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Risk Factors for First-Ever Diabetes-Related Foot Ulcer: A Systematic Review and Meta-Analysis

Tao Yan[1] | Zhang Dou[2] | MacGilchrist Claire[1,3] | Kirwan Ellen[1] | McIntosh Caroline[1,3]

[1]Discipline of Podiatric Medicine, School of Health Sciences, University of Galway, County Galway, Ireland | [2]School of Nursing and Midwifery, University of Galway, County Galway, Ireland | [3]Alliance for Research and Innovation in Wounds, College of Medicine, Nursing & Health Sciences, University of Galway, County Galway, Ireland

Correspondence: Tao Yan (y.tao2@universityofgalway.ie)

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ABSTRACT

We aimed to systematically review and quantify risk factors for first-ever diabetes-related foot ulcer (DFU). Four English and three Chinese electronic databases were searched for cohort and case–control studies reporting risk factors for first-ever DFU. Two researchers independently screened titles, abstracts and full text, extracted data and assessed the quality of included studies. Meta-analyses were performed for risk factors reported in at least two studies, using unadjusted odds ratios and standardised mean differences for dichotomous and continuous variables. Of 6736 potential studies screened, 23 were included in the meta-analysis and 24 in the systematic review. Twenty-eight significant risk factors for first-ever DFU were identified, including older age, obesity, male gender, unmarried status, alcohol consumption, current smoking, insufficient physical activity, longer diabetes duration, increased HbA1c, fasting plasma glucose, creatinine and triglyceride, decreased eGFR and high-density lipoprotein, high vibration perception threshold, albuminuria, low ankle-brachial pressure index ratio, cardiovascular, cerebrovascular and peripheral artery disease, retinopathy, nephropathy, neuropathy, myocardial infarction, foot deformity, skin dryness, insulin treatment and anti-hypertensive treatment. This study provides the first comprehensive synthesis of risk factors for first-ever DFU. Identifying high-risk individuals based on these factors can enhance early intervention strategies, reducing the burden of DFU in diabetes management.

1 | Introduction

Diabetes mellitus remains a global health challenge, with an estimated 588.7 million people aged 20 to 79 years affected worldwide in 2024, a number projected to increase to 852.5 million by 2050 [1]. This significant rise is expected to result in a corresponding increase in diabetes-related complications, particularly foot ulcers, which impose a tremendous clinical and financial burden on healthcare systems.

Diabetes-related foot ulcers (DFU) are common and complex foot complications of diabetes, with high rates of lower extremity amputations, morbidity and mortality. Globally, the prevalence of DFU is estimated to be around 6.3%, with an annual incidence of 18.6 million cases among individuals with diabetes [2]. The lifetime risk of DFU ranges between 19% and 34%, and nearly 20% of affected individuals eventually require lower extremity amputation [3]. DFUs are often characterised by prolonged healing times and poor survival prognosis, with

Summary

- This study provides the first comprehensive analysis of risk factors for first-ever DFU among patients with diabetes.
- A total of 41 potential risk factors were analysed in meta-analysis, with 28 showing significant associations with first-ever DFU.
- Strong predictors included insufficient physical activity, skin dryness, cardiovascular disease, peripheral artery disease, retinopathy, nephropathy, and neuropathy, as well as higher vibration perception threshold.
- A comprehensive and interdisciplinary approach is essential to prevent or mitigate risk factors contributing to first-ever DFU.

a one-year post-diagnosis mortality rate of 13.1%, increasing to 49.1% at 5 years and 76.9% at 10 years [4]. Even after ulcer healing, recurrence is common, with approximately 40% of patients experiencing recurrence within 1 year and up to 65% within 5 years [3].

Beyond their devastating health consequences, DFUs already place a significant financial strain on healthcare systems and society, exceeding that of many common cancers [5, 6]. Foot ulcers are a major cause of hospitalisations and emergency department visits among individuals with diabetes. The annual excess expenditures for DFU management are 50% to 200% higher than the baseline costs of diabetes-related care [7]. Inpatient costs for DFU-related hospitalisations are 49.6% higher than those for diabetes admissions unrelated to DFU, with direct costs escalating further in cases requiring amputations [8]. In the United States, individuals with DFU need significantly more healthcare resources compared to matched diabetes controls without DFU, with nearly doubled direct care costs [7]. Furthermore, DFU-related disability and medical leave contribute to substantial productivity losses, exacerbating the socioeconomic burden on patients and employers alike [8]. Consequently, early detection and management of independent risk factors for DFU, particularly before the onset of the first ulcer, are essential for effective prevention.

Several empirical studies and reviews have explored potential risk factors for DFU, with core contributors including diabetes-related neuropathy, peripheral arterial disease (PAD), foot deformity, prior ulcer and a history of lower-extremity amputation [4, 9, 10]. However, most systematic reviews have either qualitatively summarised risk factors for DFU in general or focused on DFU associated with recurrent DFU [9–12]. To date, no systematic review has quantitatively synthesised factors specifically for first-ever DFU, though some reviews have provided partial quantitative insights into general DFU risk factors without distinguishing first-time occurrence from recurrences. Currently, the findings of published research suggest that the risk factors for first-ever DFU may differ from those for DFU recurrence [13, 14]. For example, depression has been identified as a predictor of first-ever DFU; however, depression may not be an independent risk factor for recurrence of DFU [14]. Further supporting this distinction, Cheng et al. [15] found that compared to individuals with first-ever DFU, those with recurrent DFU exhibited lower glycosylation levels, a longer duration of diabetes and were more likely to wear outdoor sports shoes. These findings reinforce the notion that risk factors for DFU recurrence are not necessarily identical to those for first-ever DFU, highlighting the importance of tailored preventive strategies for different patient populations to mitigate disease progression and improve patient outcomes.

Therefore, the aim of this systematic review and meta-analysis is to identify and synthesise the evidence of risk factors for first-ever DFU and quantify the strength of association of these risk factors to guide effective prevention strategies and adequate public health policies. This is the first comprehensive synthesis of risk factors for first-ever DFU, highlighting its novelty in addressing a critical gap in the literature.

2 | Materials and Methods

This review was completed in accordance with the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) reporting guidelines. Prior to the initial search, methods were documented and registered in the PROSPERO repository (ID: CRD42024508855).

2.1 | Data Sources and Searches

We systematically searched PubMed/MEDLINE, Embase, Web of Science, Cochrane Library, China National Knowledge Infrastructure (CNKI), Weipu Data (VIP) and Wanfang Data, from the time of their inception to 13 July 2024, limited to studies published in the English and Chinese languages. The search strategy consisted of terms for three core concepts: "diabetes mellitus," "foot ulcers" and "risk factors" (Tables S1 and S2). We also checked the references and citation lists of included studies to find additional potential eligible articles.

