	 47 (32.6%) 19 (13.2%) 126 (87.5%) 144 (89.6%)	 99 (25.4%) 87 (22.3%) 308 (79.0%) 317 (81.3%)	 0.095 **0.019** **0.025** **0.022**

Foot note

MMMC; Modified Monash Model Classification, IHD; ischemic heart disease, PAD; peripheral artery disease, ESRF; end stage renal failure

Bold indicates significant results

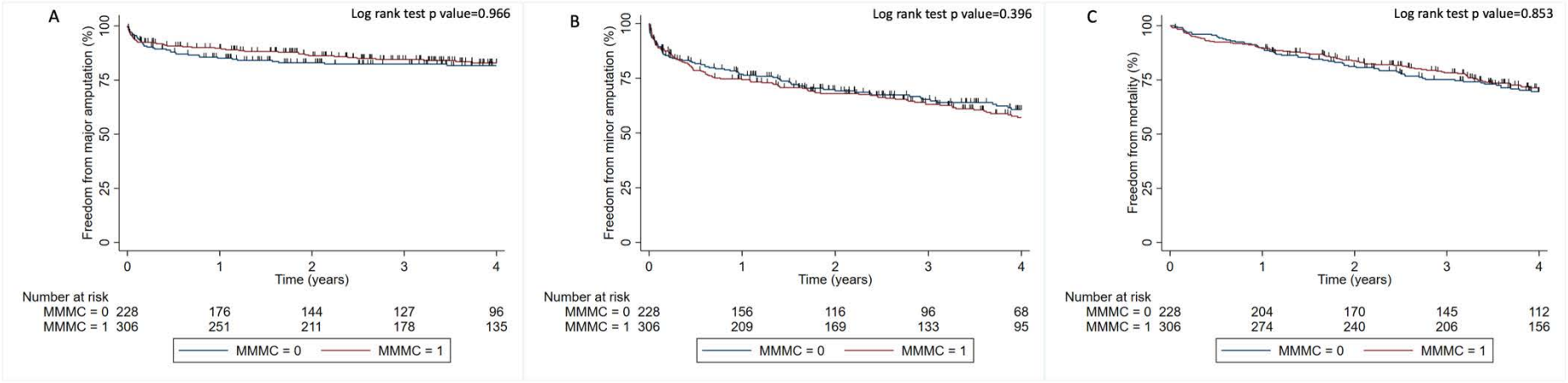

Figure 6-1 Kaplan-Meier curves by remoteness

Kaplan-Meier curve illustrating the freedom from events in participants presenting from large towns or cities (MMMC=1) and small towns or reginal towns (MMMC=0) with an index minor amputation A; Major amputation, B; Minor amputation, C; All-cause mortality. MMMC: Modified Monash Model Classification.

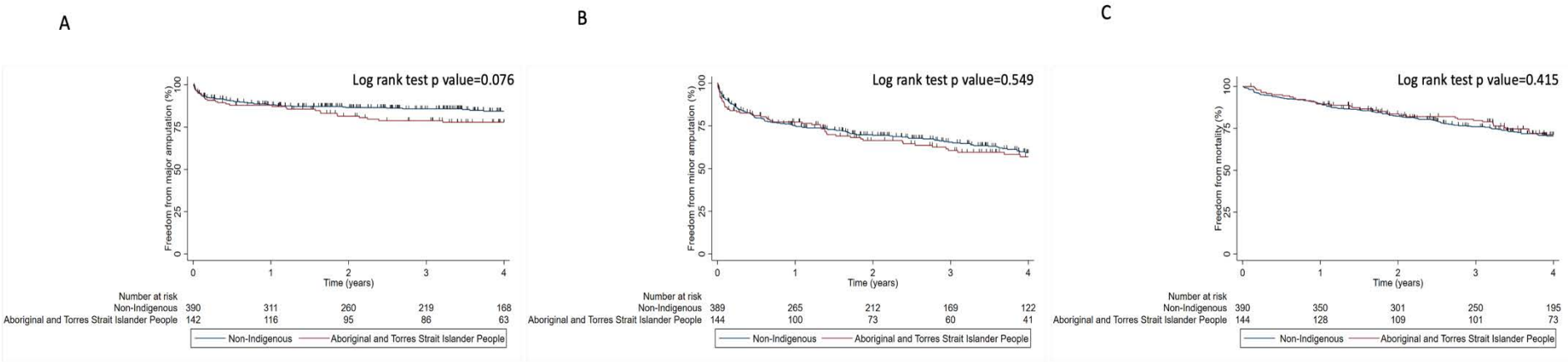

Figure 6-2 Kaplan-Meier curves by ethnicity

Kaplan-Meier curve illustrating the freedom from events in Aboriginal and Torres Strait Islander and non-Indigenous participants with an index minor amputation A; Major amputation, B; Minor amputation, C; All-cause mortality

6.4.2 Association of remoteness and major amputation

Note: two separate analyses were conducted, and two separate cox regression models were built including other risk factors with remoteness and Aboriginal and Torres Strait Islander status following the significant association between the two factors (Table 1).

Unadjusted analyses suggested no association between remoteness of residence and risk of major amputation (HR 0.97, 95% CI 0.67 to 1.47, p=0.966). After adjusting for age, sex, smoking, IHD, PAD, ESRF, osteomyelitis and foot ulcer the results remained unchanged (HR 0.96, 95% CI 0.64 to 1.42, p=0.826) (Table 3). Likelihood ratio test of the risk factors included in the model suggested that IHD, PAD, osteomyelitis and presence of ulcer were significant predictors of major amputation in people living in remote areas (Supplementary Table S1). However, the cox regression model did not achieve a good discrimination to predict the outcomes (c-index 0.505, 95% CI 0.442, 0.569) (Supplementary Table S2). Visual representation of the model illustrating the major amputation and remoteness is provided in the Kaplan-Meier curve (Figure 1A) and the analysis suggest that there was no significant difference between major amputation rates over time based on remoteness (Log rank test p value=0.966).

Table 6-3 Association of remoteness with major amputation following a minor amputation to treat diabetes-related foot disease

Risk factor	Univariate analysis HR [95% CI]	P value	Multivariate analysis		Likelihood ratio test statistic
Age	1.00 [0.99-1.02]	0.624	0.99 [0.98-1.01]	0.668	NA
Sex	1.14 [0.76-1.78]	0.540	1.16 [0.76-1.75]	0.492	0.910
Smoking	1.05 [0.71-1.55]	0.797	0.89 [0.60-1.31]	0.549	0.294
IHD	2.15 [1.46-3.17]	**<0.001**	1.81 [1.19-2.74]	**0.005**	29.484
PAD	2.13 [1.45-3.13]	**<0.001**	2.53 [1.69-3.78]	**<0.001**	21.694
ESRF	1.85 [1.07-3.20]	**0.029**	1.37 [0.78-2.41]	0.276	2.642
Osteomyelitis	2.61 [1.77-3.851]	**<0.001**	2.83 [1.90-4.23]	**<0.001**	54.518
Ulcer	4.71 [2.06-10.77]	**<0.001**	5.15 [2.25-11.81]	**<0.001**	48.76
Remoteness	0.97 [0.67-1.47]	0.966	0.96 [0.64-1.42]	0.826	2.515

IHD; ischemic heart disease, PAD; peripheral artery disease, ESRF; end stage renal failure, NA; not applicable. Bold indicates significant results

6.4.3 Association of Aboriginal and Torres Strait Islander status and major amputation

Unadjusted analyses suggested no association between Aboriginal and Torres Strait Islander status and risk of major amputation (HR 1.44, 95% CI 0.96 to 2.16, p=0.078). After adjusting for age, sex, smoking, IHD, PAD, ESRF, osteomyelitis and foot ulcer the results were unchanged (HR 1.29, 95% CI 0.83-2.00, p=0.096) (Table 4). Likelihood ratio test of the risk factors included in the model suggested that IHD, PAD, osteomyelitis and foot ulcer were significant predictors of major amputation in people from Aboriginal and Torres Strait Island (Supplementary Table S3). However, the cox regression model did not achieve a good discrimination to predict the outcomes (c-index 0.541, 95% CI 0.477, 0.606). Visual representation of the model illustrating the major amputation and Aboriginal and Torres Strait Islander status is provided in Figure 2A and the analysis suggest that there was no significant difference between major amputation rates over time based on Aboriginal and Torres Strait Islander status (Log rank test p value=0.076).

6.4.4 Risk factors for repeat minor amputation

None of the risk factors were independently associated with repeat minor amputation).

6.4.5 Risk factors for deaths

None of the risk factors were independently associated with deaths.

Table 6-4 Association of ethnicity with major amputation following a minor amputation to treat diabetes-related foot disease

Risk factor	Univariate analysis, HR [95% CI]	P value	Multivariate analysis		Likelihood ratio test statistic
Age	1.00 [0.99-1.02]	0.624	1.00 [0.98-1.02]	0.917	NA
Sex	1.14 [0.76-1.78]	0.540	1.10 [0.72-1.69]	0.650	0.910
Smoking	1.05 [0.71-1.55]	0.797	0.89 [0.60-1.32]	0.567	0.294
IHD	2.15 [1.46-3.17]	**<0.001**	1.83 [1.21-2.77]	**0.005**	29.484
PAD	2.13 [1.45-3.13]	**<0.001**	2.51 [1.68-3.76]	**<0.001**	21.694
ESRF	1.85 [1.07-3.20]	**0.029**	1.35 [0.77-2.38]	0.298	2.642
Osteomyelitis	2.61 [1.77-3.851]	**<0.001**	2.79 [1.87-4.16]	**<0.001**	54.518
Ulcer	4.71 [2.06-10.77]	**<0.001**	5.02 [2.19-11.51	**<0.001**	48.76
Aboriginal and Torres Strait Islander status	1.44 [0.96-2.16]	0.078	1.29 [0.83-2.00]	0.258	0.096

IHD; ischemic heart disease, PAD; peripheral artery disease, ESRF; end stage renal failure, NA; not applicable. Bold indicates significant results

6.5 Discussion

This study is the first to assess the impact of remoteness on the outcome of people with diabetes related minor amputations and their subsequent outcomes; major amputations, repeat minor amputations, and all-cause mortality over a period of 20 years. The setting in North Queensland, Australia is well suited for this based on the geographic dispersion of the population. This study included 534 participants with diabetes following an index minor amputation with 27.0% identifying as Aboriginal and/or Torres Strait Islanders. We found that one fifth of the participants underwent a major amputation and about half of participants died during the follow up period. There were no significant differences between the rates of major amputation or other outcomes by remoteness or by Aboriginal and Torres Strait Islander status which may reflect equivalent care given to participants presenting from diverse backgrounds (27). IHD, PAD, presence of osteomyelitis or foot ulcer during index minor amputation were independent predictors of major amputations, regardless of place of residence or Aboriginal and/or Torres Strait Islander identity, which has been shown in previous studies (15, 16).

More than one million people undergo a lower extremity amputation each year following DFD globally (28). Such amputations cause significant morbidity and mortality (8, 29). A recent systematic review reported that global rates of hospital admission for all DFD conditions are considerably higher compared to those for amputations alone (30). In the USA the rate of non-traumatic limb amputation increased by 50% between 2009 to 2015 (31). It is also noteworthy that repeat amputations 1-year after an initial amputation were reported to be high as 26% in a study of 71300 participants (29). Despite the availability of studies investigating the overall rates of amputations (32), there were no studies conducted to look at subsequent major amputation following an index minor amputation in Australia.

In our study, the median follow-up period was 4 years and we noted that 46.8% of the participants died during the study which indirectly suggests that these participants are a

debilitated group of participants with concurrent multiple co-morbidities. Similar results have been shown in participants with diabetes in USA (33). This warrants the need to further investigate the impact of the prevention of DFD and related minor amputations on subsequent amputations and deaths associated DFD (8, 34).

According to our study the significant predictive factors of major amputation were IHD, PAD, osteomyelitis and foot ulcers. These factors continued to remain significant in different cox regression models we created and was proven to be significant contributors to the overall model. IHD, PAD and osteomyelitis were weak classifiers of a subsequent major amputation following a minor amputation for DFD based on the c-index. Previous studies have confirmed that PAD and osteomyelitis are major predictors of subsequent major amputation in patients with diabetes and foot ulcers (35, 36).

One of the key findings in our study is the association of PAD with subsequent major amputations. PAD remained as a risk factor in models that were adjusted for multiple risk factors including remoteness and Aboriginal and Torres Strait Islander status. In all instances the hazard ratio indicated that those with PAD were twice as likely of a subsequent major amputation in this cohort of patients with diabetes. This finding is similar to results reported in previous studies that suggest Aboriginal and Torres Strait Islander participants with PAD tends to have higher rates of major amputations (15, 20). The underlying reason for this risk associated with PAD among Aboriginal and Torres Strait Islanders maybe attributed to the relatively low levels of previous revascularisation procedures in these participants (Table 2) following tibial vessel disease. In practice, revascularisation of distal vessel disease is considered to be more challenging (37). It is also important to note that ESRF was an independent predictor of major amputation and is common in participants with poorly controlled diabetes following diabetic nephropathy (38). There is a high incidence of IHD

among participants with PAD as the underlying pathology is similar and this may explain the association of IHD with major amputation in our cohort of participants (39).

This is the first study to look at subsequent minor amputations by remoteness or by Aboriginal and Torres Strait Islander status in an Australian setting. Even though a minor amputation is considered to be less detrimental to the patient compared to a major amputation, the social, psychological and physical debilitation of such an amputation is immense and is similar to those with active DFD (40, 41). In our study 43.1% participants had a repeat minor amputation. Measures should be implemented to uplift the patient as a whole and improve all aspects of care to reduce the subsequent minor amputations among patients with diabetes (42).

A number of previous studies have reported higher major amputation rates in rural locations (43). In contrast, our study found that there is no significant difference between the rates of minor amputation rates or major amputation rates between those who present from remote localities and those who present from larger cities. This may reflect the massive effort put in by the state to improve diabetes foot care in remote and rural localities by implementing continuous podiatry services, telehealth services and continuous patient education (27).

The current study has a number of strengths and limitations. The strengths include the large sample size and the inclusion of 27% Aboriginal and Torres Strait Islander participants in a single study compared to previous studies published in this area of research (15, 16). Limitations of the study include classification of remoteness using Modified Monash Model, a classification unique to the Australian setting, retrospective study design and possibility of missing outcomes such as a major amputation being carried out in a different state that may not be accessible through TUH hospital data base following relocation of the participant. It is also important to note that these findings should be generalised with caution to other regions

of Australia or any parts of the world where delivery of health care and composition of the population may be different.

6.6 Conclusion:

Major amputation and death are very common following minor amputation to treat DFD. Remoteness and Aboriginal and Torres Strait Islander status was not associated with subsequent major amputation following an index minor amputation for DFD which can potentially be attributed to uniform access and utilisation of care delivered to different populations. Risk of major amputation is increased by IHD, PAD, osteomyelitis and foot ulceration. IHD, PAD and osteomyelitis were weak classifiers of a subsequent major amputation following a minor amputation.

6.7 Acknowledgments

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6.8 Conflict of interest statement/Funding

The authors have no conflicts of interest to declare.

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6.10 Supplementary Material

Supplementary Table S1: Contribution of individual risk factors for the overall cox regression model that included rurality

Risk factor removed at each step	-2 Log Likelihood value of each model	Log Likelihood ratio following comparison with the previous model	Risk factor contribution: significant or not
Model with all factors	1141.766		
Residency status	1141.814	0.096	Not significant
Ulcer	1166.194	48.76	**Significant**
Osteomyelitis	1193.453	54.518	**Significant**
ESRF	1194.774	2.642	Not significant
PAD	1205.621	21.694	**Significant**
IHD	1220.363	29.484	**Significant**
Smoking	1220.510	0.294	Not significant
Sex	1220.965	0.910	Not significant
Age	NA		

Note: According to the Chi-square distribution table, the critical value for distribution of one degree of freedom is 3.84, which is the significance level. After removal of one factor from the model if the Log Likelihood ratio value becomes higher than the critical value of 3.84, that particular factor is considered to have contribute significantly to the overall model.

IHD; ischemic heart disease, PAD; peripheral artery disease, ESRF; end stage renal failure, NA; not applicable

Supplementary Table S2: Contribution of individual risk factors for the overall cox regression model that included Aboriginal and Torres Strait Islander status

Risk factor removed at each step	-2 Log Likelihood value of each model	Log Likelihood ratio following comparison with the previous model	Significant or not
Model with all factors	1140.556		
Aboriginal and Torres Strait Islander status	1141.814	2.515	Not significant
Ulcer	1166.194	48.76	**Significant**
Osteomyelitis	1193.453	54.518	**Significant**
ESRF	1194.774	2.642	Not significant
PAD	1205.621	21.694	**Significant**

IHD	1220.363	29.484	**Significant**
Smoking	1220.510	0.294	Not significant
Sex	1220.965	0.910	Not significant
Age	NA	NA	NA

Note: According to the Chi-square distribution table, the critical value for distribution of one degree of freedom is 3.84, which is the significance level. After removal of one factor from the model if the Log Likelihood ratio value becomes higher than the critical value of 3.84, that particular factor is considered to have contribute significantly to the overall model.

IHD; ischemic heart disease, PAD; peripheral artery disease, ESRF; end stage renal failure, NA; not applicable

Supplementary Table S3: C statistic or the area under the curve of receiver operating characteristic curves for each risk factor and its ability to predict the outcome of a major amputation among participants who underwent a minor amputation following diabetes-related foot disease

Risk factor	c-index [95% confident intervals]	P value	Predictive ability
Age	0.494 [0.431-0.558]	0.860	failed
Sex	0.531 [0.467-0.595]	0.343	failed
Smoking	0.495 [0.432-0.559]	0.884	failed

IHD	0.601 [0.539-0.664]	**0.002**	poor
PAD	0.601 [0.537-0.664]	**0.002**	poor
ESRF	0.526 [0.461-0.590]	0.429	failed
Osteomyelitis	0.614 [0.549-0.678]	**<0.001**	poor
Ulcer	0.577 [0.519-0.635]	**0.017**	failed
Residency status	0.505 [0.442-0.569]	0.871	failed
Aboriginal and Torres Strait Islander Status	0.541 [0.477-0.606]	0.204	failed

Note: Predictive ability of a risk factor based on the area under the curve: 0.9-1; excellent, 0.8-0.9; good, 0.7-0.8; fair, 0.6-0.7; poor and <0.6; failed.

IHD; ischemic heart disease, PAD; peripheral artery disease, ESRF; end stage renal failure

Bold indicates significant results

7. Meta-analyses of randomised controlled trials reporting the effect of home foot temperature monitoring, patient education or offloading footwear on the incidence of diabetes-related foot ulcers.

Short Title: Systematic review and Diabetic Foot Ulcers

Disclosure: This chapter has been submitted to the journal "Diabetic Medicine"

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What is already known?

- Diabetes-related foot ulcers are common and precipitated by high plantar pressures that stimulate localised foot inflammation and subsequent ulcer development.
- Previous meta-analyses have suggested that home foot temperature monitoring and offloading footwear, but not patient education, reduce diabetic foot ulcers incidence.