2.2 | Study Selection

All studies identified by the search strategy were exported to Covidence software for screening. After the removal of duplicates, two researchers independently scanned the titles and abstracts of the retrieved articles. The full text of potentially eligible studies was further assessed for inclusion. Any discrepancies during the process were resolved through a consensus discussion, or consultation with the third researchers. To be eligible for inclusion, previously published studies had to meet the following criteria: (1) Patients were diagnosed with either type 1 or type 2 diabetes mellitus and had no prior history of DFU; (2) Studies reported the risk factors for the development of first-ever DFU. In this review, the term "first-ever foot ulcer" is defined as "a foot ulcer occurring in a patient who has never before had a foot ulcer" in accordance with agreed definitions and criteria [16]. (3) Effect estimates for risk factors contributing to the first-ever DFU were reported as hazard ratio (HRs), odds ratio (ORs), relative risks (RRs) or standardised mean differences (SMD), or the study provided enough original data to calculate these measures; (4) Studies

had to be of cross-sectional, cohort or case–control study design; (5) Published in English or Chinese. Intervention studies, review articles, letters, comments, conference abstracts, case reports or studies not published in peer-reviewed journals were excluded. We also excluded incomplete or non-full text articles.

2.3 | Data Extraction and Quality Assessment

Two researchers independently extracted data from included studies using a predefined Excel spreadsheet. The following data were recorded, including study characteristics (first author, publication year, enrolment year, country, setting, study design and follow-up period), characteristics of participants (sample size, age, gender, diabetes type and diabetes duration), the number of participants who developed first-ever DFU, and reported estimated effects (e.g., HRs ORs, RRs or SMD) for risk factors of first-ever DFU. The Newcastle-Ottawa Scale (NOS) was applied to evaluate the methodological quality of the included studies, with total scores ranging from 0 to 9 stars [17]. Scores of 6–9 stars indicate a low risk of bias, 4–5 stars indicate a medium risk of bias, and 1–3 stars indicate a high risk of bias. Finally, we assessed the certainty of evidence for each risk factor with the Grading of Recommendations, Assessment, Development and Evaluations (GRADE) framework [18].

2.4 | Data Synthesis and Analysis

All statistical analyses were undertaken using STATA version 15. For each risk factor, unadjusted ORs, RRs, HRs or SMD were recorded. RRs and HRs reported in the included studies were treated as OR estimates. Pooled ORs for nominal data and SMD for continuous variables were calculated when risk factors were reported in at least two studies. For studies without reported risk estimates, SMD for continuous variables with corresponding 95% confidence intervals (CIs) was calculated using the original means and SDs; ORs with 95% CI for nominal data were calculated using raw counts. Heterogeneity was assessed using the Cochran Q-test and the I^2 test and was considered substantial if $I^2 \geq 50\%$ [19]. Fixed-effects or random-effects models were employed to pool the results based on the absence of heterogeneity ($I^2 < 50\%$ for the fixed-effects model and $I^2 \geq 50\%$ for the random-effects model). For data analysed using a fixed-effects model, additional sensitivity analyses were performed using a random-effects model [19]. Heterogeneity was explored through subgroup analysis based on study type, publication year (< 2019 vs. ≥ 2019) and quality if at least 10 studies were included in the meta-analysis. We chose 2019 as the cut-off year for temporal subgroup analysis to reflect potential shifts in clinical practice and research priorities following the publication of updated International Working Group on the Diabetic Foot (IWGDF) guidelines around that time [20]. Publication biases were evaluated using funnel plots and quantified by Egger's test for the same risk factors reported in more than five studies [19]. We used the trim-and-fill method to correct potential bias [19]. A descriptive presentation was conducted for risk factors identified in only one study that was not suitable for meta-analysis.

3 | Results

3.1 | Description of Included Studies

The initial search found 10 892 studies from electronic databases and 167 additional studies from manual reference reviews and citation searches. After screening the titles and abstracts of potential articles and reading the full text of eligible articles, 24 studies were included in the qualitative synthesis, with 23 of these included in the meta-analysis (Figure 1). One study, Eckert et al. [21] reported risk factor data separately for patients with type 1 and type 2 diabetes without providing an overall combined estimate. To ensure accurate data extraction and a more precise synthesis of risk factor associations, we treated this study as two separate datasets.

The details of the 24 included studies are summarised in Table 1, all published in English. Regarding study design, seven were case–control studies, while the remaining 17 studies used a cohort design. Three studies focused on individuals aged ≥ 40 years [30, 36, 42], one targeted participants aged ≥ 25 years [26] and another only included participants aged ≥ 45 years [35]. Three studies did not report the age of participants [28, 32, 41]. The quality of the included studies ranged from 4 to 9 based on assessment criteria, reflecting moderate to high methodological rigour (Tables S3 and S4).

3.2 | Risk Factors for First-Ever DFU

Overall, 41 potential risk factors for first-ever DFU were extracted and analysed quantitatively, of which 28 showed significant association. These factors are summarised in Figures 2 and 3 and Table 2. The remaining risk factors reported in only one study were analysed through a systematic review.

3.2.1 | Demographic and Lifestyle Factors

A total of nine demographic and lifestyle factors were included in the meta-analysis, and seven of them showed a significant association with first-ever DFU. Age and BMI were analysed as both continuous and categorical variables. When treated as continuous variables, neither age nor BMI showed significant associations, and both showed high heterogeneity ($I^2 = 83.8\%$ and 67.5%, respectively). Subgroup analysis based on publication year revealed a significant association between age and first-ever DFU risk in studies published before 2019 (SMD = 0.19, 95% CI, 0.02 to 0.36; $p = 0.03$), but not in those published after 2019 (SMD = 0.10, 95% CI, −0.31 to 0.50; $p = 0.64$). When analysed categorically, individuals aged ≥ 60 years had a significantly higher risk of first-ever DFU (pooled OR = 1.60, 95% CI, 1.29 to 2.0; $p < 0.01$). Similarly, a small but significant association was found for obesity (BMI ≥ 30 kg/m^2, pooled OR = 1.03, 95% CI, 1.01 to 1.06; $p = 0.43$), with no heterogeneity observed ($I^2 = 0\%$). The pooled estimate showed that male gender was associated with a 1.30-fold increased risk (pooled OR = 1.20, 95% CI, 1.06 to 1.60; $p = 0.01$), but between-study heterogeneity was high ($I^2 = 78.8\%$). Notably, subgroup analysis revealed that this association was not significant in studies published before 2019 (pooled OR = 1.03, 95% CI, 0.90 to 1.18; $p = 0.68$), but became