New Findings

- This meta-analysis incorporated data from 17 randomised clinical trials including 2 not included in previous pooled data analyses.
- Offloading footwear (Odds ratio [OR] 0.48, 95% confidence interval [CI] 0.29 to 0.80, n=1438) and home foot temperature monitoring (OR 0.51, 95% CI 0.31 to 0.84, n=468) but not patient education (OR 0.59, 95% CI: 0.29-1.20, n=823) reduced the incidence of diabetes-related foot ulcers.
- Findings for offloading footwear but not home foot temperature monitoring were consistent in sensitivity analyses.

Impact on clinical practice

- People at high-risk of diabetes-related foot ulcers should be offered offloading footwear. Home foot temperature monitoring appears efficacious but larger trials are needed.

7.1 Abstract

Background: The aim of this study was to perform an up-to-date systematic review and meta-analysis of randomised controlled trials (RCTs) examining the efficacy of home foot temperature monitoring, patient education and offloading footwear in reducing the incidence of diabetes-related foot ulcers.

Methods: A literature search was performed using MEDLINE, PubMed, CINAHL, Scopus and Cochrane databases to identify relevant original studies. Meta-analyses were performed using intention-to-treat principals for worst (main analysis) and best (sub-analysis) case scenarios. Leave-one-out sensitivity analyses were used to assess the consistency of findings. The study was registered in PROSPERO (Registration number: CRD42019135226).

Results: Out of 7,575 unique records, seventeen RCTs involving 2729 participants were included. Four tested home foot temperature monitoring (n=468), six examined patient education (n=823) and seven assessed offloading footwear (n=1438). Participants' who performed home foot temperature monitoring (Odds ratio [OR] 0.51, 95% confidence interval [CI] 0.31 to 0.84, n=468) and those provided offloading footwear (OR 0.48, 95% CI: 0.29 to 0.80, n=1438) were less likely to develop a diabetes-related foot ulcer. Patient education programs did not significantly reduce diabetes-related foot ulcer incidence (OR 0.59, 95% CI: 0.29-1.20, n=823). Sensitivity analyses suggested that offloading footwear findings were consistent, but home foot temperature findings were dependent on the individual inclusion of one trial. All RCTs had either high or unclear risk of bias.

Conclusion: This meta-analysis suggests that offloading footwear is effective in reducing the incidence of diabetes-related foot ulcers. Home foot temperature monitoring also appears beneficial but larger trials are needed.

7.2 Introduction

Diabetes-related foot ulcers are the commonest presentation of diabetes-related foot disease and a leading cause of hospitalisation, disability and healthcare costs (1). A current priority is the identification and implementation of effective ways to reduce the incidence of diabetes-related foot ulcers (1-3). A number of past systematic reviews (4-7) and meta-analyses (1, 8-11) have identified that the most widely investigated approaches to reduce the incidence of diabetes-related foot ulcers are home foot temperature monitoring (12-15), patient education (16-21) and offloading footwear (22-28). Past research suggests that high plantar pressures in people with peripheral neuropathy is a key mechanism responsible for diabetes-related foot ulcer development (29-33). These high plantar pressures can be reduced by offloading footwear (29, 30). Furthermore, the presence of high plantar pressures can be identified by monitoring foot temperature regularly as a warning sign of impending ulceration (34-38). Hot spots identified in the foot can provide an opportunity for revision of the offloading approach in time to prevent ulcer development (34, 39). Education of patients regarding how to prevent foot ulcers is a standard part of practice (2, 40) but there are mixed findings from past randomised trials on the efficacy of formal education programs in reducing the incidence of diabetes-related foot ulcers (8, 9).

Despite the previous publication of a number of systematic reviews (4-7) and meta-analyses (8-11) there remain questions about the evidence to support home foot temperature monitoring, patient education and offloading footwear in reducing the incidence of diabetes-related foot ulcers. The recent International Working Group on the Diabetic Foot (IWGDF) guidelines noted the overall quality of evidence to be low-to-moderate for these interventions (2). Prior meta-analyses have a number of weaknesses. Firstly, a number of randomised controlled trials (RCTs) were not included (20, 28). Secondly, how missing data were handled was not specified (8-11). Given the importance of intention to treat analyses in the

assessment of randomised trial data this may have an important effect on findings (41). Thirdly, current guidelines for meta-analysis highlight the important of assessing the robustness of findings in meta-analyses through sensitivity analyses (41) but past systematic reviews have seldom performed these (8-11).

There is therefore a need for an up to date and comprehensive meta-analysis to clarify the pooled evidence of benefit for home foot temperature monitoring, patient education and offloading footwear. The aim was to perform a systematic review and meta-analyses of RCTs examining the efficacy of these three interventions in reducing the incidence of diabetes-related foot ulcers.

7.3 Methods

7.3.1 Search strategy and eligibility criteria

This systematic review was conducted according to the Preferred Reporting Items for Systematic reviews and Meta-Analyses (PRISMA) statement and registered in PROSPERO (Registration number: CRD42019135226) (42). The search was performed on the 11th of October 2019 using multiple databases [MEDLINE via OvidSP, CINAHL, Scopus, Pubmed, Cochrane Central Register of Controlled Trials]. These subject headings (MeSH terms) and key words were used: “Diabetic foot” OR “Diabetic Peripheral Neuropathy” AND “Nursing care” OR “Patient care” OR “Preventive health services” OR “Health education” OR “Primary prevention” OR “Secondary prevention” (See supplementary material for the specific search strings). No language or date restrictions were used. Reference lists of the studies identified were also searched. Eligibility criteria for inclusion were that studies reported: participants that all had diabetes and were at risk of developing DFU due to being in IWGDF risk categories 2 or 3 (category 2 include patients with peripheral neuropathy or peripheral arterial disease or foot deformities while category 3 include patients with

peripheral neuropathy and a history of foot ulceration or amputation (29, 43)); interventions that were one of the following: home foot temperature monitoring, patient education or offloading footwear; a control group not receiving the intervention under study; an outcome of the incidence of diabetes-related foot ulcers during follow-up; and was a RCT. Studies including participants with an active diabetes-related foot ulcers were excluded. Home foot temperature monitoring was defined as regular assessment of foot temperature using an objective temperature monitoring device by the participants at home (44). Patient education was defined as structured education provided to participants aimed at improving their knowledge and foot care (44). Offloading footwear were defined as any shoes or insoles designed with the intention of relieving mechanical pressure from specific regions of the feet (29). Diabetes-related foot ulcer was defined as a full thickness wound on the foot of a person with diabetes (1). Corresponding authors of three trials were contacted to clarify data. Only one responded and provided additional data on the number of participants who were randomised into each group.

7.3.2 Data extraction and analysis

The primary outcome was diabetes-related foot ulcer incidence. Secondary outcomes were minor, major and total amputations (minor and major amputations). Data on adherence to offloading footwear were also extracted. Outcome data were extracted for the latest time point reported. Other data extracted included age, sex, body mass index (BMI), duration of diabetes, glycosylated haemoglobin levels (HbA1C) and ankle-brachial pressure index (ABPI) (45). Data were extracted by three authors separately and inconsistencies were resolved through discussion.

Meta-analyses were performed for any of the primary and secondary outcomes of any of the interventions studied if data were reported for the specific combination of outcome and intervention in at least three RCTs. If one trial included two separate interventions, the two

interventions were considered separately dividing the number of participants in the control group into two equal groups to provide consistency with the total number of participants that were recruited to the study. Meta-analyses for different populations and intervention sub-groups were also eligible under the same criteria, i.e. at least three RCTs reporting. All analyses used intention-to-treat principles, i.e. participants were assumed to have received the intervention they were allocated to. Missing outcome data from participants who were lost to follow-up were handled using two different approaches. The main analysis approach assumed all participants with missing outcome data had the outcome of interest (worst case scenario) (46). In a sub-analysis, a second approach assumed that all participants with missing outcome data did not develop the outcome of interest (best case scenario). All meta-analyses were performed using Mantel-Haenszel's statistical method and random effect models anticipating substantial heterogeneity (47). The results were reported as odds ratios (OR) and 95% confidence intervals (CI). Relative risks are also reported in the supplement (Supplementary Table S1). All statistical tests were two-sided and p values <0.05 were considered significant. Heterogeneity was assessed using the I^2 statistic and interpreted as low (0 to 49%), moderate (50 to 74%) or high (75 to 100%) (48). Leave-one-out-sensitivity analyses were performed to assess the contribution of each study to the pooled estimates by excluding individual studies one at a time and recalculating the pooled estimates (49). Publication bias was assessed by funnel plots comparing the summary estimate of each study and its precision (1/standard error) (49). All analyses were conducted using Review Manager 5 (RevMan 5) version 5.3. (Copenhagen: Nordic Cochrane Centre, The Cochrane Collaboration, 2014).

7.3.3 Quality assessment

Risk of bias of all included studies was assessed independently by three authors using the Cochrane Collaboration's tool for assessing risk of bias in randomised trials (41). Total risk of bias for each study was then defined as: low risk: if low risk of bias was scored for each

item; unclear risk: if low or unclear risk of bias was scored for each item; high risk: if high risk of bias was scored on one or more items (41). Any inconsistencies were resolved through discussion until consensus was reached.

7.4 Results

7.4.1 Included trials

A total of 7,575 unique records were identified from the initial search and ultimately 17 trials included (Figure 1). A total of 2729 participants were recruited to 4 trials testing home foot temperature monitoring (n=468), 6 trials examining patient education (n=823), and 7 trials assessing offloading (n=1438). All trials included participants of diabetes foot risk category 2 or above in the IWGDF grading system (26). The trials were conducted in Brazil (16), China (18, 20), Italy (21, 22, 25), Netherlands (27), Norway (14), Spain (28), Sweden (17), the UK (19) and the USA (12, 13, 15, 23, 24, 26). Tables 1 and 2 display summaries of the participants and outcome data. Details of the inclusion criteria, interventions and controls and outcome measures are shown in Supplementary Table S2. Supplementary Table S3 contains details of the quality assessment findings (41).

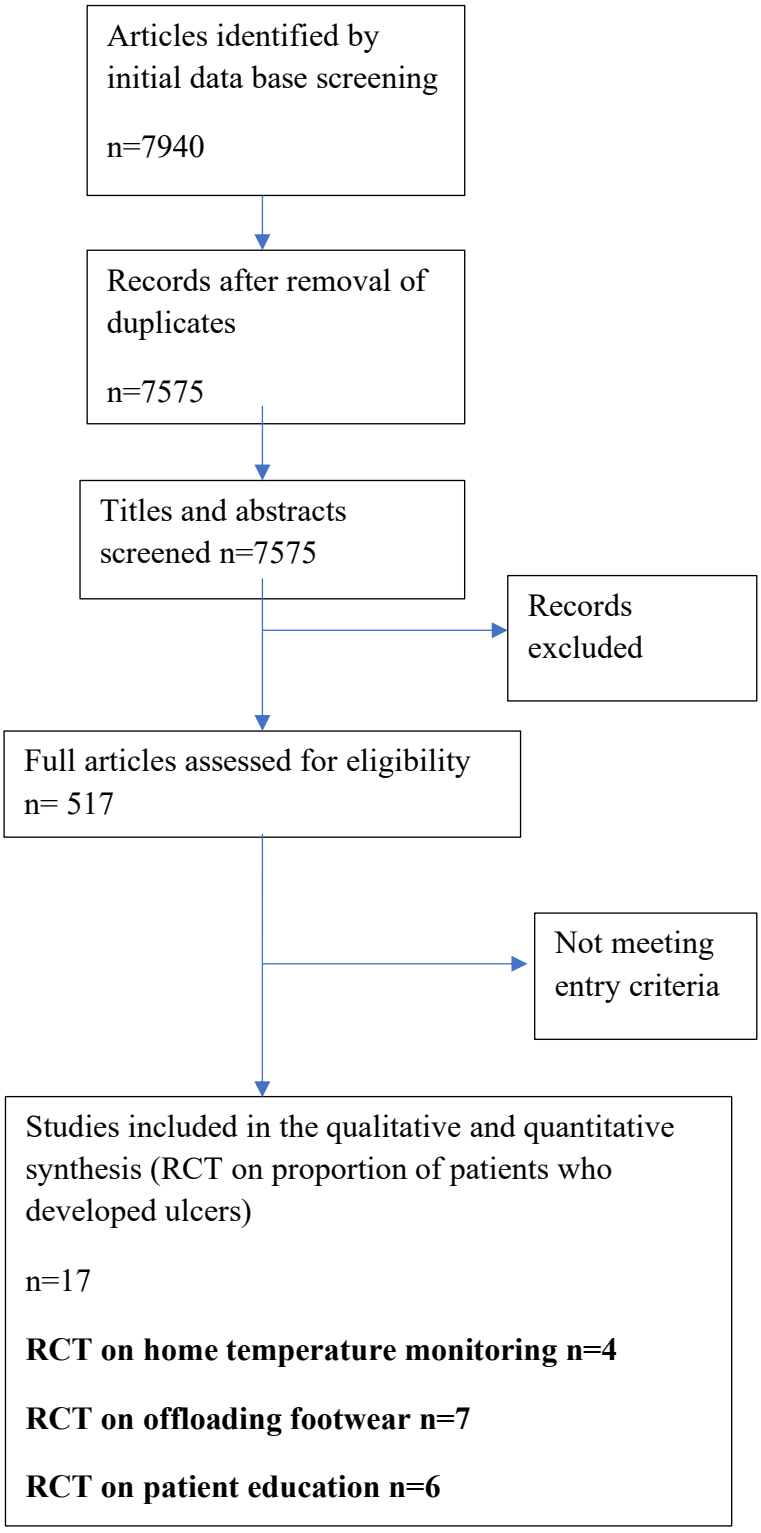

Figure 7-1 PRISMA diagram illustrating the identification and selection of the included studies

Table 7-1 Baseline characteristics of participants

Study	Group	Number of patients randomised	Age (years)	Male%	Follow up (months)	Previous history of DFU %	Previous history of amputations %	Duration of DM in years	HbA1c%
Home foot temperature monitoring									
Armstrong et al. (2007)[12]	Intervention	111	68.2±9.6	98	18	15	NR	13.6±11.6	8.1±1.9
	Control	114	69.7±10.4	95	18	17	NR	12.6±9.1	7.4±1.4
Lavery et al. (2004)[13]	Intervention	41$^{\infty}$	55.0±9.3	49	6	41	2	14.8±11.5	NR
	Control	44$^{\infty}$	54.8±9.6	52	6	41	2	12.7±10.0	NR
Lavery et al. (2007)[15]	Intervention	59	65.4±9.3	56	15	100	22	12.7±9.7	NR
	Control	58	65.0±9.6	53	15	100	31	13.7±10.3	NR
Skafjeld et al. (2015)[14]	Intervention	21	57.1±10.2	86	12	62	33$^{\kappa}$	17.0 (NR)$^{\delta}$	8.3±1.5
	Control	20	59.4±13.0	75	12	85	40$^{\kappa}$	19.5 (NR)$^{\delta}$	7.9±1.7
Patient education									
Cisneros et al. (2010)[16]	Intervention	30	64.4±9.2	64	24	30	NR	14.0±10.0	NR
	Control	23	59.8±9.0	36	24	20	NR	15.0±10.5	NR

Gershater et al. (2011)[17]	Intervention	61	64 (37-78)[δ]	75	6 [μ]	100	26	NR	8.1±3.9
	Control	70	64 (35-79)[δ]	71	6 [μ]	100	23	NR	8.6±3.8
Lincoln et al. (2008) [19]	Intervention	87	NR	71	12	100	30	NR	NR
	Control	85	NR	62	12	100	21	NR	NR
Monami et al. (2015) [21]	Intervention	61	72.0±8.9	67	6	12	NR	14.2±12.4	7.4±1.3
	Control	60	69.4±11.3	53	6	10	NR	15.9±11.2	7.3±1.4
Liang et al. (2012)[18 σ]	Intervention	31	56.2 (22-70)[δ]	47	24	0	0	11.2 (3-26)[δ]	9.7±2.3
	Control	31	55.8 (20-68)[δ]	65	24	0	0	10.1 (5-25)[δ]	9.4±2.5
Liu et al. (2019)[20]	Intervention	142	58.2±9.8	60	24	NR	NR	9.1±6.7	9.3±2.2
	Control	142	59.3±8.7	55	24	NR	NR	8.7±7.3	9.2±2.1
Offloading footwear									
Bus et al. (2013)[27]	Intervention	85	62.6±10.2	82	18	100	NR	19.9±15.1*	7.5±1.4
	Control	86	63.9±10.1	83	18	100	NR	14.7±11.2*	7.6±1.5
Lavery et al. (2012)[24]	Intervention	149	69.4±10.0	68	18	28	12	13.0±8.7	NR
	Control	150	71.5±7.9	67	18	25	9	12.0±4.9	NR

Reiber et al. (2002)[23 α]	Intervention 1(cork inserts)	121	61.0±10.1	78	24	NR	NR	35%,11%,54% [ε]	NR
	Intervention 2 (polyurethane inserts)	119	62.0±10.1	77	24	NR	NR	35%, 8%, 57% [ε]	NR
	Control	160	63.0±10.0	77	24	NR	NR	30%,14%, 55% [ε]	NR
Uccioli et al. (1995)[22]	Intervention	33	59.6±11.0	61	12	NR	0	16.8±12.7	NR
	Control	36	60.2±8.2	64	12	NR	0	17.5±8.0	NR
Rizzo et al. (2012)[23]	Intervention	148	68.1±14.1	NR	12[π]	Overall 20[λ]	Overall 25[λ]	18.1±12.1	8.6±1.4
	Control	150	66.2±9.4	NR	12[π]			17.4±10.9	8.7±1.1
Ulbrecht et al. (2014)[26]	Intervention	79	60.5±10.1	76	15	100	32	NR	NR
	Control	71	58.5±10.7	81	15	100	38	NR	NR
Lopez-Moral et al. (2019)[28]	Intervention	26	61.0±8.1	92	6	100	50	14.0±8.4	7.5±1.2
	Control	25	60.0±8.6	92	6	100	36	17.0±10.0	7.5±1.9

Data is shown as numbers or mean ± standard deviation or percentages unless otherwise highlighted.

[δ] Data were reported as median (inter quartile range)

[ε] Percentage of individuals with a diabetes duration of <6, 6-24, >25-years

DFU: Diabetes-associated foot ulcer

DM: Diabetes mellitus

HbA1c: glycated haemoglobin Measurement

NR: Not reported

[∞]Based on the data presented in results in-contrast to the numbers presented in the abstract

[κ] Included participants with a history of toe amputations

[μ] Interim analysis at 6 months

[σ]All data from this study were reported only for the patients who completed the study; 30 in the intervention group and 29 in the control group

[α] This study had two intervention groups (intervention 1: custom cork-insert group, intervention 2: polyurethane insert group). For the meta analyses the control group was divided equally into two groups to be consistent with the total number of patients included in the study

[π] Data reported for 12-month outcomes only

[λ] Only reported a combined value for both groups.