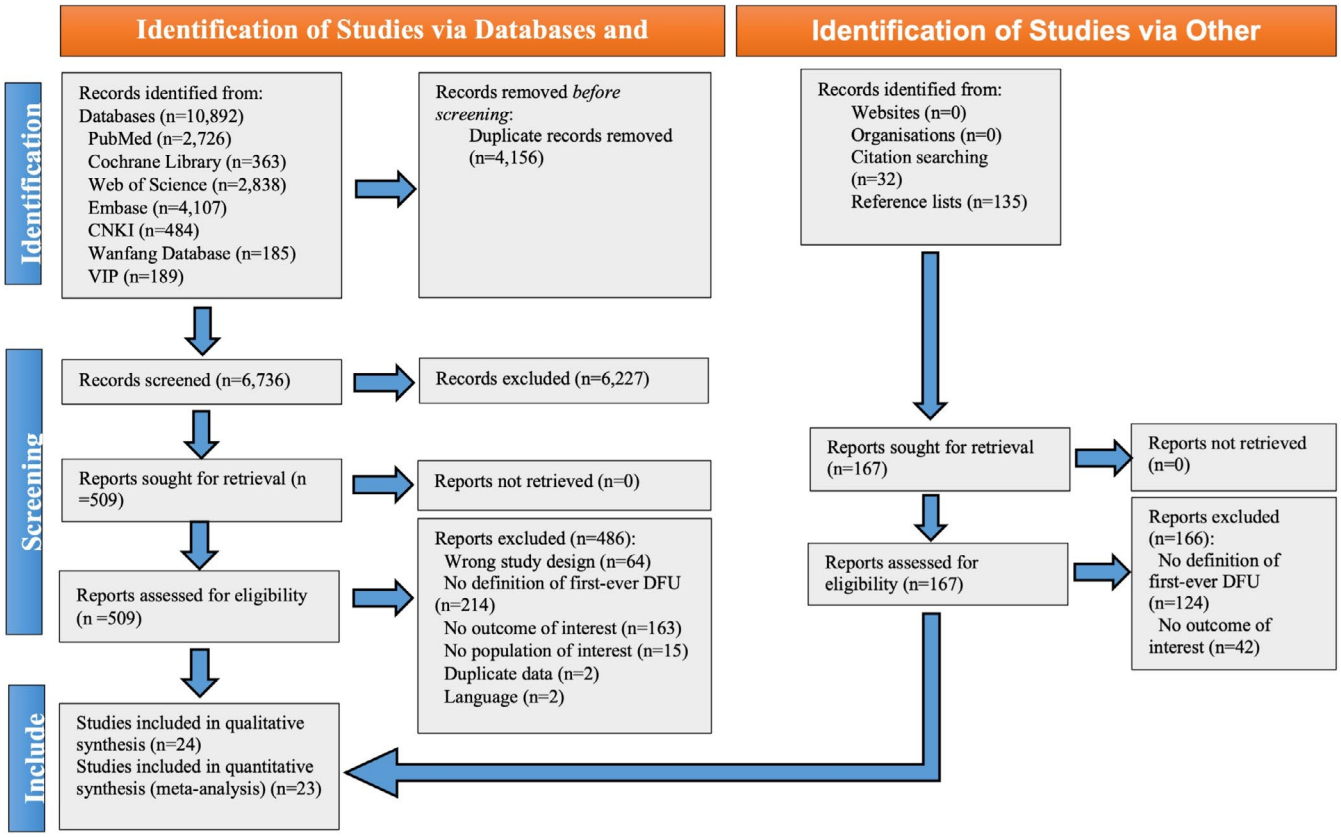

FIGURE 1 | Flowchart of study selection.

more pronounced in later studies (pooled OR = 1.66, 95% CI, 1.50 to 1.85; $p < 0.01$), indicating a potential source of heterogeneity and temporal increase in sex disparity. Unmarried individuals had a significantly higher risk (pooled OR = 1.16, 95% CI, 1.13 to 1.18; $p < 0.01$), with no heterogeneity detected ($I^2 = 0\%$). Lifestyle behaviours such as alcohol consumption and current smoking were also significant risk factors, associated with 1.50-fold and 1.58-fold increases in risk, respectively. In contrast, past smoking showed no significant association. No evidence of publication bias was found for age, gender, BMI or current smoking. The quality of evidence was rated moderate for marital status and age (≥ 60 years), and high for the remaining significant factors.

Additional factors not included in the meta-analysis, including reduced family disposable income [41], social deprivation [22], low economic status [36], prolonged sedentary time [42] and spending a long time standing at work [39], were also linked to increased risk of first-ever DFU.

3.2.2 | Chronic Conditions

Twelve chronic conditions were assessed in the meta-analysis, six of which were significantly associated with first-ever DFU. Longer diabetes duration showed a significant positive association with first-ever DFU risk (pooled SMD = 0.46, 95% CI, 0.14 to 0.78; $p = 0.01$), with high between-study heterogeneity ($I^2 = 87.4\%$). Hypertension, in contrast, showed no overall significant association with DFU (pooled OR = 1.06, 95% CI, 0.78 to 1.44; $p = 0.70$), but subgroup analysis revealed a significant effect in studies before 2019 (pooled OR = 1.40, 95% CI, 1.06 to 1.86; $p = 0.02$), which was not observed in more recent studies (pooled OR = 0.98, 95% CI, 0.64 to 1.43; $p = 0.91$). HbA1c levels, whether analysed as continuous or categorical variables, were positively associated with DFU risk, although heterogeneity was high and publication bias was detected in continuous analyses. Trim-and-fill analysis suggested four potentially missing studies. Fasting plasma glucose was also significantly associated with DFU (pooled SMD = 0.47, 95% CI, 0.06 to 0.89; $p = 0.02$), with high heterogeneity ($I^2 = 85.0\%$).

Regarding lipid profiles, higher triglycerides levels (pooled SMD = 0.16, 95% CI, 0.06 to 0.89; $p = 0.02$) and lower HDL-C levels (pooled SMD = −0.26, 95% CI, −0.31 to −0.20; $p < 0.01$) were significantly associated with first-ever DFU, and there was homogeneity ($I^2 = 48.1\%$ and $I^2 = 0\%$, respectively). For the index of blood pressure, the combined results showed no significant association between hypertension ($p = 0.70$), systolic blood pressure (SBP; $p = 0.09$), or diastolic blood pressure (DBP; $p = 0.21$) and first-ever DFU, and all these variables showed high heterogeneity ($I^2 > 50\%$). Interestingly, Brennan et al. [32] found that patients with higher SBP variability had higher adjusted ORs for first-ever DFU incidence.

3.2.3 | Laboratory Values

There are five laboratory factors for first-ever DFU that were analysed in the meta-analysis. First-ever DFU was significantly

TABLE 1 | Characteristics of the included studies.

Author	Country; Continents	Study type	Follow-up period	Sample size	Events	Age (years)	Female/male	T1DM/ T2DM	Study quality
Anderson et al. 2018 [22]	UK; Europe	Retrospective cohort study	Median: 10.5 years	13 955	1147	Total mean: 69.4 Range: 16–89 DFU:74.2 (73.3, 74.2) No-DFU: 69.0 (68.8, 69.3)	6011/7914	1370/12585	6
Adem et al. 2020 [23]	Ethiopia; Africa	Retrospective cohort study	Median: 95 months Range: 4–120 months	387	66	Total median: 46 (35, 58)	154/233	131/256	7
Panagoulias et al. 2020 [24]	Bulgaria, Greece, Serbia, and the UK; Europe	Prospective cohort study	Median: 3.0 (3.0, 4.0) years	308	55	DFU: 65.7 ± 11.2 No-DFU: 62.0 ± 1.3	155/153	20/288	7
Williams et al. 2010 [25]	USA; North America	Population-based prospective cohort study	5-year period Median: 4.1 years	3474	28	Total: 64.1 ± 12.6	1667/1807	0/3474	7
Yun et al. 2016 [26]	Korea; Asia	Prospective cohort study	Median: 13.3 years	449	22	Range: 25–75 Total: 53.5 ± 9.7 DFU: 55.6 ± 11.4 No-DFU: 53.4 ± 9.6	271/178	0/449	7
Kästenbauer et al. 2001 [27]	Austria; Europe	Prospective cohort study	Median: 3.6 years	187	10	DFU: 59.3 ± 7.6 No-DFU: 58.6 ± 8.0	85/102	0/187	7
Hangaard et al. 2019 [28]	Denmark; Europe	Retrospective cohort study	15-year period	25 220	692	NR	10 842/14378	11 108/14112	6
Sriussadaporn et al. 1997 [29]	Thailand; Asia	Case–control study	NR	165	55	DFU: 57.16 ± 13.66 No-DFU: 57.55 ± 10.20	125/40	0/165	5
Chen et al. 2023 [30]	Australia; Oceania	Prospective cohort study	4-year period	191	13	Total: ≥ 40 DFU: 63.9 ± 12.1 No-DFU: 60.3 ± 10.1	83/108	NR	7
Saydam et al. 2021 [31]	Turkey; Asia	Retrospective cohort study	NR	90	9	DFU median: 34 (26, 52) No-DFU median: 35 (25, 51)	72/18	NR	4

(Continues)

TABLE 1 | (Continued)

Author	Country; Continents	Study type	Follow-up period	Sample size	Events	Age (years)	Female/male	T1DM/ T2DM	Study quality
Eckert et al. 2024 (A) [21]	Germany, Austria, Switzerland, Luxembourg; Europe	Retrospective cohort study (matched cohort)	NR	5352	2676	≥ 18	2042/3310	5352/0	6
Eckert et al. 2024 (B) [21]	Germany, Austria, Switzerland, Luxembourg; Europe	Retrospective cohort study (matched cohort)	NR	58 112	29 056	≥ 18	20 806/37306	0/58112	6
Brennan et al. 2018 [32]	USA; North America	Retrospective nested case–control	5-year period	180 358	51 111	NR	3066/177292	NR	7
Rastogi et al. 2020 [33]	India; Asia	Prospective case–control study	NR	5760	2880	DFU median: 58 (50, 65) No-DFU median: 59 (52, 65)	1498/4262	0/5760	7
Young et al. 1994 [34]	UK; Europe	Prospective cohort study	4-year period	469	48	Total mean: 53.7 Range: 17–85	241/228	192/277	6
Gazzaruso et al. 2012 [35]	Italy; Europe	Case–control study	NR	122	70	Range: 45–70 Neuropathic DFU: 54.1 ± 6.6 Vascular DFU: 57.2 ± 6.8 No-DFU: 55.3 ± 6.1	57/65	0/122	6
Kim et al. 2024 [36]	Korea; Asia	Retrospective nested case–control study	DFU: 9.17 ± 3.6 years No-DFU: 9.18 ± 3.6 years	4691	791	≥ 40	1493/3198	0/4691	9
Baba et al. 2014 [37]	Australia; Oceania	Community-based prospective cohort study	NR	1272	79	DFU: 65.5 ± 9.4 No-DFU: 63.8 ± 1.4	655/617	0/1272	6
Rossboth et al. 2021 [38]	Austria; Europe	Retrospective cohort study	Mean: 9.75 years (DFU patients)	10 688	140	Total: 63.21 ± 12.58 DFU: 63.0 ± 11.9 No-DFU: 63.2 ± 12.6	4736/5952	0/10688	7
Badedi et al. 2019 [39]	Saudi Arabia; Asia	Case–control study	NR	323	108	DFU: 56.9 ± 12.2 No-DFU: 54 ± 9.8	131/192	0/323	5

(Continues)

TABLE 1 | (Continued)

Author	Country; Continents	Study type	Follow-up period	Sample size	Events	Age (years)	Female/male	T1DM/T2DM	Study quality
Abuhay et al. 2022 [40]	Ethiopia; Africa	Retrospective cohort study	Median: 64 (43.9, 85.5) months Range: 6.3–120 months	539	65	Total: 46.05 ± 16.02	238/301	194/345	6
Schäfer et al. 2021 [41]	Denmark; Europe	Population-based retrospective cohort study	DFU: 7.74 ± 5.8 years No-DFU/ Amputation: 9.4 ± 5.8 years	243 376	13 695	NR	102004/141372	NR	6
Orlando et al. 2021 [42]	Italy; Europe	Prospective cohort study	8-year period	175	62	Total: 72.6 ± 9.5 DFU: 69.1 ± 9.7 No-DFU: 74.6 ± 9	73/102	10/165	6
Premkumar et al. 2017 [43]	India; Asia	Case–control study	NR	132	66	Range: 35–81	42/90	18/114	7
Francia et al. 2015 [44]	Italy; Europe	Prospective cohort study	8-year period	40	7	DFU: 65.3 ± 6.6 No-DFU: 62.5 ± 5.8	19/21	0/40	6

associated with higher creatinine levels (pooled SMD = 2.06, 95% CI, 1.36 to 2.76; $p < 0.01$) and lower estimated glomerular filtration rate (pooled SMD = −0.12, 95% CI, −0.17 to −0.07; $p < 0.01$). However, between-study heterogeneity was high in creatinine ($I^2 = 99.4\%$), and evidence quality for both factors was rated low. The risk of first-ever DFU increased 5.3-fold (95% CI, 2.38 to 11.79; $p < 0.01$) among patients with VPT ≥ 25 V. While the combined estimates for VPT ≥ 25 V indicated a strong association, the evidence quality was rated low, and the between-study heterogeneity was high ($I^2 = 52.9\%$). Similarly, albuminuria showed a strong positive association with first-ever DFU (pooled OR = 2.99, 95% CI, 2.70 to 3.32; $p < 0.01$), with homogeneity ($I^2 = 13.8\%$). A significant negative association between low ankle-brachial pressure index (ABPI) ratio and first-ever DFU was detected (pooled SMD = −0.49, 95% CI, −0.91 to −0.06; $p = 0.03$).

Additional laboratory factors not included in the meta-analysis, significant predictors for first-ever DFU included joint mobility [44], dorsal and plantar flexion [44], foot or pedal pulse [28, 42], homocysteine levels [35], lipoprotein (a) [35], visual acuity [28, 29] and vitamin B12 deficiency [39].