* Indicates studies with significant differences between the intervention and the control groups

To convert percentage HbA1c values to mmol HbA1c per mol Hb use the following equation 10.93 x % hbA1c – 23.5 mmol/mol.

Table 7-2 Outcome data from individual studies

Study		Incidence of DFU (reported per number initially randomised)	Incidence of major amputations	Incidence of minor amputations	Adherence to offloading footwear (%)
Home foot temperature monitoring					
Armstrong et al. (2007)[12]	Intervention	5/111 (4.5%) *	NR	NR	NA
	Control	14/114 (12.2%) *	NR	NR	NA
Lavery et al. (2004)[13 ∞]	Intervention	1/41 (2.4%) *	0/41 (0.0%)	0/41 (0.0%)	NA
	Control	7/44 (15.9%) *	0/44 (0.0%)	0/44 (0.0%)	NA
Lavery et al. (2007)[15]	Intervention	5/59 (8.5%) *	NR	NR	NA
	Control	17/58 (29.3%) *	NR	NR	NA
Skafjeld et al. (2015)[14]	Intervention	7/21 (33.3%)	NR	NR	NA
	Control	10/20 (50.0%)	NR	NR	NA
Patient education					
Cisneros et al. (2010)[16]	Intervention	8/30 (26.7%)	NR	NR	NA
	Control	8/23 (34.8%)	NR	NR	NA
	Intervention	19/61 (31.1%)	NR	NR	NA

Gershater et al. (2011)[17]	Control	22/70 (31.4%)	NR	NR	NA
Lincoln et al. (2008)[19]	Intervention	36/87 (41.4%)	1/87 (1.4%)	8/87 (9.2%)	NA
	Control	35/85 (41.2%)	1/85 (1.2%)	8/85 (9.4%)	NA
Monami et al. (2015)[21]	Intervention	0/61 (0.0%) *	0/61 (0.0%)	0/61 (0.0%)	NA
	Control	6/60 (10.0%) *	0/60 (0.0%)	0/60 (0.0%)	NA
Liang et al. (2012)[18σ]	Intervention	1/31 (3.2%) *	0/31(0.0%)	0/31(0.0%)	NA
	Control	7/31 (22.5%) *	0/31 (0.0%)	2/31(6.4%)	NA
Liu et al. (2019)[20]	Intervention	16/142(11.3%) *	Overall 0/142 (0.0%)[η]		NA
	Control	33/142(23.3%) *	Overall 4/142 (2.8%)[η]		NA
Offloading footwear					
Bus et al. (2013)[27]	Intervention	33/85 (38.8%)	NR	NR	41.2%*
	Control	38/86 (44.2%)	NR	NR	51.2%*
Lavery et al. (2012)[24 σ]	Intervention	3/149 (2.0%)	NR	NR	4h: 15.5% 4-8h: 52.0% 8-12h: 25.7% 12-16h: 6.8%

	Control	10/150 (6.6%)	NR	NR	4h: 10.6% 4-8h: 55.0% 8-12h: 30.5% 12-16h: 3.9%
Reiber et al. (2002)[23] α	Intervention (custom cork inserts)	18/121(14.9%)	Overall, 5/400 (1.0%)γ	Overall, 6/400 (1.5%)γ	83.0%
	Intervention (polyurethane inserts)	17/119(14.3%)			86.0%
	Control	27/160 (16.8%)			NR
Uccioli et al. (1995)[22]	Intervention	9/33 (27.7%) *	NR	NR	100% adhered either frequently or occasionally
	Control	21/36 (58.3%) *	NR	NR	NR
Rizzo et al. (2012)[25]	Intervention	17/148 (11.5%) *	NR	NR	NR
	Control	58/150 (38.7%) *	NR	NR	NR
Ulbrecht et al. (2014)[26]	Intervention	6/79 (7.6%) *	NR	NR	NR
	Control	16/71(22.5%) *	NR	NR	NR

Lopez-Moral (2019)[28]	Intervention	6/26(23.1%) *	NR	NR	88.4%*
	Control	16/25(64.0%) *	NR	NR	92.0% *

DFU: Diabetes-related foot ulcer

NR: Not reported

NA: Not applicable

[∞]Based on the data presented in results of the study as opposed to conflicting data presented in the abstract

[σ]Based on data presented in the results as opposed to conflicting data presented in a table from the study

[η]Data reported as total amputations

[σ]Adherence data reported as the percentage of patients who adhered to offloading footwear <4, 4-8, 8-12 and 12-16 hours

[α] This study had two intervention groups (intervention 1: custom cork-insert group, intervention 2: polyurethane insert group). For the meta analyses the control group was divided equally into two groups to be consistent with the total number of patients included in the study

[γ]Data reported as total number of minor and major amputations in the entire study

* Indicates studies with significant differences between the intervention and the control groups

7.4.2 Risk of bias

Table 3 displays a summary of the findings of the quality assessment. All studies had a total risk of bias score of high or unclear risk of bias, included 14 with high risk of bias (12, 13, 15-21, 23-26, 28) and three with unclear risk of bias (14, 22, 27). Most high risk of bias was due to a combination of incomplete outcome data due to high dropout rates in seven studies (13, 16-18, 23, 26, 28), lack of blinding of participants or personnel in six studies (12, 13, 15, 24, 26, 28), other biases (significant baseline differences between the intervention and the control groups, participants being assigned to a different group during the study from the initial randomised group or premature termination of studies) in six studies (16, 17, 19, 21, 25) and/or lack of ITT in four studies (17, 18, 21, 26). Eight studies did not report blinding of participants and personnel (17-23, 25). Blinding of assessors were not reported in seven studies (14, 17, 18, 20-22, 25).

Table 7-3 Summary table of the quality assessment

Study	Random sequence generation	Blinding of participants/ personnel	Blinding of assessors	Sample size estimate	Incomplete outcome data (>10% loss)	Clear primary outcome	Intention to treat analysis	Other biases #	Total risk of bias
Home foot temperature monitoring									
Armstrong et al. (2007)[12]	(+)	(-)	(+)	(+)	(?)	(+)	(?)	(?)	High
Lavery et al. (2004) [13]	(?)	(-)	(+)	(?)	(+)	(-)	(+)	(?)	High
Lavery et al. (2007) [15]	(+)	(-)	(+)	(+)	(-)	(+)	(+)	(+)	High
Skafjeld et al. (2015) [14]	(+)	(+)	(?)	(?)	(+)	(+)	(+)	(?)	Unclear
Patient education									
Cisneros et al. (2010) [16]	(?)	(+)	(+)	(-)	(-)	(+)	(?)	(-)	High
Gershater et al. (2011) [17]	(+)	(?)	(?)	(+)	(-)	(+)	(-)	(-)	High
Lincoln et al. (2008) [19]	(+)	(?)	(+)	(+)	(-)	(+)	(+)	(-)	High
Monami et al. (2015) [21]	(+)	(?)	(?)	(+)	(+)	(+)	(-)	(-)	High
Liang et al. (2012) [18]	(?)	(?)	(?)	(?)	(+)	(-)	(-)	(?)	High
Liu et al. (2019) [20]	(?)	(?)	(?)	(?)	(+)	(-)	(+)	(?)	High

Offloading footwear									
Bus et al. (2013) [27]	(+)	(+)	(+)	(?)	(+)	(+)	(+)	(+)	Unclear
Lavery et al. (2012) [24]	(?)	(-)	(+)	(+)	(?)	(+)	(+)	(?)	High
Reiber et al. (2002) [23]	(+)	(?)	(+)	(+)	(-)	(+)	(+)	(?)	High
Uccioli et al. (1995) [22]	(?)	(?)	(?)	(?)	(?)	(+)	(?)	(?)	Unclear
Rizzo et al. (2012) [25]	(+)	(?)	(?)	(?)	(?)	(+)	(?)	(-)	High
Ulbrecht et al. (2014) [26]	(+)	(-)	(+)	(+)	(-)	(+)	(-)	(-)	High
Lopez-Moral et al. (2019) [28]	(+)	(-)	(+)	(+)	(-)	(+)	(+)	(?)	High

Key: (+) Low risk of bias, (-) High risk of bias, (?) Unclear risk of bias

[#]Other biases include significant baseline differences between the intervention and the control groups, participants being assigned to a different group during the study from the initial randomised group or premature termination of studies

7.4.3 Home foot temperature monitoring

All four trials testing home foot temperature monitoring used a similar infrared thermometer (The Temp Touch by Xilas Medical, San Antonio, Texas) to monitor temperature at six sites on each foot either once (14, 15) or twice (12, 13) daily (Supplementary Table S2). All studies informed the participants to contact a study nurse if they observed a temperature difference of 4° Fahrenheit (2.2° Celsius) between either foot on two consecutive days. One trial instructed the participants to reduce the number of steps taken during the following days until the temperature difference was < 4° Fahrenheit (13). The action taken when a temperature difference was detected was unclear in the other trials (5, 7, 8). All control groups had access to therapeutic footwear, diabetic foot education and regular foot care (Supplementary Table S2).

Three of the four trials reported that the intervention significantly reduced the incidence of DFUs compared to the control after 6 to 18 months (12, 13, 15) (Table 2). Only one trial reported amputation outcomes with no amputations in any groups (13).

The main meta-analysis suggested that infrared thermometry with follow-up preventive care, halved the odds of diabetes-related foot ulcer incidence (OR 0.51, 95% CI 0.31 to 0.84, p=0.009) (Figure 2 and Supplementary Table S4). There was no heterogeneity between studies (I^2=0%). Leave-one-out sensitivity analyses showed that these findings were dependent on the inclusion of a single trial (12) (Supplementary Table S6.1). A sensitivity analysis based on the best-case scenario intention-to-treat analysis showed similar findings to the main analysis (OR 0.30, 95% CI 0.16 to 0.56, p<0.001) (Supplementary Figure 1 and Supplementary Table S4).

7.4.4 Patient education

Five of the six patient education trials conducted education sessions in a health care center (16-18, 20, 21) and the other trial delivered a face-to-face session at participants' homes (19). Two trials included multiple education sessions (16, 18), three trials tested a single session (17, 19, 21), while one trial did not specify the number of education sessions (20). The duration of the sessions varied between 60 to 120 minutes. All programs contained information on diabetes-related foot ulcer risk factors and preventive footcare. Instructions on footcare and access to regular health care services were provided to all control groups (Supplementary Table S2). The method of delivery of instructions on footcare were markedly different between the studies with some trials offering the participants written information or leaflets (17, 19, 21) and some offering them advice from podiatrists or nurses in a clinic set-up (18-20). Three trials reported that patient education significantly reduced diabetes-related foot ulcer incidence (18, 20, 21) (Table 2). Three trials reported no significant benefit of the patient education program tested (16, 17, 19) (Table 2).

Four trials reported the incidence of amputations (18-21) (Supplementary Table S5). One trial only reported the total amputations (20). Three trials reported the incidence of minor and major amputations (18, 19, 21). Amputation rates in these trials were not significantly different between the intervention and the control groups [12-14, 16] (Table 2).

The main meta-analysis suggested that patient education programs did not reduce the odds of diabetes-related foot ulcer occurrence (OR 0.59, 95% CI 0.29 to 1.20, p=0.140) (Figure 3 and Supplementary Table S4). There was moderate heterogeneity among studies (I^2=71%). Leave-one-out sensitivity analyses showed that these results were changed when one trial was removed (17) (Supplementary Table S7.1). A sensitivity analysis based on the best-case intention-to-treat analysis had similar findings to the main analysis (OR 0.61, 95% CI 0.34-1.07, p=0.080) (Supplementary Figure 2 and Supplementary Table S4).

Meta-analysis of four trials (18-21) suggested that patient education programs did not significantly reduce the odds of total amputations (OR 0.63, 95% CI 0.24-1.68, p=0.360) (Supplementary Figure 3 and Supplementary Table S5). Leave-one-out sensitivity analyses suggested that these findings were not dependent on the inclusion of a single trial (Supplementary Table S7.2). Meta-analysis of three trials suggested that patient education did not significantly reduce the odds of major amputations (OR 0.85, 95% CI 0.42-1.71, p=0.650) (Supplementary Figure 4 and Supplementary Table S5). Leave-one-out sensitivity analyses suggested that these findings were consistent (Supplementary Table S7.3). Meta-analysis of the same three trials suggested that patient education did not significantly reduce the odds of minor amputations (OR 0.81, 95% CI 0.43-1.52, p=0.520) (Supplementary Figure 5 and Supplementary Table S5) and the results were consistent (Supplementary Table S7.4).

7.4.5 Offloading footwear

Six trials tested either custom-made orthoses (pressure or shape based) or custom-made footwear (22-27). The remaining trial tested prefabricated therapeutic footwear with rigid rocker soles in the intervention arm against prefabricated therapeutic footwear with semi-rigid soles in the control arm (28). Management of the control groups varied between trials with some prescribing off the shelf footwear (22, 23, 25), some prescribing therapeutic footwear (24, 26, 28) and one prescribing custom-made footwear without plantar pressure-guided modifications (27). Four trials provided footcare education to all participants (22, 24-26) (Supplementary Table S2). Six trials monitored adherence to footwear (22-24, 26-28) (Table 2 and Supplementary Table S8.1). Four trials reported that offloading footwear significantly reduced diabetes-related foot ulcer incidence (22, 25, 26, 28) (Table 2). Three trials reported no benefit of offloading footwear (23, 24, 27) (Table 2). One trial reported the incidence of major and minor amputations, with no significant differences found between groups (23) (Table 2).

The main meta-analysis suggested that offloading footwear reduced the incidence of diabetes-related foot ulcers (OR 0.48, 95% CI 0.29 to 0.80, p=0.005) (Figure 4 and Supplementary Table S4). Heterogeneity among the studies was moderate (I^2=72%). Leave-one-out sensitivity analyses showed these results were consistent (Supplementary table S8.2). The best-case scenario sensitivity analysis showed similar findings (OR 0.41, 95% CI 0.24 to 0.68, p<0.001) (Supplementary Figure 6 and Supplementary Table S4). A sub-group meta-analysis was also eligible and suggested that custom-made orthoses/footwear reduced diabetes-related foot ulcer incidence (OR 0.47, 95%CI 0.27 to 0.82, p=0.008) despite moderate heterogeneity (I^2=70%) (Supplementary Figure 7) (22-27). Leave-one-out sensitivity analyses showed that these findings were consistent (Supplementary Table S8.3).

7.4.6 Publication bias

The funnel plots (Supplementary figures 8, 9 and 10) based on the primary analyses showed asymmetry suggesting the possibility of publication bias.

7.5 Discussion

This meta-analysis suggests that offloading footwear is effective at reducing the incidence of diabetes-related foot ulcers. The main analysis also suggested that home foot temperature monitoring reduced the incidence of foot ulcers, however, the findings were not robust in all sensitivity analyses. The meta-analysis suggested that previously tested patient education programs are not effective in reducing the incidence of diabetes-related foot ulcers but again findings were not robust in sensitivity analyses.

Superficially, the findings of this meta-analysis are similar to a recently published systematic review (9) but a number of important differences should be noted. Firstly, the current meta-analysis employed a strict and clearly stated way of handling missing data not present in past systematic reviews. Intention to treat is an established cornerstone of analysis of data from

RCTs (41). Missing data has an important impact on such analyses. In order to include all participants randomised we performed analyses to assess both the worst (where the participant with missing data was assumed to have developed an ulcer) and best (where the participant with missing data was assumed not to have developed an ulcer) case scenarios, as we have previously described (46). Secondly, in order to further assess the robustness of findings leave one out sensitivity analyses were performed, as recommended by the PRISMA guidelines (42). As a result of these further analyses, it was evident that the findings for home foot temperature monitoring were not completely robust as they were dependent on the inclusion of a single trial (12). Similarly, the findings for the patient education programs also changed in one of the sensitivity analyses. In contrast, the findings for offloading footwear were consistent in all sensitivity analyses. Our interpretation of these findings is that there is robust evidence on the benefit of offloading footwear. In contrast, the current evidence for home foot temperature and against patient education programs is less robust. Thirdly, in the meta-analysis reported by Crawford and colleagues, data were handled differently to the current study [9]. Crawford et al. combined data from two different offloading interventions [23] into one group. They also extracted data on ulcer incidence per participant years from one trial [23] mixed with actual ulcer incidence from other trials. In contrast, in the current meta-analysis all data were allocated to individual groups as actual ulcer numbers. Finally, Crawford and colleagues reported relative risk rather than OR as reported in the current meta-analysis. These differences likely explain the disparity in reported effect sizes and 95% CIs between the current and previous meta-analyses.

The findings of this meta-analysis for home foot temperature may be reflective of the relatively small number of past RCTs and the small sample sizes included in these trials (12-15). A larger RCT testing home foot temperature monitoring is currently ongoing (35) and the addition of these data to the current meta-analysis is expected to have an important effect

on interpretation. It should also be noted that this ongoing RCT and the prior trials included in this review all used the same hand-held infra-red thermometer (12-15, 35). This approach may not be feasible for widespread use and a number of alternative ways of assessing foot temperature have been developed (50-55). A recent RCT tested the use of an infra-red camera used by clinicians to assess patients attending out-patient clinics. Assessments were performed at monthly intervals rather than on a daily basis. This trial reported no benefit of the intervention studied, suggesting that much more frequent assessment of foot temperature is needed for this approach to be effective (56). Recently, a temperature assessment mat (Podimetrics) has been developed for easy participant use within the home (55). This is marketed within the USA and has been reported to be sensitive at identifying hots spots that predict ulcers (57). RCTs employing this and other easy to use home foot temperature monitoring techniques (52, 55, 58) are needed to thoroughly examine the potential of this intervention in preventing foot ulcers.

Despite a strong recommendation in the IWGDF guidelines that at-risk people should receive structured patient education programs, previous meta-analyses and systematic reviews (6, 8, 9) have suggested no benefit of patient education programs in reducing diabetes-related foot ulcer incidence. The current meta-analysis supports these prior findings with the addition of a recent trial to the pooled estimate (20). The main analysis showed no benefit of the programs tested (8). A leave one out sensitivity analysis, however, suggested findings were not completed robust. There was noted to be a high percentage of patients who were lost to follow-up among three trials (16, 17, 19). The current meta-analyses suggested no benefit of the previously tested education programs in reducing the number of total, minor or major amputations. This result was dependent on one study which only reported an interim analysis with a high drop-out rate (17). The patient education programs tested varied considerably in terms of their design, such as the number of sessions, group or one-on-one programs and their

content. The education programs in the three trials which showed benefit included discussions with the participants that encouraged them to ask questions (16, 17, 19), was delivered to the patient at their own home with an individualised approach (19) and included games and teaching aids not typical of commonly used education sessions (16, 17). Most programs only included one education session (17, 19, 21, 59) and it is possible that a more effective outcome might have been achieved with more intensive education or through combining education with behaviour change support interventions, such as motivational interviewing (60). Further trials are needed to test well-designed patient education programs.

This meta-analysis provides robust evidence that use of offloading footwear reduces the incidence of diabetes-related foot ulcers, which is consistent with a previous meta-analysis (9). There was a high heterogenicity noted within the included trials that may reflect the different types of footwear tested, the variation in footwear in the control groups and the variable footwear adherence rates reported in the trials (24, 27). A sub-analysis suggested the benefit of custom-made orthoses or footwear which supports the recommendations given by the IWGDF guidelines about prescribing shoes that uniquely address each patient's problem (2). Bus et al. reported that participants who adhered to their offloading shoes had significantly lower recurrence rates of diabetes-related foot ulcers compared to the control group (27). Combining offloading with methods to improve adherence may provide further benefit, although this remains to be demonstrated. Methods that have been reported to improve footwear adherence include behaviour change support systems (60-62) such as motivational interviewing and coaching (63, 64), regular monitoring (63) and individualised education (64).

A number of limitations of the included trials and this meta-analysis should be acknowledged. The risk of bias of the included RCTs was considered to be either high or unclear using the Cochrane collaborative tool. Other risk of bias assessments is available and

using another tool may have led to different findings. Identified deficiencies of the trials included lack of reporting of sample size calculations (13, 14, 16, 18, 22, 25, 27, 59), absence of outcome assessor blinding (14, 17, 18, 21, 22, 25, 59, 65), large patient drop-out rates (15-17, 19, 23, 26, 59) and failure to comment on the method of randomisation (13, 16, 18, 22, 24). There was also heterogeneity in follow-up frequency and in reporting patient characteristics. Furthermore, funnel plots suggested a risk of publication bias. Therefore, well-designed trials are still needed to clearly define the best combination of interventions in preventing diabetes-related foot ulcers.

In conclusion, this meta-analysis provides robust evidence that offloading footwear reduces the incidence of diabetes- related foot ulcers in high-risk people (44). The meta-analyses also suggests that there may be benefit for home foot temperature monitoring but that further trials are needed. The value of patient education programs in preventing diabetes-related foot ulcers is currently unclear despite strong recommendations given by the IWGDF.

7.6 Declaration of interest

The authors have no conflicts to declare.

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7.10 Supplementary Material

Search terms:

Medline: “exp diabetic foot” OR “exp diabetic neuropathies” AND “exp nursing care” OR “exp patient care” OR “exp health education” OR “exp primary prevention” OR “exp secondary prevention”

CINHAL: “diabetic foot” OR “foot orthoses” OR “foot ulcer” AND “prevention” OR “patient education” OR “patient centred care” OR “patient care”

Cochrane: “diabetic foot ulcer” OR “diabetic foot syndrome”

Pubmed: “diabetic foot” OR “diabetic neuropathies” OR “foot ulcer” OR “foot ulcer, diabetes” OR “foot diseases” AND “disease prevention” OR “primary prevention” OR “secondary prevention” OR “early therapy”

Scopus: “diabetic foot” OR “diabetic foot ulcer” AND “preventive health services” OR “health education” OR “primary prevention” OR “secondary prevention”

Supplementary Table S1: Relative risks of the meta-analyses (worst-case scenario)

Intervention	**Heterogeneity (I^2)**	**Relative risk**	**95% confidence interval**
Home foot temperature monitoring	1%	0.66	0.46-0.94
Patient education	75%	0.75	0.50-1.13
Offloading footwear	73%	0.62	0.44-0.88

Supplementary Table S2: Study Characteristics

Study	**Sample size** (Screened/ randomised/ completed)	**Number of patients lost for follow up in intervention /control**	**Inclusion and exclusion criteria**	**Intervention**	**Compliance assessment of thermometry**	**Control**	**Primary outcome**	**Other outcomes**
Armstrong et al. (2007)[12]	1942/225 /NR	NR	Inclusion: Diabetes type II, Age 18-80, Consenting participants, IWGDF risk category>2 Exclusion: current diabetic foot complications, severe PAD, cognitive impairment/dementia, substance abuse	Care offered to the control group + infrared thermometry in 6 sites of the foot twice a day. T > 2.2°C difference between either of the sides should be notified	NA	Therapeutic footwear, diabetic foot education and regular foot care.	incidence of foot ulcers	Effect of the intervention on type of ulcer, health-related quality of life, self-efficacy, satisfaction with care, and modulation of activity

Lavery et al. (2004)[13]	NR/85/78	4 and 3	Inclusion: Diabetes type I or II, Age 18-80, Consenting participants, IWGDF risk category>2 Exclusion: current diabetic foot complications, severe PAD, cognitive impairment/dementia, substance abuse	Care offered to the control group + infrared skin thermometry to measure temperatures on the sole twice daily on 6 sites. If a toe ± metatarsal had been amputated, adjacent anatomic area was measured. T > 2.2°C difference between the left and right corresponding sites should be notified and the number of steps reduced	NA	Therapeutic footwear, diabetic foot education, and foot evaluation by a podiatrist every 10 –12 weeks.	incidence of foot ulcers	Infarctions, Charcot's fractures, amputations
Lavery et al. (2007)[15]	211/173/151*	10 and 6 (additional 6 dropped out of the 56 who were	Inclusion: Diabetes type I or II, Age 18-80, Consenting participants,	Care offered to the control group + digital infrared thermometry to measure	Compliance assessment method was not reported. Compliance rates were 20% in those	Lower extremity evaluation by a physician every 8 weeks, an education	incidence of foot ulcers	Adherence to preventive practices: temperature monitoring,

		allocated to structured foot-examination)	IWGDF risk category>2, previous history of DFU Exclusion: current diabetic foot complications, severe PAD, cognitive impairment/dementia	temperatures on each foot on 6 sites daily, counselling sessions on adherence three monthly. T > 2.2 °C between right and left corresponding sites to be notified	who developed ulcers and 80% in those who did not.	program on foot complications and self-care + footwear		footwear use, contacting the study nurses
Skafjeld et al. (2015)[14]	110/41/38	3 in intervention group	Inclusion: Diabetes type I or II, Age 18-80, Consenting participants, IWGDF risk category>2, previous history of DFU Exclusion: current diabetic foot	Care offered to the control group + digital infrared thermometry to monitor foot temperature on six sites on the foot on daily basis. Recording of daily physical activity using a step-counter during the first week of the study. T>2.2°C	Compliance assessed in a graded scale. 67% of the patients monitored their feet more than 80% of the time.	Daily inspection of feet under, below and between the toes, and daily recording, advise on always wearing their customized footwear, General practitioner care	incidence of foot ulcers	Difference between those who measured T >80% and <80%

			complications, severe PAD	difference in temperature between corresponding sites on two consecutive days to be notified.				
Study	**Sample size** (Screened/ randomised/ completed)	**Number of patients lost for follow up in intervention /control**	**Inclusion and exclusion criteria**	**Intervention**	**Frequency of visits/follow up**	**Control**	**Primary outcome**	**Other outcomes**
Cisneros et al. (2010)[16]	563/53/35	7 and 7, (additional 4 patients in the intervention group did not comply with the intervention)	Inclusion: Diabetes type I or II, PN Exclusion: NR	Four group meetings (weekly) on therapeutic education (complications of diabetes, treatment, foot hygiene, inspection and choice of footwear) + a pair	Follow up at every 3 months up to 18 months and the last follow up at 24 months.	Routine care assistance offered by the centre with instructions on footcare and footwear	incidence of ulcers	Ulcer recurrence

				of special protective shoes (open and close therapeutic shoes). The sessions involved games as teaching aids and patients were encouraged to ask questions. Duration: 90 min				
Gershater et al. (2011)[17]	657/131/98	21 and 12 (3 and 2 deaths included)	Inclusion: Diabetes type I or II, PN, previous history of DFU Exclusion: interpreter requirement, inability to be followed up, major amputations	A single session for each patient: active participation in discussions that started from the question 'Where do foot ulcers come from?', asking questions of each other and of a diabetes specialist nurse, to build self-confidence. In all, 14 group sessions	Followed up at 6 months.	Adjusted shoes and individually fitted insoles for use, regular chiropody. Oral and written instructions on self-care, regular health care services	the number of new foot ulcers during six-month observation period	NR

				were held by a specialised nurse. 2-5 people per group separately for males and females Duration: 60 min				
Lincoln et al. (2008)[19]	1729/178 (included only 172)/140	15 and 17 (4 and 1 death included), 6 other patients were excluded after randomisation due to withdrawal of consent, etc)	Inclusion: Diabetes type I or II, previous history of DFU Exclusion: participants requiring interventions, interpreter requirement, inability to be followed up, cognitive impairment, involvement in similar studies	A single education session (within 4 weeks of randomisation) delivered to participants in their homes, by a trained researcher. The content contained causes of foot ulcers. Additional feet examination, risk factors identification and explanations. Footwear examined for wear and tear, patterns of use to	A phone call at 4 weeks, Outcomes assessed at 6 and 12 months.	Routine management which included regular podiatric care and suitable orthoses when appropriate. A foot care leaflet was provided.	ulcer incidence at 12 months	Ulcer incidence at 6 m, incidence of amputation, mood (Hospital Anxiety and Depression Scale) and quality of life (Diabetic Foot Ulcer Scale) at 6 and 12 m. Protective foot care behaviours at 12 m

				identify particular risks for new ulcerations. Illustrations included. Leaflets were supplemented. Duration:60 min				
Monami et al. (2015)[21]	NR/121/ 120	1 in the intervention group	Inclusion: Diabetes type II, PN, previous history of DFU Exclusion: participants requiring interventions for PAD, cognitive impairment	A single program provided to groups of 5–7 patients (a 30-min face-to-face lesson on risk factors for foot ulcers + a 90-min interactive session with practical exercises on behaviours for reducing ulcer risk). This involved a physician for 15 min and a nurse for 105 min. Leaflet on	Follow up at 3 and 6 months.	Usual care and a leaflet were provided containing information on recommendations for ulcer prevention.	incidence of foot ulcers	Patient Interpretation of Neuropathy questionnaire to all patients and at the end to the intervention group.

				recommendations for ulcer prevention included. Duration: 120 min				
Liang et al. (2012)[18]	208/62/59	1 and 2	Inclusion: Diabetes type I or II, Exclusion: NR	Initial session: care offered to the control group + use of a foot care kit (nail clippers, foot care cream, a monofilament of 10-g pressure, a thermometer to measure temperature of the water for washing feet, alcohol cotton pieces, and a mirror) and foot inspection using a mirror by the patient and a family member. Group education sessions every 3	Patients were followed up every month with an endocrinologist and a diabetes nurse in the diabetes foot clinic for a systematic foot exam.	Medication adjustment, foot assessment, and 2 hours of diabetes/foot care education. All participants were tested by diabetes knowledge questionnaire and diabetic foot scale	knowledge and self-foot care behaviours	HbA1c, ulcers, amputations

				to 6 months, for knowledge reinforcement and foot care skill re-demonstration. Duration: 120 min				
Liu et al. (2019)[20]	NR/284/ 284	NR	Inclusion: Diabetes type II, high risk of DFU (previous foot lesions, ABPI<0.9, PN), participants willing to participate Exclusion: Severe liver or kidney disease, severe lower extremity vascular disease requiring surgery, speech or hearing problems, history of drug	Care given to the control group + individualised education sessions on risk factors and problems of foot care, good foot care, goal setting and foot self-management, importance of regular return visits, monitoring of the diabetes and foot disease, importance of assistant management of callosities on	Patients were followed up every three months for two years	Nursing education on diabetes and DFU, instructions on the right way of washing feet, foot skin care, appropriate choice of socks and shoes	blood glucose, lipid levels in blood, blood pressure, foot dorsal artery pulse, 10-g monofilament test results, knowledge of foot care score, diabetes quality of life score	Incidence of foot ulcers, Wagner's ulcer grade and prognosis

			abuse, critical illnesses	time, importance of evaluating quality of life at every three months				
Study	**Sample size** (Screened/ randomised/ completed)	**Number of patients lost for follow up in intervention /control**	**Inclusion and exclusion criteria**	**Intervention**	**Frequency of visits/ compliance assessment of footwear/ ulcer assessment**	**Control**	**Primary outcome**	**Other outcomes**
Bus et al. (2013)[27]	267/171/ 161	6 and 4 (2 deaths in each included)	Inclusion: Diabetes type I or II, age>18 years, PN, participants on prescribed footwear, history of DFU Exclusion: active ulcers, major amputations, inability to	Offloading improved custom-made footwear (both the footwear and orthotic improved based on pressure) custom made insoles with multiple layers + custom made footwear in 85%, custom made insoles in extra	Three months/a temperature-based monitor/digital photography reviewed blindly by 3 members using Texas score.	Non-improved (no pressure-based improvement) custom-made footwear	plantar foot ulcer recurrence in 18 months	Ulcer recurrence in patients with adherence >80% to footwear

			follow instructions	depth shoes in 15%. Offloading improvement protocol applied every 3 months.				
Lavery et al. (2012)[24]	NR/299/ NR	NR	Inclusion: Diabetes type I or II, age>18 years, PN, history of DFU Exclusion: active ulcers, foot deformities, inability to use over the counter shoes	Standard care + a novel orthotic designed to reduce both pressure and shear on the sole of the foot. Orthotics were replaced every 4 months.	Three months/a questionnaire/ lower extremity evaluation by a physician every 10-12 weeks.	Therapeutic orthotics and shoes replaced every 4 months, diabetic foot education (video on aetiology, risk factors, self-care, early warning signs of ulcers),	Incidence of foot ulceration	Time to ulceration
Reiber et al. (2002)[23]	21000/400/334	17 (custom cork-insert group), 23 (polyurethane insert group) and 26 (control group). This included 6,7,	Inclusion: Diabetes type I or II, age >45 years, history of DFU or foot infection requiring antibiotics,	Care offered to the control group + 121 men and women received 3 pairs of therapeutic shoes (extra depth and width), 3 pairs of customised medium-density	4 visits within the first month and visits every 17 weeks/a questionnaire/blinded team based on descriptions, photographs and study records.	Regular health care and usual footwear. No patient education on clinical care at the study site.	Incidence of foot re-ulceration	NR

		and 9 deaths respectively)	ability to walk 1 block, consent Exclusion: active ulcers, major amputations, foot deformities, inability to use over the counter boots, ambulatory status	cork inserts with a neoprene closed-cell cover; 119 received 3 pairs of therapeutic shoes and 3 pairs of prefabricated, tapered polyurethane inserts which were not customised with a brushed nylon cover.				
Uccioli et al. (1995)[22]	NR/69/NR	NR	Inclusion: Diabetes type I or II, age >18 years, history of DFU or high risk of DFU Exclusion: active ulcers, major amputations, foot deformities	Care offered to the control group + specialised / therapeutic shoes with custom-made orthotics.	Six months/a graded scale/ NR	Educational guidelines on foot care, importance of appropriate footcare given to both groups + ordinary nontherapeutic footwear	number of ulcer relapse	Ulcer free time

Rizzo et al. (2012)[23]	1874/298 /NR	NR	Inclusion: Diabetes type I or II, age >18 years, PAD or deformities associated with PN or history of DFU or amputations, duration of diabetes >5 years Exclusion: active ulcers, foot deformities, ambulatory status, life expectancy <1 year	Care offered to the control group + custom-made orthotics (pressure based) and semi-orthopaedic shoes available from the market. Patients were instructed to report ulceration within 24 hours (cause, site, type of ulcer was recorded).	Four months/NR/ cause, site and type of ulcer, general condition was recorded.	In depth education on how to prevent ulceration + non-traumatizing comfortable shoes	incidence of new/recurrent diabetic foot ulcers	Cumulative incidence of foot ulcers, economic burden
Ulbrecht et al. (2014)[26]	185/150/ 118	8 and 4 (additional 13 in the intervention and 7 in the control group did not	Inclusion: Diabetes type I or II, age>18 years, PN, plantar pressure >450kPa at previous ulcer site, history of	Care offered to the control group + shape-and pressure-based orthotics (3pairs) with one pair of therapeutic shoes with DX2	Visits at 1 week, 3 weeks, 6 weeks and then every 3 months/ a questionnaire/foot photography was	Education on self-care behaviours, adherence to orthotics, educational brochures + standard non-	incidence of forefoot plantar ulcers	Non ulcerative lesions, ulcer prevention effect of experimental orthoses

		receive the intervention)	recently healed DFU Exclusion: active ulcers, major amputations, inability to follow instructions, current use of orthoses, ambulatory status	specification + a non-customised therapeutic shoe pair for occasional steps at home.	reviewed blindly by 3 members.	customised extra depth shoes and a non-customised therapeutic shoe pair		
Lopez-Moral et al. (2019)[28]	NR/51/55	3 in each group	Inclusion: Diabetes type I or II age>18 years, PN, history of DFU Exclusion: active ulcers, trans-metatarsal or major amputations, history of rheumatoid disease, critical	Therapeutic footwear with multilayer orthotics were worn by both groups. The experimental group wore shoes with rigid rocker soles (composite fibres).	Monthly/a questionnaire/blindly by two physicians	Therapeutic footwear with multilayer orthotics and semi-rigid rocker soles (Well-walk technology with vibrant strips)	Incidence of foot ulcer recurrence (foot or ankle)	Physical activity (IPAQ) Footwear adherence (by a questionnaire)

			limb ischaemia, Charcot's foot, severe deformities, requirement of walking aids, offloading surgery					

* Includes a group of patients who underwent structured foot examination as an intervention which is not included in the analysis.

ABPI: Ankle-brachial pressure index

DFU-Diabetic foot ulcer

IWGDF-International working group of diabetic foot (the study inclusion criteria were grouped according to the criteria given by the IWGDF to provide consistency)

IPAQ: International physical activity questionnaire

min: minutes

NA-Not Applicable, NR-Not Reported, PN-Peripheral neuropathy, PAD-Peripheral arterial disease, HbA1C-Haemoglobin A1c level, T-temperature

Supplementary Table S3: Quality assessment using the Cochrane Tool

Study	**Random sequence generation (Computerised list, Block method, Stratification, Off site or not)**	**Blinding of participants and personnel (yes, no, not mentioned)**	**Blinding of outcome assessors (yes, no, not mentioned)**	**Sample size estimate (method if mentioned, or not mentioned)**	**Incomplete outcome data: ≥ 90% of participants included in primary outcome (yes, no with the percentage of loss)**	**Clear primary outcome reported (yes, no)**	**Analysis (intention to treat+/- and presence of imputation +/-)**	**Other biases**
Lower extremity temperature monitoring								
Armstrong et al. (2007)[1][2]	Biostatistician generated randomised assignment list. Consented patients were sequentially assigned to each group	No	Yes (Physician blind)	SS=70 per group. Assumption: Incidence of ulceration in controls=70%, intervention group=30-45%, For a sample of 70 per group, α=0.05, 99% power would detect 40% difference.	NR	Yes	NR	

Lavery et al. (2004)[13]	NR	No	Yes (Physician blind)	NR	8.2% loss	No (4 outcomes)	ITT	
Lavery et al. (2007)[15]	Computer generated randomisation list	No- asked not to discuss with other patients or training physicians	Yes (Physician blind)	SS=60 per group. Power=0.8, p<0.05. 10% drop out rate. Assumption: 9% of the enhanced group and 30% of the standard group would get ulcers.	12.7% loss	Yes	ITT	Good study design with a visual monitoring group to look at the confounding effect of such monitoring.
Skafjeld et al. (2015)[14]	Block randomisation- each four subjects into blocks with 2 in each group	Yes single	NR	NR	7.3% loss (only in the intervention group)	Yes	ITT, Imputation+	Nephropathy and vascular risk factor levels were above the recommended limits and were more prevalent in the intervention group at baseline.