3.2.4 | Clinical Factors

A total of 10 clinical factors for first-ever DFU were investigated in the meta-analysis, of which 8 were significantly linked to first-ever DFU. Macrovascular and microvascular complications such as cardiovascular disease, cerebrovascular disease, PAD, retinopathy, nephropathy, neuropathy and myocardial infarction significantly increase the risk of first-ever DFU. Foot deformities and skin dryness were associated with a 2.19-fold (95% CI, 1.35 to 3.56; $p = 0.01$) and 6.78-fold (95% CI, 1.58 to 29.04; $p = 0.01$) increased risk, respectively. Strong associations were observed for cardiovascular disease, PAD, retinopathy, nephropathy, neuropathy and skin dryness. The pooled effect estimates for all reported clinical factors showed high between-study heterogeneity ($I^2 > 50\%$), and subgroup analyses did not identify any definitive sources of this heterogeneity. There was evidence of publication bias in meta-analyses for retinopathy and nephropathy, with the trim-and-fill method identifying six and four potentially missing studies, respectively.

For risk factors not included in meta-analysis, a significantly higher risk of developing first-ever DFU was associated with renal failure [32], chronic renal disease [36], heart failure [36], haemodialysis [36], metabolic syndrome [21], intermittent claudication [37], vascular bypass [38], chronic venous stasis [32], foot trauma [39], foot fissures [39], family history of coronary artery disease [35], podiatry visit frequency [38], cognitive dysfunction [30], depression [25] and mental disorders [41]. A significantly lower risk of first-ever DFU was associated with foot care practices [39], foot inspection [38] and health literacy [30].

3.2.5 | Treatment-Related Factors

Six treatment-related factors in meta-analysis, with insulin use and anti-hypertensive treatments emerging as significant predictors. Insulin use increased first-ever DFU risk by 2.31-fold

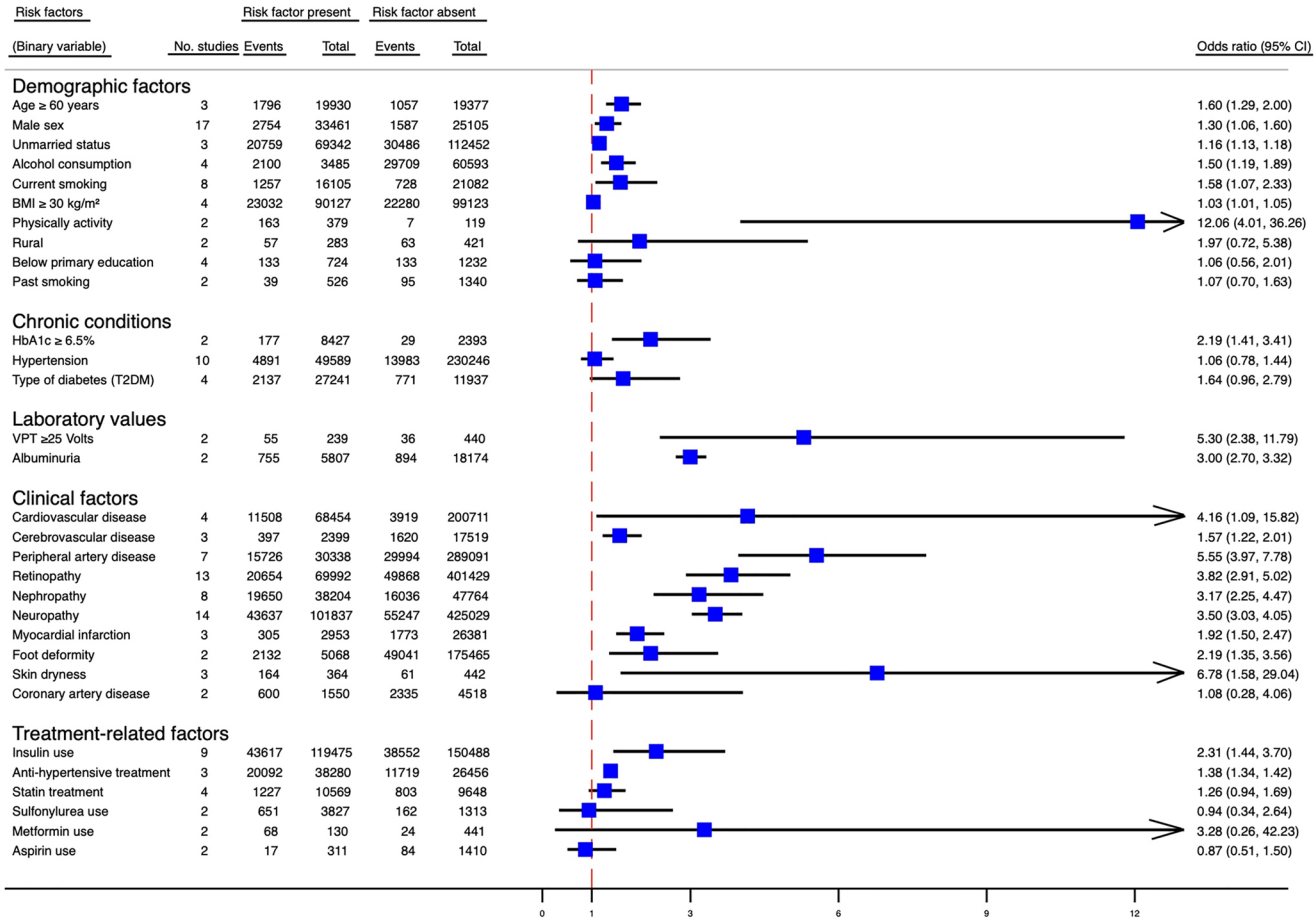

FIGURE 2 | Pooled odds ratio of risk factors for first-ever DFU (binary variables). Data are presented as odds ratios with 95% confidence intervals. BMI: Body Mass Index; HbA1c: Haemoglobin A1c; VPT: Vibration perception threshold.

(95% CI, 1.44 to3.78; $p = 0.01$), while antihypertensive treatment raised the risk by 1.38-fold (95% CI, 1.33 to 1.42; $p = 0.01$). Considerable heterogeneity was only observed among studies evaluating insulin use ($I^2 = 99.6\%$).

Additional treatment factors not included in the meta-analysis, such as specific antihyperglycaemic medications (e.g., dipeptidyl peptidase-4 inhibitors, thiazolidinediones) [32, 36], antihypertensive drugs (e.g., calcium channel blocker, beta blockers, ACE inhibitors) [32, 36] and other medications like antiplatelet agents [36], cholesterol-lowering drugs [32], second-generation antipsychotics [36] and antidepressants [36], were also significantly associated with first-ever DFU.

4 | Discussion

We systematically quantified, for the first time, the major factors associated with first-ever DFU in persons with diabetes. A total of 41 potential risk factors were extracted and analysed in meta-analysis, and 28 showed significant association. Our data suggest that patients with insufficient physical activity, skin dryness, cardiovascular disease, PAD, retinopathy, nephropathy and neuropathy, as well as those with higher VPT, face an extremely high risk.