Patient education								
Cisneros et al. (2010)[16]	NR	Yes	Yes	Convenient sample	33.9% loss	Yes	NR	
Gershater et al. (2011)[17]	Computer generated list, no stratification	NR	NR	SS=72, power 0.8, p<0.05, reduction on ulcer incidence in 24m from 35-15%	25.1%loss (18% in the intervention group)	Yes	No (only those remaining at the end were considered in final analysis)	Control and Intervention groups were given similar education except the additional discussion session delivered to the intervention group. Some patients changed from the initially assigned groups after randomisation.
Lincoln et al. (2008)[19]	Done at an independent randomisation centre which held a computer-	No	Yes	SS=82, power 0.8, p<0.05, reduction on ulcer incidence in 12m from 35-15%	21.3% loss	Yes	ITT, Imputation+	Non-English speaking and distant patients were excluded. Control group received

	generated random allocation sequence							opportunistic education in addition to standard care.
Monami et al. (2015)[21]	Computer generated list	NR	NR	SS=100, power 0.8, p<0.05, 20% difference between groups	0.8% loss	Yes	No	Premature termination of the study. Outcomes were not collected as a part of study and were sourced from administrative databases
Liang et al. (2012)[18]	NR	NR	NR	NR	4.8% loss	No	No (only those remaining at the end were considered in final analysis)	Rural patients were excluded
Liu et al. (2019)[20]	NR	NR	NR	NR	NR	No	ITT	
Footwear								

Bus et al. (2013)[27]	Online accessible computer-generated allocation sequence using non-deterministic minimisation method conducted by a non-involved person	Yes	Yes	NR	5.8% loss	Yes	ITT, Imputation+	
Lavery et al. (2012)[24]	NR	No	Yes (Physician blind)	SS=120. Binominal outcome: if 35% of the controls would have an ulcer, a sample size of 120 is required to detect 25% difference between groups: power:0.8, p<0.05)	NR	Yes	ITT	
Reiber et al.	Computer generated block	NR	Yes	SS=400 (all three groups). Assumption: Re-ulceration rates will be 30%, 35%, and 58% in cork inserted,	16.5% loss	Yes	ITT, Imputation+	Women were recruited only from one health care system. The number of foot deformities

(2002)[23]	randomisation			polyurethane inserted and control groups with 20% drop out rate. Power:97% to detect a difference between cork inserted group vs controls, and 89% to detect a difference between polyurethane group vs controls.				in the polyurethane group was less. Footwear cross-over occurred in the control group
Uccioli et al. (1995)[22]	NR	NR	NR	NR	NR	Yes	NR	
Rizzo et al. (2012)[23]	Computer generated randomisation list	NR	NR	NR	NR	Yes	NR	VPT was different between the groups at baseline. Loss to follow-up, shoe replacement was not factored in the design
Ulbrecht et al.	Block randomisation stratified	No	Yes	SS=286, power 0.8, $p<0.05$, 15% withdrawal rate, to detect 50%	21.3% loss	Yes	ITT was mentioned	Mean ABPI was higher in controls, and they had a

(2014)[26]	by site and sex; the person responsible was not involved in the trial			reduction in ulceration in 15 months			but not done	higher tendency to avoid foot damaging behaviour at baseline. Early termination of the study.
Lopez-Moral et al. (2019)[28]	Online accessible computer-generated allocation	NR	Yes	SS=138 (not met), power 0.8, $p<0.05$, 20% difference between the ulcer recurrence rate in the two groups and a 20% drop out rate was assumed in the calculation	11.7%	Yes	ITT	

ABPI: Ankle brachial pressure index

ITT: Intention to treat

NR: Not reported

SS: Sample size

VPT: Vibration perception threshold.

Supplementary Table S4: Best-case and worst-case data extraction of diabetic foot ulcers

Study	Group	Number randomised	Reported number	Dropouts	Number of DFUs reported	Numbers of DFUs based on ITT and the best-case scenario	Numbers of DFUs based on ITT and the worst-case scenario
Armstrong et al. (2007)[12]	Intervention	111	111	0[β]	5	5	5
	Control	114	114	0[β]	14	14	14
Lavery et al. (2004)[13]	Intervention	41	41	4	1	1	5
	Control	44	44	3	7	7	10
Lavery et al. (2007)[15]	Intervention	59	59	10	5	5	15
	Control	58	58	6	17	17	23
Skafjeld et al. (2015)[14]	Intervention	21	21	3	7	7	10
	Control	20	20	0	10	10	10
	Intervention	30	21	9	8	8	17

Cisneros et al. (2010)[16]	Control	23	14	9	8	8	17
Gershater et al. (2011)[17]	Intervention	61	40	21	19	19	40
	Control	70	58	12	22	22	34
Lincoln et al. (2008)[19]	Intervention	87	87	15	36	36	51
	Control	85	85	17	35	35	52
Monami et al. (2015)[21]	Intervention	61	60	1	0	0	1
	Control	60	60	0	6	6	6
Liang et al. (2012)[18]	Intervention	31	30	1	1	1	2
	Control	31	29	2	7	7	9
Liu et al. (2019)[20]	Intervention	142	142	0[β]	16	16	16
	Control	142	142	0[β]	33	33	33
Bus et al. (2013)[27]	Intervention	85	85	6	33	33	39
	Control	86	86	4	38	38	42

Lavery et al. (2012)[24]	Intervention	149	149	0[β]	3	3	3
	Control	150	150	0[β]	10	10	10
Reiber et al. (2002)[23 α]	Intervention 1	121	121	17	18	18	35
	Intervention 2	119	119	23	17	17	40
	Control	160	160	26	27	27	53
Uccioli et al. (1995)[22]	Intervention	33	33	0[β]	9	9	9
	Control	36	36	0[β]	21	21	21
Rizzo et al. (2012)[25]	Intervention	148	148	0[β]	17	17	17
	Control	150	150	0[β]	58	58	58
Ulbrecht et al. (2014)[26]	Intervention	79	66	13	6	6	19
	Control	71	64	7	16	16	23
	Intervention	26	26	3	6	6	9

Lopez-Moral et al. (2019)[28]	Control	25	25	3	16	16	19

DFU: Diabetic foot ulcers

ITT= Intention to treat analysis.

β The number of patients who were lost to follow-up was not reported and was assumed to be zero.

α this study had two intervention groups (intervention 1: custom cork-insert group, intervention 2: polyurethane insert group). For the meta analyses the control group was divided equally into two groups to be consistent with the total number of patients included in the study

Supplementary Table S5: Best case and worst-case data extraction of amputation data (minor/major/total amputations) from patient education trials

Study	Group	Number randomised	Reported number	Dropouts	Reported major amputations	Reported minor amputations	Reported total amputations	Major amputations based on ITT and the best-case scenario	Minor amputations based on ITT and the best-case scenario	Total amputations based on ITT and the best-case scenario	Major amputations based on ITT and the worst-case scenario	Minor amputations based on ITT and the worst-case scenario	Total amputation based on ITT and the worst-case scenario
Lincoln et al. (2008)[19]	Intervention	87	87	15	1	8	9	1	8	9	16	23	24
	Control	85	85	17	1	8	9	1	8	9	18	25	26
Monami et al. (2015)[21]	Intervention	61	60	1	0	0	0	0	0	0	1	1	1
	Control	60	60	0	0	0	0	0	0	0	0	0	0

Liang et al. (2012)[18]	Intervention	31	30	1	0	0	0	0	0	0	1	1	1
	Control	31	29	2	0	2	2	0	2	2	2	4	4
Liu et al. (2019)[20]	Intervention	142	142	0[β]	NR	NR	0	NR	NR	0	NR	NR	0
	Control	142	142	0[β]	NR	NR	4	NR	NR	4	NR	NR	4

[β] The number of patients who were lost to follow-up was not reported and was assumed to be zero.

NR: Not reported

ITT= Intention to treat analysis.

Home monitoring of foot temperature

Supplementary Table S6.1: Leave-one out sensitivity analysis of home foot temperature monitoring in prevention of diabetic foot ulcers (worst-case scenario)

Study excluded	**Heterogeneity ($I^{2)}$**	**Odds ratio (95% Confidence intervals)**	**P value**
Armstrong et al. (2007)[12]	0%	0.57 (0.32-1.02)	0.060
Lavery et al. (2004)[13]	0%	0.52 (0.29-0.91)	0.020
Lavery et al. (2007)[15]	0%	0.50 (0.26-0.97)	0.040
Skafjeld et al. (2015)[14]	0%	0.45 (0.26-0.79)	0.005

Patient education

Supplementary Table S7.1: Leave-one out sensitivity analysis of patient education in prevention of diabetic foot ulcers (worst-case scenario)

Study excluded	**Heterogeneity (I^2)**	**Odds ratio (95% Confidence intervals)**	**P value**
Cisneros et al. (2010)[16]	76%	0.60 (0.26-1.37)	0.230
Gershater et al. (2011)[17]	40%	0.47 (0.26-0.84)	0.010
Lincoln et al. (2008)[19]	76%	0.49 (0.18-1.28)	0.150
Monami et al. (2015)[21]	73%	0.66 (0.32-1.37)	0.270
Liang et al. (2012)[18]	71%	0.69 (0.34-1.43)	0.320
Liu et al. (2019)[20]	69%	0.63 (0.27-1.48)	0.290

Supplementary Table S7.2: Leave-one out sensitivity analysis of patient education in prevention of total diabetic foot amputations (minor + major amputations), (worst-case scenario)

Study excluded	**Heterogeneity (I^2)**	**Odds ratio (95% Confidence intervals)**	**P value**
Lincoln et al. (2008)[19]	19%	0.35 (0.06-2.03)	0.240
Monami et al. (2015)[21]	34%	0.49 (0.15-1.62)	0.240
Liang et al. (2012)[18]	21%	0.75 (0.24-2.39)	0.630
Liu et al. (2019)[20]	0%	0.82 (0.44-1.52)	0.520

Supplementary Table S7.3: Leave-one out sensitivity analysis of patient education in prevention of diabetic foot major amputations, (worst-case scenario)

Study excluded	**Heterogeneity (I^2)**	**Odds ratio (95% Confidence intervals)**	**P value**
Lincoln et al. (2008)[19]	0%	0.92 (0.13-6.25)	0.940
Monami et al. (2015)[21]	0%	0.80 (0.39-1.64)	0.540
Liang et al. (2012)[18]	0%	0.90 (0.43-1.86)	0.770

Supplementary Table S7.4: Leave-one out sensitivity analysis of patient education in prevention of diabetic foot minor amputations, (worst-case scenario)

Study excluded	**Heterogeneity (I^2)**	**Odds ratio (95% Confidence intervals)**	**P value**
Lincoln et al. (2008) [19]	42%	0.62 (0.05-7.77)	0.710
Monami et al. (2015) [21]	26%	0.66 (0.23-1.93)	0.450
Liang et al. (2012)[18]	0%	0.91 (0.47-1.74)	0.770

Offloading footwear

Supplementary Table S8.1: Adherence to offloading footwear

Study	**Method of data collection**	**Definition of good adherence**	**Intervention group number**	**Control group number**	**Adherence in intervention %**	**Adherence in control %**	**Significance**	**Odds ratio (95% Confidence intervals) of each study to the pooled estimate**
Lavery et al. (2012)[24]	Questionnaire, Data collected as number of patients who used offloading footwear <4h, 4-8h,8-12h,>12h in	Undefined	149	150	4h: 15.5% 4-8h: 52.0% 8-12h: 25.7% 12-16h: 6.8%	4h: 10.6% 4-8h: 55.0% 8-12h: 30.5%	No significance	0.29 (0.08-1.07)

	both intervention and control groups separately.					12-16h: 3.9%		
Reiber et al. 1 (2002)[23]	Data collected as patients time spent as “in shoes” or “not in shoes” when they are out of the bed.	Undefined	121	80	83.0%	Not reported	Not reported	0.80 (0.44-1.47)
Reiber et al. 2 (2002)[23]	Data collected as patients time spent as “in shoes” or “not in shoes” when they are out of the bed.	Undefined	119	80	86.0%	Not reported	Not reported	1.05 (0.58-1.92)
Ulbrecht et al. (2014)[26]	Questionnaire on footwear use. (Appendix attached)	Undefined	79	71	Not reported	Not reported	Not reported	0.66 (0.32-1.35)
Uccioli et al. (1995)[22]	Use of specific footwear was rated as “infrequent”, “occasional”,	Undefined	33	36	100% adhered either frequently or occasionally	Not reported	Not reported No difference between those who developed ulcers and those who did not	0.27 (0.10-0.74)

	"frequent" or "continuous"						within the intervention group	
Lopez-Moral et al. (2019)[28]	Adherence >60% or not measure by a questionnaire	60% as measured by a questionnaire	26	25	88.4% (23/26)	92.0% (23/25)	In the intervention arm 4 patients developed ulcers while 14 in the control group developed ulcers. This difference is statistically significant (p=0.003)	0.17 (0.05-0.57)
Bus et al. (2013)[27]	Adherence >80%: was measured by a temperature sensitive monitor installed to the shoes and was interpreted with the physical activity data recorded from a monitor placed in the ankle over 7 days.	80% as measured objectively	85	86	41.2% (35/85)	51.2% (44/86)	In the intervention arm 9 patients developed ulcers while 21 patients in the control arm developed ulcers. This difference was statistically significant (p=0.045)	0.89 (0.49-1.62)

Supplementary Table S8.2: Leave-one out sensitivity analysis of offloading footwear in prevention of diabetic foot ulcers (worst case scenario)

Study excluded	**Heterogeneity (I^2)**	**Odds ratio (95% Confidence intervals)**	**P value**
Bus et al. (2013)[27]	73%	0.43 (0.24-0.76)	0.004
Lavery et al. (2012)[24]	75%	0.50 (0.29-0.87)	0.010
Reiber et al. (2002)[23] (custom cork inserts)	74%	0.44 (0.24-0.79)	0.006
Reiber et al. (2002)[23] (polyurathane inserts)	70%	0.42 (0.24-0.72)	0.020
Uccioli et al. (1995)[22]	74%	0.51 (0.30-0.89)	0.020
Rizzo et al. (2012)[23]	54%	0.59 (0.38-0.91)	0.020
Ulbrecht et al. (2014)[26]	76%	0.45 (0.25-0.82)	0.009
Lopez-Moral et al. (2019)[28]	72%	0.53 (0.32-0.90)	0.020

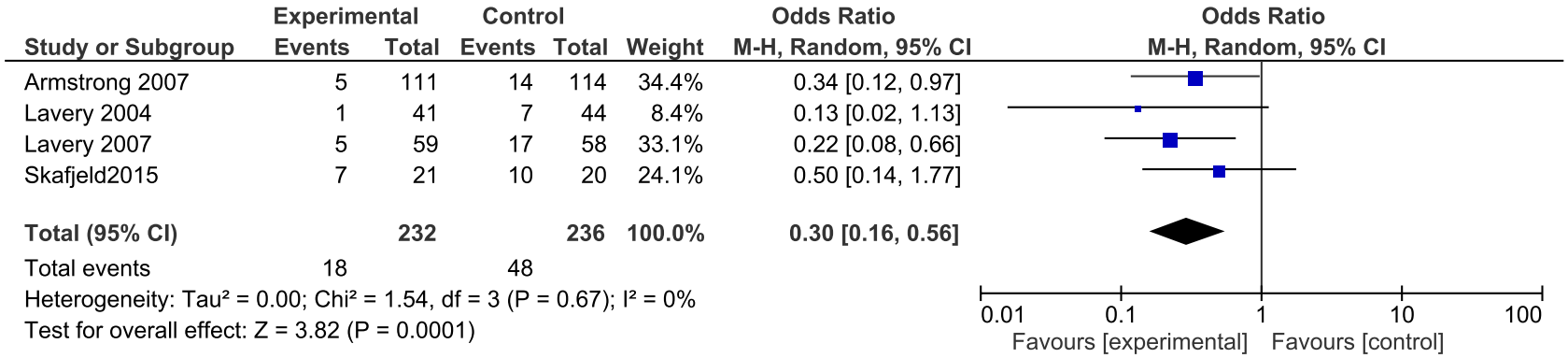
Supplementary Table S8.3: Leave-one out analysis of the sub-group analysis of custom-made orthoses or custom-made shoes in prevention of diabetic foot ulcers.

Study excluded	**Heterogeneity (I^2)**	**Odds ratio (95% Confidence intervals)**	**P value**
Bus et al. (2013)[27]	68%	0.40 (0.22-0.75)	0.004
Lavery et al. (2012)[24]	75%	0.50 (0.27-0.92)	0.030
Reiber et al. (2002)[23] (custom cork inserts)	71%	0.41 (0.21-0.79)	0.008
Uccioli et al. (1995)[22]	74%	0.51 (0.27-0.95)	0.030
Rizzo et al. (2012)[23]	32%	0.62 (0.41-0.95)	0.030
Ulbrecht et al. (2014)[26]	75%	0.43 (0.22-0.85)	0.020

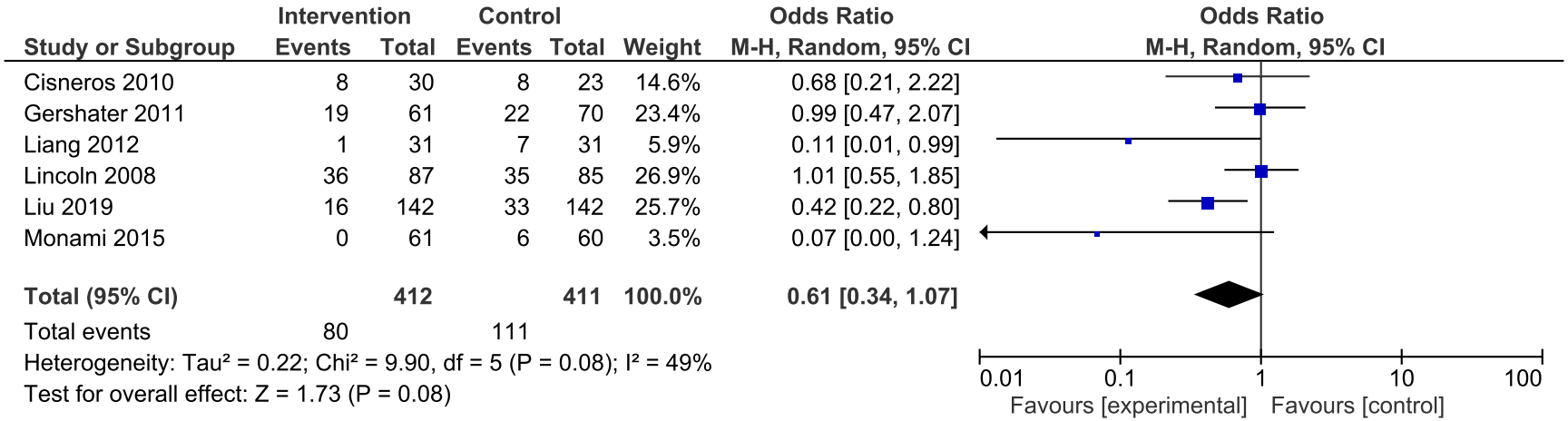
Supplementary Figures

Results indicate the pooled effect estimates of the included studies. The centre of the diamond represents the summary odds ratio and the edge of the diamond represents the 95% confidence intervals. M-H, Mantel-Haenszel's statistical method; CI, Confidence Interval

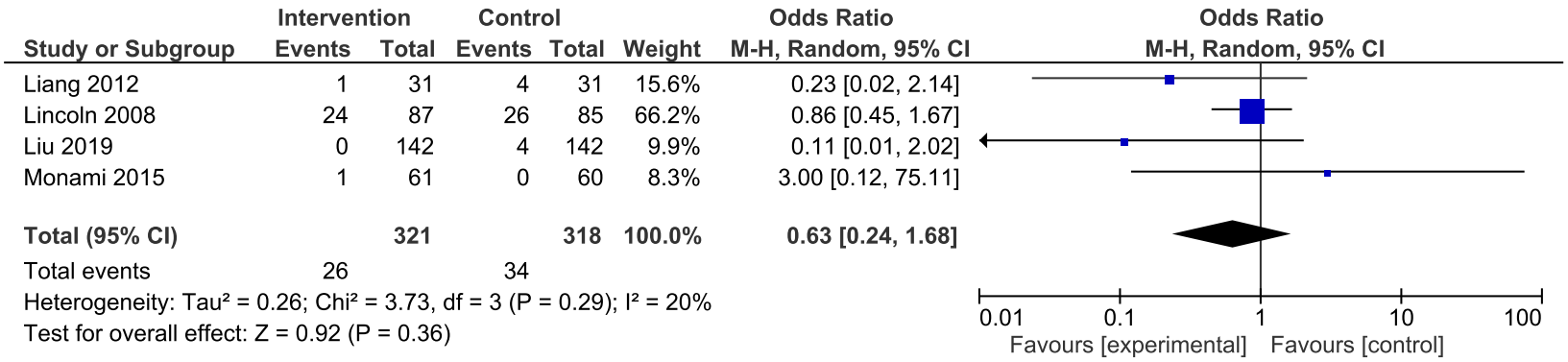
Supplementary Figure 1: Forest plot of the group of studies looking at home foot temperature monitoring in prevention of diabetic foot ulcers (best case scenario)



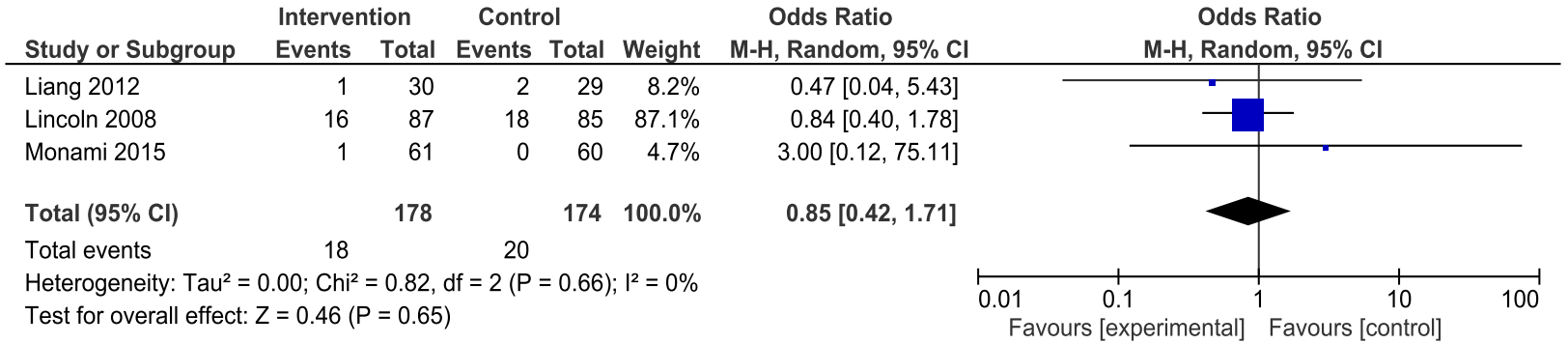
Supplementary Figure 2: Forest plot of the group of studies looking at patient education in prevention of diabetic foot ulcers (best case scenario)



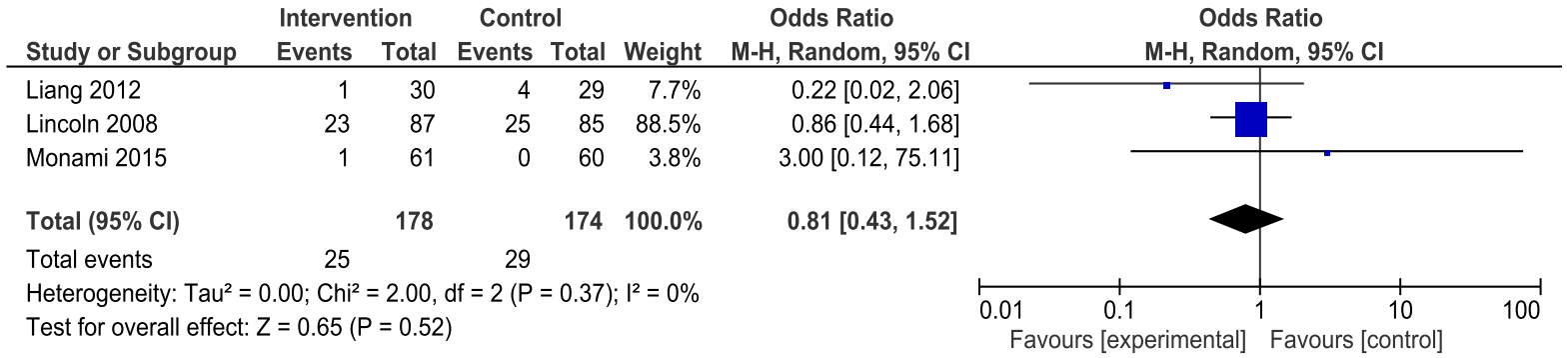
Supplementary Figure 3: Forest plot of the group of studies looking at patient education in prevention of total amputations (minor + major amputations), (worst case scenario)



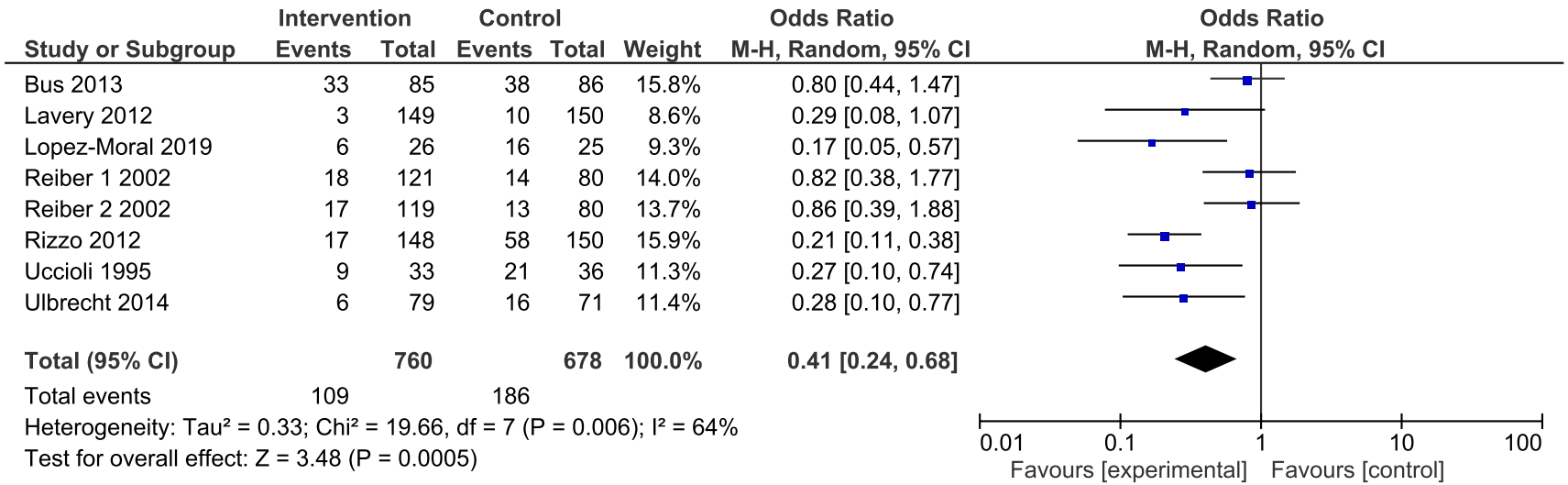
Supplementary Figure 4: Forest plot of the group of studies looking at patient education in prevention of major amputations, (worst case scenario**)**



Supplementary Figure 5: Forest plot of the group of studies looking at patient education in prevention of minor amputations, (worst case scenario)

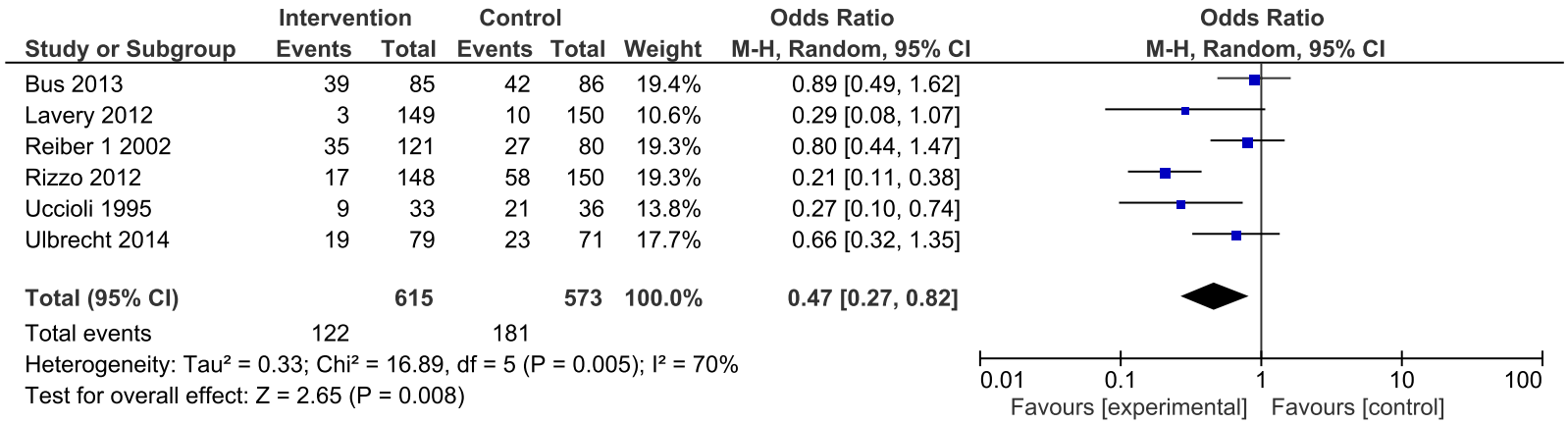


Supplementary Figure 6: Forest plot of the group of studies looking at offloading footwear in prevention of diabetic foot ulcers (best case scenario)



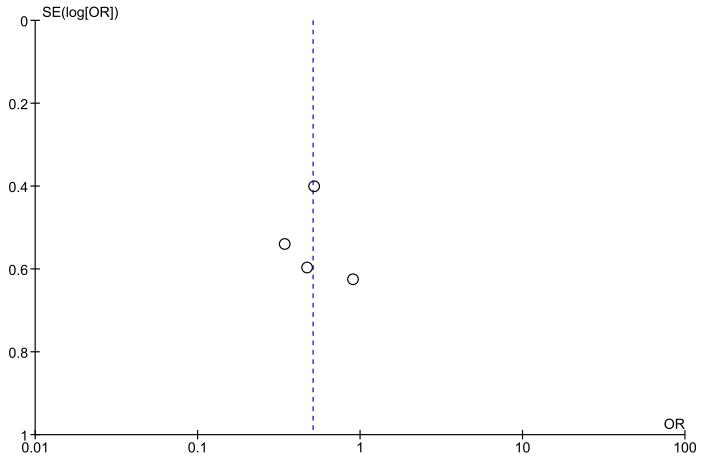
“Reiber 1” in all figures refers to the 1st intervention group using custom-cork inserts and “Reiber 2” refers to the 2nd intervention group using polyurethane inserts of the RCT conducted by Reiber et al in 2002

Supplementary Figure 7: Forest plot of the sub-group analysis of studies looking at custom made offloading orthoses/footwear in prevention of diabetic foot ulcers (worst case scenario)



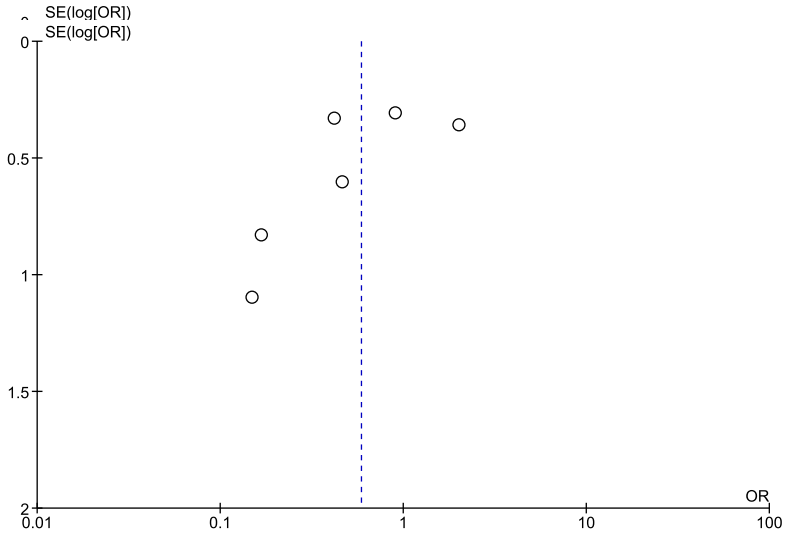
"Reiber 1" in all figures refers to the 1st intervention group using custom-cork inserts of the RCT conducted by Reiber et al in 2002

Supplementary Figure 8: Funnel plot of the group of studies looking at home foot temperature monitoring in prevention of diabetic foot ulcers (worst case scenario)



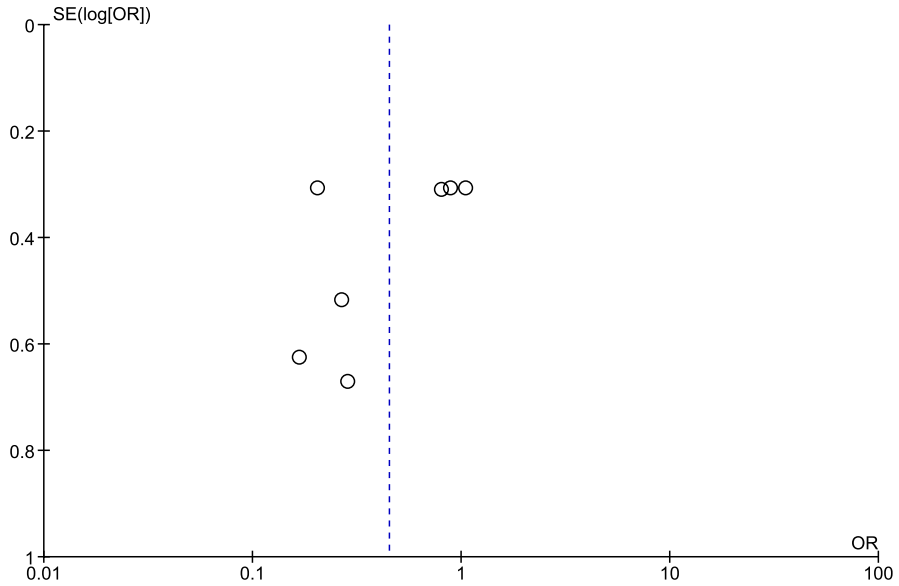
SE, standard error; OR, odds ratio

Supplementary Figure 9: Funnel plot of the group of studies looking at patient education in prevention of diabetic foot ulcers (worst case scenario)



SE, standard error; OR, odds ratio

Supplementary Figure 10: Funnel plot of the group of studies looking at offloading footwear in prevention of diabetic foot ulcers (worst case scenario)



SE, standard error; OR, odds ratio

8. Discussion and Recommendations

This concluding chapter will summarise the main findings from the previous chapters, list the limitations and strengths, and outline recommendations for future research.

The objectives we aimed to answer were:

1. To systematically review the incidence and risk factors for readmission to hospital to treat DFD

2. To compare the inter- and intra-observer reproducibility of the Wound Ischemia Foot Infection classification (WIFI), University of Texas Wound Classification System (UTWCS), Site, Ischemia, Neuropathy, Bacterial Infection, Area of the ulcer and Depth (SINBAD) classification system and Wagner classification using photographs of diabetes-related foot ulcers.

3. To prospectively examine the rate and risk factors for DFD related readmission to hospital at a regional tertiary care hospital facility in North Queensland, Australia.

4. To compare the severity and distribution of PAD between Aboriginal and Torres Strait Islander Australians and non-Indigenous Australians presenting with symptomatic PAD

5. To assess the association of remoteness of place of residence with a requirement for repeat amputation (either minor or major) and mortality in residents of North Queensland, Australia.

6. To perform a systematic review and meta-analysis of data from randomized controlled trials (RCT) examining the efficacy of home foot temperature monitoring, patient education and offloading preventing DFU.

8.1 Disease burden associated with diabetes-related foot disease and rationale of the studies

Diabetes-related foot disease (DFD) is a global problem causing a substantial health care burden to both developed countries (1-3) as well as developing countries (4). It is an ongoing disease that results in recurrent diabetic foot ulcers (DFU) and diabetic foot infections (DFI) (5). Recurrence of DFD results in hospital readmission for further surgical management or for minor or major amputations (5, 6). DFD is associated with high rates of morbidity and mortality resulting in reduced health-related quality of life and a substantial economic burden to the healthcare system (7). With this rising problem, the focus and studies published on DFD had increased considerably since the year 2015 focusing on the prevention of DFD (8).

The burden of DFD in Australia is also known to be high and is a leading cause of disability (9). Approximately there are 28,000 hospital admissions in Australia occur following DFU with possibly over 4500 amputations (10). It is also associated with high mortality rate and the overall cost of healthcare expenditure is around 1.6 billion Australian dollars per year (11). However, hospital readmission in the Australian context is not very well understood. The disease burden related to DFD and peripheral artery disease (PAD) among Aboriginal and Torres Strait Islander People is also reported to be 3 to 6 times higher (12). Given the instance where 5-7% of the North Queensland population comprise of Aboriginal and Torres Strait islander people, there is a place to investigate the disease burden of DFD in North Queensland, to improve outcomes and to explore possible methods of prevention. Based on the above background we conducted multiple studies, and the summary findings of our research are given in Table 8.1.