4.1 | Demographic and Lifestyle Factors

Our study identified male gender, older age (≥60 years), higher BMI (≥30 kg/m^2) and unmarried status as significant risk factors for first-ever DFU. These findings align with previous studies, which have consistently reported gender and age as risk factors for recurrent DFU [9, 10]. However, the associations of age and BMI with DFU remain debated. A meta-analysis in Ethiopia identified BMI ≥24.5 kg/m^2, diabetes duration ≥10 years, and age ≥45 years as predictors of DFU, though without distinguishing between first-ever and recurrent cases [45]. The link between age and DFU may be largely attributed to longer diabetes duration. Sohn et al. [46] further reported a J-shaped association between BMI and DFU risk, suggesting a more complex relationship. Notably, our subgroup analysis showed that male gender became a more prominent risk factor in studies published after 2019, while no significant association was observed in earlier studies. This trend may reflect changes in clinical detection, healthcare engagement or evolving patient demographics [3, 4], and highlights the potential value of tracking risk factor dynamics over time.

Current smoking and alcohol use were also significant lifestyle risks in our study, consistent with previous findings [10, 21, 28]. Both behaviours are associated with increased levels of blood glucose, vascular disease and neuropathy [47–49], which may

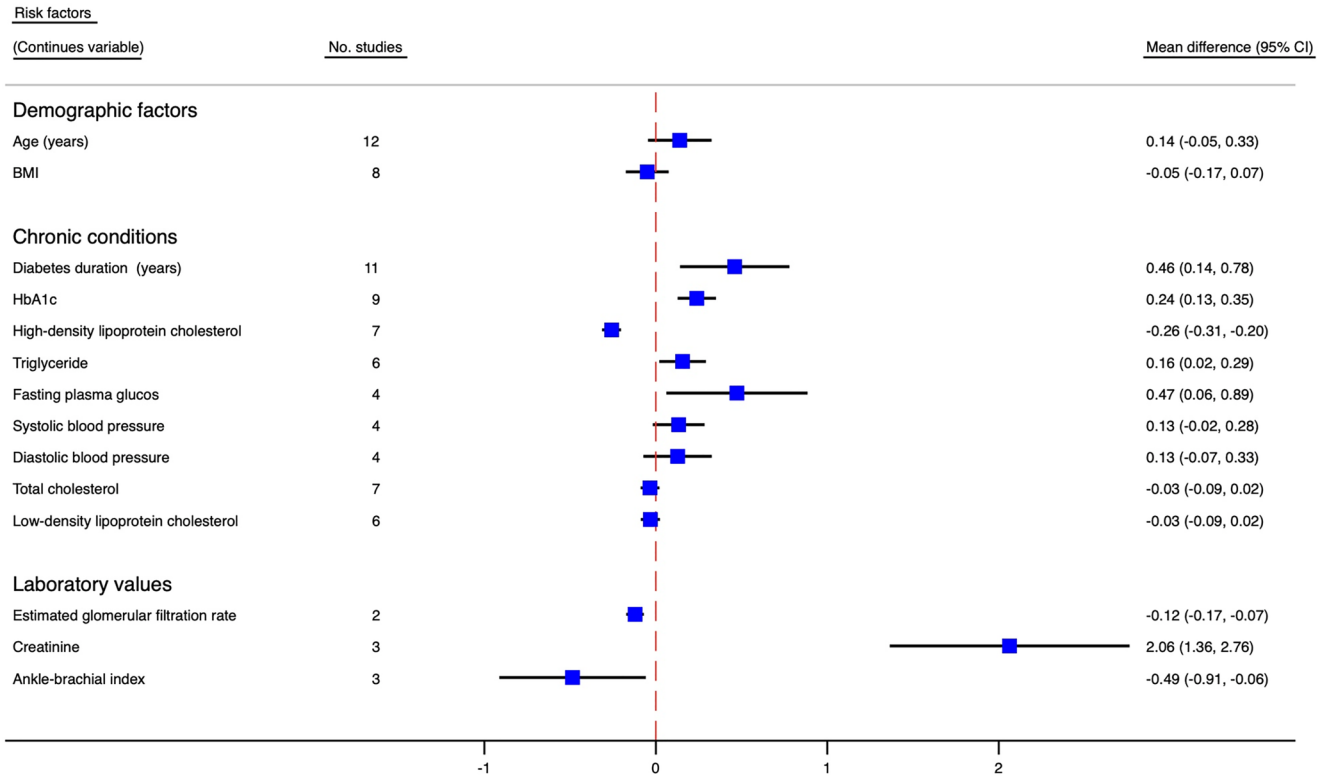

FIGURE 3 | Pooled standardised mean differences of risk factors for first-ever DFU (continues variables). Data are presented as standardised mean differences with 95% confidence interval. BMI: Body Mass Index; HbA1c: Haemoglobin A1c.

partially explain their role in DFU development. However, dose–response relationships (e.g., smoking pack-years, alcohol intake thresholds) specific to DFU remain unclear. While smoking pack-years have been associated with type 2 diabetes [50], similar analyses specifically examining DFU are lacking. The potential impact of smoking intensity and alcohol consumption levels (e.g., moderate vs. excessive) on DFU risk warrants further investigation.

Insufficient physical activity, defined as less than 150 min of weekly exercise, was another significant predictor of first-ever DFU. This result is consistent with previous studies [39, 42]. The protective role of physical activity against lower extremity amputation in individuals with diabetes is recognised [36]. Orlando et al. [42] found that prolonged sedentary time was an independent and powerful predictor of first-ever DFU in individuals with diabetes-related peripheral neuropathy. Interestingly, prolonged standing at work has also been associated with first-ever DFU [39], suggesting a U-shape risk curve where both inactivity and excessive standing contribute. Multiple studies confirmed that daily weight-bearing activities would not increase DFU risk and targeted exercises appeared safe and acceptable among individuals with diabetes [51, 52]. Encouraging gradual increases in daily activity, as recommended by IWGDF [53], is important, though unique physical and psychological barriers may limit participation [54]. Future research should focus on identifying the optimal type, intensity and dosage of exercise to maximise safety and efficacy in this population.

4.2 | Glycaemic Control, Hypertension and Dyslipidaemia

Maintaining glycaemic control is fundamental to preventing the onset and progression of diabetes-related complications. Consistent with previous studies [32, 39], our findings confirm that effective glycaemic management, including lower HbA1c levels and lower fasting plasma glucose, significantly reduces the risk of first-ever DFU. The incidence of first-ever DFU was also significantly influenced by 3-month lagged fasting blood sugar levels [40]. The significant association between insulin use and first-ever DFU should be interpreted cautiously, as it may reflect more severe underlying disease.

Hypertension and dyslipidaemia are quite common in individuals with diabetes and play important roles in the development and acceleration of late complications. Although hypertension was statistically non-significant in our pooled results, subgroup analysis by publication year revealed a significant association in studies published before 2019, but not in more recent studies. This temporal trend may reflect improvements in hypertension management and multidisciplinary care pathways over time, aligning with global shifts in diabetes care. A large case–control study demonstrated that increased SBP variability is a potential and independent risk factor for first-ever DFU [32]. Targeting control of SBP could provide a novel therapeutic strategy to reduce the burden of DFU. Calcium channel blockers, one kind of antihypertensive medication, were found to be significantly associated with reduced ulcer risk in patients with diabetes but

TABLE 2 | Level of evidence for each risk factor.