Table 8-1 Summary table of the quality assessment

Chapter	Title	Key findings	Conclusion
2	A systematic review and meta-analysis of the incidence and risk factors for readmission to hospital in people with diabetes-related foot disease	We were able to summarise the total and DFD related rate of 30-day readmission through a systematic review and meta-analysis. Meta analysis findings suggested that the total 30-day readmission rate was 22.0% and that the DFD-related readmission rate was 10.0%. Meta-regression confirmed that risk factors for total 30-day readmission were male sex and peripheral neuropathy (PN). Having private health insurance was protective of total 30-day readmission. Coronary artery disease was a risk factor DFD related 30-day readmission.	This systematic review suggested that about 20% of patients with DFD are readmitted to hospital within 30 days. Risk factors for readmission included male gender, PN and coronary artery disease.
3	Repeatability, completion time and predictive ability of four diabetes-related foot ulcer classification systems	WIFI had substantial agreement between observers compared to other foot ulcer classification systems and therefore is a reliable foot ulcer classification to be used in clinical practice.	The WIFI score can be completed with substantial agreement between trained observers.
4	Risk factors for hospital readmission for diabetes-related foot disease: A prospective cohort study	Over 50% of the patients who were admitted for treatment of DFD were readmitted over the next year. Male sex, absence of pedal pulses (a surrogate marker of PAD) and loss of protective sensation (LOPS) (a surrogate marker of poorly controlled diabetes) were independent risk factors for readmission. After risk adjustment absent pedal pulses and LOPS continued to be risk factors for readmission.	Over 50% of patients admitted to hospital for treatment of DFD are readmitted within one year. Patients with absent pedal pulses and those with LOPS are twice as likely to be readmitted.
5	Cohort study examining the presentation, distribution, and outcome of peripheral artery disease in Aboriginal and Torres Strait Islander Australians and non-Indigenous Australians	Aboriginal and Torres Strait Islander people are more likely to present with Chronic limb threatening ischemia (CLTI) and had a greater median Angiographic score for each limb as well as for the tibial arteries and had higher risk of major amputation and major adverse cardiovascular events (MACE).	Compared with non-Indigenous Australians, Aboriginal and Torres Strait Islander Australians had more severe tibial artery disease and were at a higher risk of major amputation and MACE.
6	Association between remoteness of residence and requirement for repeat amputation and mortality	The risk of major amputation and death were not significantly different between those who present from rural or remote areas compared to those presenting with reginal areas and for those who identified them as Aboriginal and	Major amputation and death are common following minor amputation to treat DFD. Risk of major amputation is increased by

	following a minor amputation in North Queensland Australia	Torres Strait Islander people. Major amputation rate was closer to 20% and mortality rate was closer to 50%. Risk of both major amputation and death were increased by PAD, ischemic heart disease (IHD) and osteomyelitis.	IHD, PAD and osteomyelitis. Remoteness or Aboriginal and Torres Strait Islander status were not associated with major amputation
7	Meta-analyses of randomised controlled trials reporting the effect of home foot temperature monitoring, patient education or offloading footwear on the incidence of diabetes-related foot ulcers.	We were able to summarise evidence from three types of interventions recommended to reduce recurrence of DFU, namely offloading footwear, home foot temperature monitoring and patient education. The meta-analyses findings suggested that offloading footwear and home foot temperature monitoring halved the recurrence of DFU but the findings from patient education trials did not confirm this. Sensitivity analyses confirmed that the offloading footwear findings were consistent.	This meta-analysis suggests that offloading footwear is effective in reducing the incidence of DFU. Home foot temperature monitoring also appears beneficial but pooled evidence from patient education trials did not confirm its efficacy in reducing recurrent DFU.

8.2 Discussion of the key findings from the research reported in this thesis

This section will discuss the key findings of the research presented in this thesis with relation to the original research questions outlined in Chapter 1.

8.2.1 Question 1: Has previous systematic reviews been conducted to pool evidence form cohort studies to assess the incidence and risk factors for 30-day readmission to hospital following an index admission to treat DFD? What are the risk factors for such readmissions?

To our knowledge this is the first systematic review and meta-analysis conducted to synthesize a collective rate of 30-day readmission following an index admission for DFD in accordance with Preferred Reporting Items for Systematic Reviews and Meta-Analysis (PRISMA) guidelines. The study was registered with prospectively registered systematic reviews in health and social care website (PROSPERO) and we were able to identify 16 studies (13-28). Our findings suggest that total 30-day readmission following hospital treatment of an index DFD occurs approximately in 22% of the patients and DFD related readmission occurs in about 10% of those patients.

Meta-regression findings suggested that male sex and PN significantly increased the risk of 30-day readmission and that CAD was a risk factor for DFD-related readmission. Having private health insurance was protective against total 30-day readmission. PN is a surrogate marker of poorly control diabetes and these patients may have concurrent macrovascular complications such as PAD and similar microvascular complications such as diabetes-related nephropathy which increase the risk of readmission (17). Private health insurance is a surrogate marker of higher socio-economic standards. Socio-economic aspects are important determinants of health status with deprived patients more likely to have poor outcomes possibly due to poor living conditions and limited access to care and this is reflected by the reduced risk associated with private health insurance seen in our meta-regression findings. It is also important to note that the studies included in this systematic review were published following the increasing focus on hospital readmission in the US hospitals since the introduction of the Affordable Care Act in 2015 (29, 30).

8.2.2 Question 2: What are the inter and intra-observer reproducibility characteristics of the Wound Ischaemia foot Infection (WIFI) score? Has it been compared against other foot classifications for its reproducibility, completion time and ability to predict 30-day amputation?

We found the WIFI classification system had substantial inter-observer and excellent intra-observer reproducibility. The site ischemia neuropathy, bacterial infection, area and depth (SINBAD) system had moderate inter-observer and excellent intra-observer reproducibility. Comparably, University of Texas wound classification system (UTWCS) and Wagner classifications had only fair inter-observer and moderate intra-observer reproducibility. Previous studies have examined the reproducibility of DFU classification systems excluding WIFI and these studies showed that Wagner, SINBAD and UTWCS classifications had moderate agreement (31-33) similar to our findings. The current study is the first to report the reproducibility of the WIFI classification system which had substantial agreement between different observers and almost perfect intra-observer agreement (34). Additionally, we prospectively investigated if these classification systems were able to reliably predict 30-day amputation rates, either minor or major amputations, with negative results.

8.2.3 Question 3: Have incidence of hospital readmission and risk factors for such readmissions following DFD been prospectively investigated in Australia?

To our knowledge this is the largest prospective cohort study conducted outside the USA to investigate DFD-related readmission to hospital. In this study 21.6% of the recruited cohort comprised of Aboriginal and Torres Strait Islander People. Given Aboriginal and Torres Strait Islander People is around 4-5% of the total population of North Queensland, the results indicate a substantial burden of DFD among the Aboriginal and Torres Strait Islander People in this region (35). It is noteworthy that over 50% of the participants were readmitted within one year for a DFD related cause indicating the substantial hospital burden caused by DFD (5). Absence of pedal pulses and LOPS were independent risk factors for readmission related to DFD. Similar results have

previously been shown in studies looking at risk factors for overall hospital admissions for DFD (36). Incidentally these are the key factors that contribute to develop foot ulcer in patients with long standing uncontrolled diabetes (5). Despite the high disease burden among the Aboriginal and Torres Strait Islander People, the rates of readmission were similar to that of non-Indigenous participants which shows uniform utilisation of care delivered to all populations in Queensland.

The current IWGDF guidelines recommned offloading footwear to be used by those patients especially if they have LOPS to prevent recurrence of foot ulcers (37). Planning the discharge of the patient and arranging for routine follow up may help to prevent future readmission (38). Other secondary prevention measures include regular foot care by a podiatrist, control of risk factors such as blood glucose and dyslipidaemia (39).

8.2.4 Question 4: Has there been an investigation on the anatomical distribution, severity, and outcomes of peripheral artery disease (PAD) in Aboriginal and Torres Strait Islander Australians compared with non-Indigenous Australians?

To our knowledge this is the first objective comparison of the distribution and severity of PAD in Aboriginal and Torres Strait Islander Australian people compared to non-Indigenous Australians. We found that Aboriginal and Torres Strait Islander Australians were significantly more likely to present late with chronic limb threatening ischemia (CLTI) and had significantly higher ANGIO scores, particularly in the tibial arteries compared to non-Indigenous Australians. This association remained significant even in analyses restricted to patients with diabetes or CLTI alone. We believe this finding may partly explain the higher rates of major amputation in Aboriginal and Torres Strait Islander Australians compared to non-Indigenous Australians (40) since tibial artery disease is a prognostic marker for amputation (41).

Aboriginal and Torres Strait Islander Australians included in our study were significantly younger at presentation, had a higher prevalence of diabetes and presented with CLTI. They also had a higher risk of major amputation and MACE during the follow up period, similar to previous studies

(42). There is evidence to suggest that tibial artery disease is an important risk factor for CLTI (43). Detailed assessment of the lower extremity arteries using a reproducible scoring system (44) showed that the tibial artery ANGIO score was significantly greater in Aboriginal and Torres Strait Islander than non-Indigenous participants. One possible explanation is the reduced angiogenic capacity of the high-density lipoprotein extracted from the plasma of Aboriginal and Torres Strait Islander participants with diabetes (45).

A notable difference was seen in the rate of lower limb revascularisation despite the high incidence of CLTI amongst Aboriginal and Torres Strait Islander participants compared to non-Indigenous Australians in our study may be explained by the increased challenge of revascularisation of distal arteries, but this requires further investigation.

8.2.5 Question 5: Has any previous study examined the associations between remoteness and Aboriginal and Torres Strait Islander status with risk of major amputation and death following initial treatment of diabetes-related foot disease (DFD) by minor amputation?

This study is the first in Australia aiming to assess the impact of geographic variation on the outcome of people with diabetes related minor amputations and their subsequent outcomes. The study included 534 patients and of those, 144 (27.0%) were Aboriginal and Torres Strait Islanders. Additional analyses were carried out to assess if the same outcomes would change based on the Aboriginal and Torres Strait Islander status. The main analysis was focused on a large geographic region covered by a tertiary vascular services unit in Townsville University Hospital (TUH) in North Queensland Australia with recruitment extending over 19 years. We found that around one fifth of the participants in our cohort underwent a major amputation and about half of participants died during the follow up period. Importantly there were no significant differences between the rates of major amputation or other outcomes by remoteness or by Aboriginal and Torres Strait Islander status which may reflect equitable care given to participants presenting from diverse backgrounds (46).

According to our study the significant predictive factors of major amputation were ischemic heart disease (IHD), PAD, osteomyelitis, and foot ulcers. These factors continued to remain significant in different cox regression models we created including remoteness or Aboriginal and Torres Strait Islander status. We found that IHD, PAD and osteomyelitis were weak classifiers of a subsequent major amputation following a minor amputation for DFD based on the c-index. Previous studies have confirmed that PAD and osteomyelitis are major predictors of subsequent major amputation in patients with DFU similar to our findings (47, 48).

8.2.6 Question 6: Has an updated pooled analyses been done to show the efficacy home foot temperature monitoring, patient education, and offloading footwear in reducing the incidence of DFU?

Evidence from RCTs from different interventions such as usage of offloading footwear, home-foot temperature monitoring and structured patient education to prevent recurrence of DFU lacks updated pooled evidence. Therefore, we conducted meta-analyses to synthesize and produce collective evidence for each one of the above-mentioned interventions. Meta-analyses suggested that offloading footwear is effective at reducing the incidence of DFU. The main analysis also suggested that home foot temperature monitoring reduced the incidence of foot ulcers, but the findings were not robust in all sensitivity analyses. Collective evidence suggest that previously tested patient education programs were not effective in reducing recurrence of DFU. An updated meta-analysis was conducted on home foot temperature monitoring once a new trial was published in the year 2021 (49).

This meta-analysis provides robust evidence that offloading footwear reduces the incidence of DFU, and the findings are consistent with a previous meta-analysis (50). There was a high heterogenicity noted within the included trials which may reflect the different types of footwear tested, the differences in footwear in the control groups and the variable footwear adherence rates reported in the trials (51, 52). A sub-analysis suggested the benefit of custom-made orthoses or footwear which supports the recommendations given by the IWGDF guidelines (53). Bus et al.

reported that participants who adhered to their offloading shoes had significantly lower recurrence rates of DFUs compared to the control group (52).

8.3 Strengths and limitations of the studies

8.3.1 Strengths and limitations of systematic review and meta-analyses

Both systematic reviews were conducted in accordance with Preferred Reporting Items for Systematic Reviews and Meta-Analysis (PRISMA) guidelines. Both studies were registered with prospectively registered systematic reviews in health and social care website (PROSPERO). The systematic review reported in chapter 2 was the first of its nature conducted to synthesize a collective rate of 30-day readmission following an index admission for DFD. The systematic review reported in Chapter 7 provided updated pooled evidence from three separate interventions namely, offloading footwear, home foot temperature monitoring and patient education that is used to reduce recurrence of DFU.

Both systematic reviews we conducted had several limitations. There was a substantial heterogeneity in the design of the included studies and the populations that were included in the individual studies.

The systematic review that pooled evidence from cohort studies looking at 30-day readmission rate consisted of studies mainly conducted in USA, which limited the generalisability of its results. There was a substantial heterogeneity in the study designs of the included studies and populations that were studied which limits interpretation of the regression analyses. Additional limitations of the included studies in this systematic review were retrospective study design, possible data omissions related to extraction of data using ICD 9 or 10 codes, inconsistent reporting of risk factors, small sample sizes and lack of reporting on DFD related readmission rates and reasons for readmission.

The main limitation of the studies included in the systematic review that was conducted to pool evidence from RCTs that were investigating three different interventions was the high or unclear risk of bias seen in the individual studies. Other limitations include lack of reporting of sample size

calculations, absence of outcome and assessor blinding, large patient drop-out rates as reported in a few studies and failure to comment on the method of randomisation in five studies. There was also marked heterogeneity in follow-up frequency and in reporting of patient characteristics in the included studies. Funnel plots suggested a risk of publication bias related to all three interventions.

8.3.2 Strengths and limitations of the studies conducted in the Townsville University Hospital

The strengths include recruiting large numbers of Aboriginal and Torres Strait Islander participants into the studies, prospective design of two studies (Chapter 3 and 4) and long recruitment time of 20 years in the study that looked at subsequent major amputations and other outcomes following an index minor amputation.

Limitations of the studies include single center design, retrospective design (Chapter 5 and 6), small to moderate sample sizes of all four studies and poor generalisability of outcomes to the other health care settings in other regions of Australia as well as other countries as these studies were conducted in a unique geographic location in North Queensland Australia.

It is also important to note that data collection for all studies were significantly affected following the Covid-19 global pandemic which limited access to the hospital, recruitment, and examination of participants.

8.4 Future directions

Multicentre prospective cohort studies with larger sample sizes with longer follow up periods including patients with DFD are lacking in current literature and such studies may help in confirming risk factors for DFD related readmissions. There is also a place for studies to be conducted to assess the cost of DFD related readmissions in an Australian setting.

Tele-medicine in DFD is an emerging field. Tele-Medicine may help to reduce the overall disease burden related to DFD in North Queensland by which equitable care can be delivered to patients in remote locations who find it difficult to attend routine clinics in Townsville University Hospital.

There is an avenue for future studies to be conducted on patients presenting from distant regions with DFD/DFU using Tele-medicine. We believe WIFI is a useful tool with substantial reliability to be used in recording baseline and progression of people with DFU.

We found that Aboriginal and Torres Strait Islander People had distal artery disease and revascularisation rates are low among them compared to non-Indigenous patients. Further studies need to be carried out including larger number of participants to look for possible risk factors associated with distal vessel disease as in-addition to diabetes, there may be other underlying risk factors associated with distal vessel disease.

Amputations following DFD is an established problem and multicentre studies maybe useful to quantify the disease burden associated with major amputation in Australia. There is also a lack of potential studies looking at the costs associated with such amputations. These estimates will benefit the re-formation of future practices to reduce hospital readmissions, amputations, and possible deaths associated with DFD.

Trials looking at home foot temperature monitoring have not been conducted in tropical regions in the world, and North Queensland may be a good location to conduct a similar trial given the tropical nature of the location. It will be interesting to see if differences of temperature between the two feet can be accurately measured using infrared thermometry.

Offloading footwear is recommended to use in all patients at risk of developing a DFU and is recommended by IWGDF as well as the current Australian guidelines (54). Offloading footwear trials using custom-made shoes have not been conducted in Australia, and there is a place for similar studies to be carried out in Australia.

Since Australian population comprise of multicultural and patients from different ethnicities there is a place for culturally accepted patient education programs to be developed.

8.5 Conclusion

The findings of this thesis suggest there still exists a substantial disease burden related to DFD in North Queensland Australia. Readmission following DFD is significant in the region and is associated with absent pedal pulses and LOPS. Disease burden related to PAD is significantly greater in Aboriginal and Torres Strait Islander People. Aboriginal and Torres Strait Islander people tend to present with severe tibial artery disease which may contribute to the associated higher rates of major amputation observed. Major amputation and death are common following minor amputation to treat DFD and the risk of major amputation is increased by IHD, PAD and osteomyelitis. Offloading footwear is shown to be effective and is recommended in preventing recurrence of DFD.

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9. Appendix

Symposium/Special Issue

Repeatability, Completion Time, and Predictive Ability of Four Diabetes-Related Foot Ulcer Classification Systems

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Abstract

Introduction: The inter and intra-observer reproducibility of measuring the Wound Ischemia foot Infection (WIfI) score is unknown. The aims of this study were to compare the reproducibility, completion times and ability to predict 30-day amputation of the WIfI, University of Texas Wound Classification System (UTWCS), Site, Ischemia, Neuropathy, Bacterial Infection and Depth (SINBAD) and Wagner classifications systems using photographs of diabetes-related foot ulcers.

Methods: Three trained observers independently scored the diabetes-related foot ulcers of 45 participants on two separate occasions using photographs. The inter- and intra-observer reproducibility were calculated using Krippendorff's α. The completion times were compared with Kruskal-Wallis and Dunn's post-hoc tests. The ability of the scores to predict 30-day amputation rates were assessed using receiver operator characteristic curves and area under the curves.

Results: There was excellent intra-observer agreement ($\alpha > 0.900$) and substantial agreement between observers ($\alpha = 0.788$) in WIfI scoring. There was moderate, substantial, or excellent agreement within the three observers ($\alpha > 0.599$ in all instances except one) and fair or moderate agreement between observers (α of UTWCS=0.306, α of SINBAD=0.516, α of Wagner=0.374) for the other three classification systems. The WIfI score took significantly longer ($P < .001$) to complete compared to the other three scores (medians and inter quartile ranges of the WIfI, UTWCS, SINBAD, and Wagner being 1.00 [0.88-1.00], 0.75 [0.50-0.75], 0.50 [0.50-0.50], and 0.25 [0.25-0.50] minutes). None of the classifications were predictive of 30-day amputation ($P > .05$ in all instances).