Risk factor	No. of included studies	Degree of association	Combined SMD/OR	*p*	Heterogeneity test		Model	Egger test	Evidence quality
					I^2 (%)	*p*			
Age									
Age (years)	12	−	0.14	0.14	83.8	< 0.01	Random	0.14	High
Age ≥ 60 years	3	+	1.60	**< 0.01**	70.4	0.03	Random	−	Moderate
Gender (male versus female)	17	+	1.30	**0.01**	78.8	< 0.01	Random	0.99	High
BMI									
BMI (kg/m^2)	8	−	−0.05	0.43	67.5	< 0.01	Random	0.17	High
BMI ≥ 30 kg/m^2	4	+	1.03	**< 0.01**	0	0.76	Fixed	−	High
Marry status (unmarried versus married)	3	+	1.16	**< 0.01**	0	0.60	Fixed	−	Moderate
Alcohol	4	+	1.50	**< 0.01**	60.3	0.06	Random	−	High
Smoking									
Current smoker	8	+	1.58	**0.02**	64.9	< 0.01	Random	0.15	High
Past smoker	2	−	1.07	0.75	0	0.89	Fixed	−	Moderate
Insufficient physical activity	2	+++	12.06	**< 0.01**	26.2	0.25	Fixed	−	High
HbA1c									
HbA1c (mmol/mol)	9	++	0.24	**< 0.01**	94.3	< 0.01	Random	0.03	Moderate
HbA1c ≥ 6.5%	2	++	2.19	**< 0.01**	0	0.51	Fixed	−	Moderate
eGFR	2	+	−0.12	**< 0.01**	0	0.69	Fixed	−	Low
Creatinine	3	++	2.06	**< 0.01**	99.4	< 0.01	Random	−	Low
Fasting plasma glucose	4	++	0.47	**0.02**	85	< 0.01	Random	−	Moderate
Triglyceride	6	+	0.16	**0.02**	48.1	0.09	Fixed	0.63	High
HDL-C	7	++	−0.26	**< 0.01**	0	0.71	Fixed	0.71	High

(Continues)

TABLE 2 | (Continued)

Risk factor	No. of included studies	Degree of association	Combined SMD/OR	*p*	Heterogeneity test		Model	Egger test	Evidence quality
					I^2 (%)	*p*			
VPT (≥25 V)	2	+++	5.30	**<0.01**	52.9	0.15	Random	–	Low
Albuminuria	2	++	3.00	**<0.01**	13.8	0.28	Fixed	–	High
ABPI	3	++	−0.49	**0.03**	70.3	0.03	Random	–	High
Diabetes duration	11	++	0.46	**0.01**	87.4	<0.01	Random	0.81	High
Cardiovascular disease	4	+++	4.16	**0.04**	99.7	<0.01	Random	–	Low
Cerebrovascular disease	3	+	1.57	**<0.01**	65.2	0.06	Random	–	Moderate
PAD	7	+++	5.55	**<0.01**	98	<0.01	Random	0.88	Moderate
Retinopathy	13	+++	3.82	**<0.01**	97.6	<0.01	Random	0.05	High
Nephropathy	8	+++	3.17	**<0.01**	97.4	<0.01	Random	0.01	Moderate
Neuropathy	14	+++	3.50	**<0.01**	96.7	<0.01	Random	0.07	High
Myocardial infarction	3	+	1.92	**<0.01**	60.4	0.08	Random	–	Moderate
Foot deformity	2	++	2.19	**<0.01**	60.5	0.11	Random	–	Low
Skin dryness	3	+++	6.78	**0.01**	92.3	<0.01	Random	–	Low
Insulin treatment	9	++	2.31	**<0.01**	99.6	<0.01	Random	0.88	Moderate
Anti-hypertensive treatment	3	+	1.38	**<0.01**	0	0.67	Fixed	–	Moderate
Residence (city versus rural)	2	–	0.51	0.19	75.7	0.04	Random	–	Very low
Education (higher versus lower primary)	4	–	0.94	0.85	74.3	<0.01	Random	–	Moderate
Hypertension	10	–	1.06	0.70	95.7	<0.01	Random	0.86	High
SBP	4	–	0.13	0.09	52.5	0.10	Random	–	Moderate
DBP	4	–	0.13	0.21	71.6	0.01	Random	–	Moderate
Total cholesterol	7	–	−0.03	0.23	0	0.75	Fixed	0.89	High

(Continues)

TABLE 2 | (Continued)

Risk factor	No. of included studies	Degree of association	Combined SMD/OR	*p*	Heterogeneity test		Model	Egger test	Evidence quality
					I^2 (%)	*p*			
LDL-C	6	–	−0.03	0.27	0	0.82	Fixed	0.89	High
Diabetes type (T2 versus T1)	4	–	1.64	0.07	89.4	<0.01	Random	–	Very low
Coronary artery disease	2	–	1.08	0.91	94.7	<0.01	Random	–	Very low
Sulfonylurea use	2	–	0.94	0.91	82.2	0.02	Random	–	Very low
Metformin use	2	–	3.28	0.36	91.3	<0.01	Random	–	Very low
Aspirin use	2	–	0.87	0.63	0	0.60	Fixed	–	Very low
Statin treatment	4	–	1.26	0.13	76.4	<0.01	Random	–	Very low

Note: In respect to the continuous variables: SMD < 0.2 = + (small association); SMD 0.2–0.8 = ++ (moderate association); SMD > 0.8 = +++ (strong association). In respect to the binary variables: OR 1.0–2.0 = + (weak association); OR 2.0–3.0 = ++ (moderate association); OR 3.0–10.0 = +++ (strong association). Bolded values indicate statistically significant results ($p < 0.05$).
Abbreviations: ABPI = ankle-brachial pressure index; DBP = diastolic blood pressure; eGFR = estimated glomerular filtration rate; HbA1c = haemoglobin A1c; HDL-C = high-density lipoprotein cholesterol; LDL-C = low-density lipoprotein cholesterol; PAD = peripheral artery disease; SBP = systolic blood pressure; VPT = vibration perception threshold.

without peripheral vascular disease or neuropathy [32], while no significant association was found in participants with type 2 diabetes [36]. Our analysis also revealed a protective role for HDL-C in reducing first-ever DFU risk, while elevated triglycerides were identified as a significant risk factor. These findings align with prior studies [42]. Meanwhile, a protective effect of taking cholesterol-lowering medications was found [32]. Early and appropriate management of blood glucose, blood pressure and lipid profiles is essential, prior to the development of foot complications, to reduce the incidence of first-ever DFU.