Conclusion: The WIfI score can be completed with substantial agreement between trained observers but was not predictive of 30-day amputation.

Keywords

diabetic foot, telemedicine, reproducibility, diabetes-related foot ulcers, prediction of amputation

Background

People with diabetes-related foot ulcers (DFUs) are at high risk of major complications such as minor and major amputation.[1] DFU is a leading cause of global disability and requirement for hospital admission.[1-3] Grading the severity of DFUs using a classification system is of potential value for predicting the risk of these complications.[4] Commonly used DFU classification systems include the Wagner,[5] University of Texas Wound Classification System (UTWCS),[6] the Site, Ischemia, Neuropathy, Bacterial Infection, and Depth (SINBAD) score,[7] and the Wound Ischemia foot Infection (WIfI) score.[8] These systems are typically designed to aid treatment decisions, communication between health professionals, in conducting audits, benchmarking between services and predicting outcomes.[9,10] It is important that any DFU classification system can be repeated by different clinicians in a rapid time frame and the findings predict outcome.[11]

The International Working Group on Diabetic Foot (IWGDF) guideline recommends the use of the WIfI classification system.[10] Whilst, the reproducibility of a number of other different DFU classification systems—such as the UTWCS, SINBAD, and Wagner—have been previously reported,[12-15] to our knowledge the reproducibility of the

WIfI score has not been assessed or compared to other systems.[16] Furthermore, whilst studies have compared the ability of these different classification systems to predict one-year risk of amputation, none to our knowledge have investigated their ability to predict 30-day amputation risk.[9,17-19]

The primary aim of this study was to compare the inter- and intra-observer reproducibility of the WIfI, UTWCS, SINBAD and Wagner classifications using photographs of DFUs. Secondary aims were to compare completion times and the ability of these scoring systems to predict 30-day risk of amputation.

Methods

This was a prospective single-centre observational cohort study of patients who were admitted to the Townsville University Hospital (TUH) in North Queensland, Australia, for inpatient treatment of a DFU. Recruitment occurred from January 1, 2020 to June 30, 2020. Inclusion criteria were diagnosis with type I or II diabetes, an active DFU, age over 18years and written informed consent. Patients who presented with gangrene or who had wound debridement or amputations before they could be recruited to the study were excluded. Ethical approval for the study was granted by the Townsville Hospital and Health Services Ethics Committee (HREC/12/QTHS/202 and HREC/12/QTHS/203) and all participants provided written informed consent.

The following data were collected on study entry, which were self-reported by the patients and later verified with the medical records: age, time since diagnosis of diabetes, height, weight, smoking history, previous history of hospital admission for the treatment of DFU or amputation. Examination was performed to assess DFU location and the presence of peripheral neuropathy using a 10-g Semmes-Weinstein monofilament and 128-Hz tuning fork. Peripheral neuropathy was defined when one or more of four sites in the foot (plantar surfaces of the great toe, the 1st, the 2nd and the 3rd metatarsal head areas) were insensitive to the monofilament or tuning fork.[20] Participant's heart rate, temperature and respiratory rate were also recorded by the admitting doctors and were obtained from the medical records. Signs of systemic infection were defined to include high pulse rate [>90 beats per minute], high respiratory rate [>20per minute], and abnormal temperature [>38°C or <36°C). White blood cell count and circulating concentrations of C-reactive protein and fasting sugar were also measured at the time of hospital admission. Ankle brachial pressure index (ABPI) was measured in all participants as previously described[21] and the toe pressure (TP) was measured in participants who did not have an ulcer or prior amputation of the hallux using a Huntleigh Dopplex S/W-V1.6 kit according to the manufacturer's instructions (Huntleigh Healthcare Ltd, UK). Ischaemia (ABPI<0.8 or TP<60mmHg) was defined as per definitions given in the WIfI classification.[6] ABPI was also categorised as high (>1.40), normal (0.90-1.40) and low (<0.9). The ABPI measurements were performed by a single investigator (first author) and were comparable with those measured by vascular sonographers (intraclass correlation coefficient=0.883, n=16).[22]

In order to standardise the assessment of DFUs, photographs were taken of the affected foot and these were used for grading using previously described methods.[23,24] All three assessors classified all ulcers based on one system and then with the next system. The photographs were taken using both a Silhouette star camera (The SilhouetteStar, Aranz Medical Ltd.) and an iPhone XR (iOS 12.0 software, Apple Inc.). These photographs along with clinical data and information on ischemia were used to classify ulcers according to the different grading systems (5-8). This allowed for the remote assessment of DFUs while following appropriate infection control protocols during the COVID-19 pandemic and minimising patient-clinician contact.[25]

Three assessors (a vascular surgeon [CG], a podiatrist [MF] and a medical physician [CA]) independently graded the DFUs. All had extensive prior experience in assessing DFUs in clinical practice. Prior to starting the study, each assessor attended a two-hour training session focused on a standardised method of using the classification systems and grading wounds aimed to optimise consistency in grading. This session involved independent evaluation and grading of three examples of DFUs using each system by each assessor. This was followed by a discussion of scores. Once training was completed, the three observers independently undertook the grading of each DFU using each classification system and then repeated the scoring a second time at least seven days later (using the same image) to assess the intra-observer agreement. The time taken to complete each score for each participant was recorded using a stopwatch.

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The main outcome measure was the reproducibility of the different classification systems and the secondary outcome was requirement for any lower limb amputation, defined to include amputation of the toes or forefoot, or below or above knee amputation (either minor or major amputations) within 30days of hospital admission. The patients were followed up while they were in hospital and then via out-patient review for 30days.[26]

The sample size was calculated based on the assumption that three observers scoring the ulcer photographs independently would have a substantial inter-observer agreement (80%), with a relative error of 10% (11). The required sample size (80% power; $\alpha = 0.05$) was 45 patients.[27]

The continuous variables were not normally distributed, as evidenced by the Shapiro-Wilk test and therefore were presented as median and inter-quartile range (IQR). Nominal and ordinal data were summarised as percentages. The inter-observer and intra-observer reproducibility of the different classification systems were measured using Krippendorff's α for ordinal data.[28] Values were interpreted as ≤0=no agreement; 0.01-0.20=slight agreement; 0.21-0.40=fair agreement; 0.41-0.60=moderate agreement; 0.61-0.80 substantial agreement; and 0.81-1.00=excellent agreement[28] and calculated using R software (R Core Team [2020]. R: A language and environment for statistical computing. R Foundation for Statistical Computing, Vienna, Austria. Version: 4.02 using rel: Reliability Coefficients. R package, version 1.4.2 and irr: Various Coefficients of Interrater Reliability and Agreement. R package version 0.84.1). The time taken to grade each ulcer was compared between the different scoring systems using the Kruskal-Wallis test and post hoc comparisons were performed using Dunn's test. The median of the six scores of each DFU was compared between participants that did and did not subsequently undergo amputation within 30days of admission using Mann Whitney U test. The scores were also used to construct receiver operating characteristic (ROC) curves to assess the predictive ability of each classification system for amputation.[29] Area under the curve (AUC) was calculated and interpreted as >0.90=excellent, 0.80-0.89=good, 0.70-0.79=fair, and 0.60-0.69=poor.[29] Analyses were performed using SPSS (released 2020, IBM SPSS statistics for Windows, Version 26.0. Armonk, NY, IB Corp). ROC curves were drawn using GraphPad PRISM software, version 7.03 (GraphPad software, Inc, La Jolla, CA).

Results

A total of 45 patients were recruited. The baseline demographic characteristics and risk factors of the participants are summarised in Table 1. The median (IQR) age of the participants was 68.1 (56.1-74.1) years and 80% were males. The median (IQR) duration of diabetes was 19.0 (10.5-25.0) years.

Time to Complete DFU Grading

The median time taken to classify each ulcer varied significantly between all four grading systems ($P<.001$; Table 2). The Wagner score had the lowest median time for completion, and this progressively increased for the SINBAD, Wagner, and WIfI scores (P values for bivariate comparisons shown in Table 2).

Table 1. Demographic Characteristics of the Included Patients.

Characteristic	Summary (n=45)
Age (years)	68.1 [56.1-74.1]
Male (%)	36 (80.0%)
Height (m)	1.74 [1.68-1.80]
Weight (kg)	90.0 [77.0-113.5]
Body mass index (kgm^{-2})	30.9 [25.9-36.7]
Duration of diabetes (years)	19.0 [10.5-25.0]
Smoking status (%)	
Current	6 (13.3%)
Ex-smokers	26 (57.8%)
Non-smokers	13 (28.9%)
Previous history of hospital admissions for diabetes-related foot disease	
Single	17 (37.8%)
Multiple	12 (26.7%)
No previous admissions	16 (35.6%)
Previous history of minor amputation	19 (42.2%)
Previous history of major amputation	1 (2.2%)
Ankle brachial pressure index in the affected foot	
>1.40 (non-compressible vessels/high)	13 (28.9%)
0.91 to 1.40 (normal)	19 (42.2%)
<0.90 (low)	13 (28.9%)
Presence of systemic features of infection on admission (%)	14 (31.1%)
White cell count ($10^3/\mu L^{-1}$)	10.0 [8.25-11.7]
C reactive protein level (mg/dL^{-1}) (n=34)	39.0 [15.7-99.7]
Location of DFU	
Forefoot (n=36)	80.0%
Midfoot (n=2)	4.4%
Hindfoot (n=7)	15.6%
Type of ulcer	
Neuropathic (n=34)	75.6%
Neuro-ischemic (n=11)	24.4%

Note. Data shown are numbers (percentage) or median (inter-quartile range).

Table 2. Median Time Taken to Assess the Severity of Diabetes-Associated Foot Ulcers Using Different Classification Systems.

Scoring system	Completion time (mins)	P values for post-hoc bivariate comparisons			
		WIfI	UTWCS	SINBAD	Wagner
WIfI	1.00 [0.88-1.00]	NA	<.001	<.001	<.001
UTWCS	0.75 [0.50-0.75]	<.001	NA	<.001	<.001
SINBAD	0.50 [0.50-0.50]	<.001	<.001	NA	.042
Wagner	0.25 [0.25-0.50]	<.001	<.001	.042	NA

Abbreviations: NA, not applicable; SINBAD, Site, Ischemia, Neuropathy, Bacterial Infection, and Depth; UTWCS, University of Texas Wound Classification System; WIfI, Wound Ischemia foot Infection.
Note. Completion time shown as median (inter-quartile range). P values were obtained from Dunn's test in post hoc comparisons following Kruskal-Wallis test.

Table 3. Krippendorff's α Values for the Inter- and Intra-Observer Agreement of Different Classification Systems for Assessing Severity of Diabetes-Associated Foot Ulcers.

	WIfI score agreement	UTWCS score agreement	SINBAD score agreement	Wagner classification agreement
Inter-observer				
All three observers	0.788	0.306	0.516	0.374
Observer 1 vs Observer 3	0.805	0.347	0.441	0.526
Observer 1 vs Observer 2	0.780	0.270	0.536	0.238
Observer 2 vs Observer 3	0.776	0.214	0.559	0.327
Intra-observer				
Observer 1	0.902	0.791	0.903	0.925
Observer 2	0.908	0.922	0.993	0.873
Observer 3	0.965	0.599	0.911	0.766

Abbreviations: SINBAD, Site, Ischemia, Neuropathy, Bacterial Infection, and Depth; UTWCS, University of Texas Wound Classification System; WIfI, Wound Ischemia foot Infection.
Note. Data shown are the Krippendorff's α values for agreement between two different observers (as listed), all three observers or within observers. Observer 1: General Practitioner/Physician: Chanika Alahakoon (CA). Observer 2: Podiatrist: Malindu Fernando (MF). Observer 3: Vascular Surgeon: Charith Galappaththy (CG).

Table 4. Median Scores and Area Under the Curve for Different Classifications of the Severity of Diabetes-Associated Ulcers in Patients That Did and Did Not Require an Amputation.

Wound classification system	Median scores of those who had amputation (n=19)	Median scores of those who did not have amputation (n=26)	P value Mann Whitney U test	AUC [95% CI]	P value of ROC curves
WIfI	2 [2-3]	2 [1-3]	.342	0.582 [0.415-0.748]	.352
UTWCS	9 [9-13]	9 [5-11]	.079	0.653 [0.492-0.813]	.083
SINBAD	4 [3-4]	3 [3-5]	.791	0.523 [0.354-0.692]	.792
Wagner	3 [2-3]	2 [1-3]	**.041**	0.671 [0.515-0.826]	.052

Abbreviations: AUC: area under the curve; CI: confidence interval; ROC: receiver operating characteristic; SINBAD, Site, Ischemia, Neuropathy, Bacterial Infection, and Depth; UTWCS, University of Texas Wound Classification System; WIfI, Wound Ischemia foot Infection.
Note. Data shown are median (inter-quartile range) of scores. Bold indicates statistical significance.

Reproducibility

The WIfI classification had substantial inter-observer agreement (α=0.788) and excellent intra-observer agreement (α>0.900) between assessors based on Krippendorff's α values (Table 3). Inter-observer agreement for SINBAD scores was moderate (α=0.516). Inter-observer agreements for Wagner and UTWCS scores were fair (α=0.374 and 0.306, respectively). Intra-observer agreement for all classification systems was moderate (α>0.599) except for observer 3 where the agreement was fair for the UTWCS score (Table 3).

Prediction of Amputations Within 30Days

Eighteen (40.0%) participants had a minor amputation and one (2.2%) had a major amputation within 30days of hospital admission. The median scores for the different classification system of participants who required an amputation and those who did not have an amputation are summarised in Table 4. The median scores for the Wagner (P=.041), but not UTWCS, SINBAD and WIfI classifications, were significantly more severe for participants who had an amputation compared to those who did not (Table 4). However, based on the AUC, none of the classifications were significantly predictive of the requirement for amputation (Table 4).

Discussion

Many classification systems are available for grading the severity of a DFU.[5-7,20] The ideal clinical grading system for DFUs would be rapid to complete, reproducible within and between different health professionals and reliably predict important clinical outcomes. In the current study, the reproducibility, completion time and ability of four commonly used grading systems to predict 30-day amputation were assessed. In this study, photographs of DFUs were examined, which simulates assessments that are commonly needed in clinical practice due to the increasing use of telehealth to access DFUs.[25] It was found the WIfI system had substantial inter-observer and excellent intra-observer reproducibility. The SINBAD system had moderate inter-observer and

excellent intra-observer reproducibility. The UTWCS and Wagner classifications had only fair inter-observer and moderate intra-observer reproducibility. None of these scoring systems were able to reliably predict 30-day amputation rates. The median time to complete all of the four ulcer grading systems was one minute or less, making them highly feasible to use in routine clinical practice by busy clinicians.

A number of previous studies have examined the reproducibility of DFU classifications systems. The Wagner, SINBAD and UTWCS classifications have previously been reported to have moderate agreement.[12-14] These findings are similar to those of the current study. The current study is the first to report the reproducibility of the WIfI classification system, which had substantial agreement between different observers and almost perfect intra-observer agreement.[10] Although prior studies have reported the reproducibility and external validity of DFU grading systems, they were not good at predicting the likelihood of amputation within 30days in the current study.[31] The WIfI classification system has however been previously reported to predict the risk of major amputation within one year for both people with and without diabetes.[32-35] The WIfI score has been predominantly used in people with peripheral arterial disease previously.[10,36-38] No prior reports of any of the scoring systems predicting early requirement for any amputation were identified.

A recent retrospective study that classified ulcers based on photographs using five ulcer classification systems reported that the Wagner and UTWCS classifications were better predictors of amputation over an unspecified follow-up time.[39] In the current study, it was found that the Wagner classification had significantly different median scores between those participants who did and did not require any amputation within 30days. Based on AUC, however, the Wagner classification was not a good predictor of 30-day amputation likelihood. Ankle brachial pressure index <0.5, toe pressure <30mmHg, and transcutaneous oxygen pressure <25mmHg have been reported to be associated with a risk of major amputation of greater than 25%.[40] It is noteworthy that WIfI is the only scoring system that objectively assesses ischemia, but it was not predictive of 30-day amputation rate in the current study.

A number of limitations of the current study should be noted, including the inability of the observers to assess DFUs in-person during a global pandemic, the use of two types of cameras to photograph the foot, the small sample size and the limited number of assessors. Given the increasing role of remote assessment of DFUs, the results of this study are highly relevant and topical within the field.[25] The study was not designed to test whether the classification systems were predictive of 30-day major amputation alone. Furthermore, the outcomes of patients were only assessed up to 30days and none of the classification systems have been previously validated for the prediction of 30-day amputation incidence. It is therefore possible that the grading systems may have had better predictive ability for outcomes assessed over a longer period, as has been previously reported[32-35] and should be the focus of future studies.

Conclusion

This study suggests that of the four classification systems examined, the WIfI score has the best inter-observer agreement. The time taken to complete the WIfI score was slightly longer than the other classification systems and WIfI did not predict immediate requirement for any amputation.

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Systematic Review Or Meta-Analysis

Meta-analyses of randomized controlled trials reporting the effect of home foot temperature monitoring, patient education or offloading footwear on the incidence of diabetes-related foot ulcers

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Abstract

Aim The aim of this study was to perform an up-to-date systematic review and meta-analysis of randomized controlled trials (RCTs) examining the efficacy of home foot temperature monitoring, patient education and offloading footwear in reducing the incidence of diabetes-related foot ulcers.

Methods A literature search was performed using MEDLINE, PubMed, CINAHL, Scopus and Cochrane databases to identify relevant original studies. Meta-analyses were performed using intention-to-treat principals for worst (main analysis) and best (sub-analysis) case scenarios. Leave-one-out sensitivity analyses were used to assess the consistency of findings.

Results Of 7575 unique records, 17 RCTs involving 2729 participants were included. Four tested home foot temperature monitoring (n = 468), six examined patient education (n = 823) and seven assessed offloading footwear (n = 1438). Participants' who performed home foot temperature monitoring [odds ratio (OR) 0.51, 95% confidence interval (CI) 0.31 to 0.84; n = 468] and those provided offloading footwear (OR 0.48, 95% CI 0.29 to 0.80; n = 1438) were less likely to develop a diabetes-related foot ulcer. Patient education programmes did not significantly reduce diabetes-related foot ulcer incidence (OR 0.59, 95% CI 0.29 to 1.20; n = 823). Sensitivity analyses suggested that offloading footwear findings were consistent, but home foot temperature findings were dependent on the individual inclusion of one trial. All RCTs had either high or unclear risk of bias.

Conclusion This meta-analysis suggests that offloading footwear is effective in reducing the incidence of diabetes-related foot ulcers. Home foot temperature monitoring also appears beneficial but larger trials are needed (PROSPERO registration no.: CRD42019135226).

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