4.3 | Diabetes-Related Complications

Our review confirmed that those with late diabetes-related complications, particularly macrovascular and microvascular diseases, were significantly more likely to develop first-ever DFU, aligning with findings from previous research [24, 28, 42]. This can be explained by well-established pathophysiological pathways, including ischaemia, sensory loss and trauma [55]. Vascular disease affects about 30% of individuals with DFU [3]. Severe atherosclerosis plaques in peripheral arteries limit lower limb perfusion, creating an ischaemic environment that promotes ulcer formation and progression [56]. Given this, vascular assessment is a crucial component in comprehensive foot care, and a low ABPI is a recognised marker of PAD severity and a strong predictor of first-ever DFU in our study. This finding reinforces the critical role of PAD in DFU development. Peripheral neuropathy is another critical causative factor for DFU, affecting nearly 50% of people with diabetes [55]. Foot ulcers often arise from chronic, repetitive trauma, as sensory neuropathy leads to loss of protective sensations, preventing patients from detecting minor wounds or pressure, which results in DFU development and delayed diagnosis [37, 39, 55]. Autonomic neuropathy impairs sweat gland function, resulting in skin dryness and fissures, which compromise the skin protective barrier and increase vulnerability to ulceration [24, 39]. Motor neuropathy can give rise to muscle wasting and altered foot biomechanics, contributing to deformities and consequently localised pressure points or abnormal pressure distribution, further elevating ulcer risk [32, 37]. These mechanisms support our findings that skin dryness and foot deformities are significant predictors of first-ever DFU. Early and more diligent screening in clinical practice is important to reduce the burden of complications associated with diabetes.

4.4 | Cognitive Dysfunction and Depression

Growing evidence suggests that cognitive dysfunction and depression in individuals with diabetes are linked to an increased risk of first-ever DFU [25, 30, 41]. One prospective study revealed that, after adjusting for all covariates, patients with major depression had a 2-fold increased risk of developing first-ever DFU within 4 years compared to those without depression [25]. Similarly, a longitudinal study with an 11-year follow-up reported a 3-fold higher risk of DFU among individuals with baseline depression, independent of age, gender and glycaemic control [57]. Another cohort study [30] further supported these findings, showing that patients with first-ever DFU had higher depression scores and lower cognitive scores than those without

DFU. Kim et al. [36] also indicated that patients who used antidepressants faced a higher risk of first-ever DFU. The underlying mechanisms remain complex and unclear. Depression is linked to poorer self-care, treatment non-adherence and unhealthy behaviours (e.g., smoking, physical inactivity and poor diet) [58, 59], all of which are known risk factors for DFU. Additionally, depression has been associated with microvascular and macrovascular complications, which may contribute to impaired wound healing and ulcer development [59–61]. Given these associations, future interventions should consider integrating mental health screening into diabetes management frameworks, particularly for high-risk groups.

4.5 | Social Determinants and Education

It is well established that the social determinants of health significantly impact diabetes outcomes and complications, including first-ever DFU. Recent studies have identified social deprivation as a key predictor of DFU onset. For instance, a UK study using the Townsend Index reported a 77% higher risk of first-ever DFU among individuals in the most socioeconomically deprived quintile compared to those in the least deprived [22]. Similarly, a Danish study using international database records found that lower household disposable income was associated with increased first-ever DFU and amputation risk [41]. These disparities may stem from a higher prevalence of PAD and neuropathy in disadvantaged groups [62, 63], as well as poor glycaemic control linked to unhealthy dietary habits [64].

In addition to economic status, diabetes-related education and basic foot care also play crucial roles in DFU prevention [65]. Studies consistently indicate that persons with DFU were more likely to have lower scores in diabetes knowledge and foot-care practices [30, 39]. A 4-year prospective study in Australia found that each unit increase in the Test of Functional Health Literacy in Adults score reduced the risk of first-ever DFU by 6% [30]. Inappropriate footwear, a preventable risk factor, further underscores the importance of patient adherence to foot care guidelines [43]. Effective prevention is heavily reliant on patient adherence to recommended practices that minimise the risk of foot complications. Simplifying clinical communication and confirming patient comprehension of health information are critical steps to minimise misunderstandings and improve self-care. However, while educational programmes have shown some promise in enhancing foot care knowledge and promoting short-term self-management behaviours, their long-term effectiveness in achieving clinical reductions in foot complications remains uncertain [66, 67]. More rigorous trials are needed to evaluate the durability and clinical impact of educational programmes in diverse health systems.

4.6 | Limitations

This study has several limitations that should be considered when interpreting the findings. First, the inclusion criteria were restricted to studies published in English or Chinese, potentially introducing publication bias. Although we mitigated this risk by conducting citation reference searches and manually reviewing reference lists of included studies, some valuable studies, particularly in Spanish, may have been missed. This is an important consideration, as individuals of Hispanic heritage represent a high-risk group for diabetes and related complications. Future systematic reviews should consider including studies published in other languages to improve the comprehensiveness and generalisability of the findings. Second, a high level of heterogeneity was observed across studies for most risk factors. While subgroup analyses based on study design, quality and publication year were conducted, not all sources of heterogeneity were explainable. Additionally, the lack of standardised definitions for certain risk factors may contribute to this variability. For example, although BMI $\geq 30\,kg/m^2$ was defined as obesity in this study, this cut-off may not be appropriate for all populations. Some guidelines suggest lower BMI thresholds (e.g., $\geq 25\,kg/m^2$ for obesity in Asian populations) due to a higher risk of metabolic and cardiovascular diseases at lower BMI levels [68]. Third, while ABPI was identified as a predictor of first-ever DFU, this study did not establish a specific cut-off value due to limited data, limiting its clinical applicability. Future studies should determine precise threshold values for ABPI, BMI and other key risk factors to enhance risk stratification and targeted prevention strategies. Fourth, subgroup analyses based on the type of diabetes were not performed. Given the distinct pathophysiological mechanisms and complications associated with type 1 and type 2 diabetes, it is plausible that the risk factors for first-ever DFU differ between these groups. This notion is supported by a cohort study conducted by Hangaard et al. [28] Future research should further investigate these differences to provide tailored preventive strategies. Finally, this review highlights several factors with strong and consistent associations, such as neuropathy, PAD, VPT $\geq 25\,V$ and insufficient physical activity, that could be prioritised in screening and prevention strategies. Conversely, factors with conflicting or limited evidence require further investigation. Improved data harmonisation and prospective cohort studies are needed to strengthen the evidence base and support clinical implementation.

5 | Conclusion

This study identified 28 significant risk factors associated with the development of first-ever DFU. These findings offer a foundation for the early identification of high-risk individuals, which could help mitigate the burden on both patients and healthcare systems. Put simply, the prevention of first-ever DFU is a multifactorial problem, requiring a comprehensive and interdisciplinary approach. Integrating multidisciplinary care teams may provide substantial benefits by addressing the diverse factors contributing to first-ever DFU incidence.

Ethics Statement

The authors have nothing to report.

Conflicts of Interest

The authors declare no conflicts of interest.

Data Availability Statement

The original contributions presented in this study are included in the articles/Supporting Information, further inquiries can be directed to the corresponding author.

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Supporting Information

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