

# Hypertension and the Risk of Diabetic Foot Ulcers: A Mendelian Randomization Analysis

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**Abstract: Objective:** This study utilized a two-sample Mendelian randomization (MR) approach to explore whether hypertension (HBP) has a causal influence on the development of diabetic foot ulcers (DFU). **Methods:** Summary statistics from genome-wide association studies (GWAS) involving European populations were analyzed. Genetic variants linked to hypertension were extracted from the FinnGen consortium, whereas diabetic foot ulcer data were obtained from the UK Biobank (UKBB). The primary analysis relied on the inverse variance weighted (IVW) method, supplemented by weighted median (WM) and MR-Egger regression to assess robustness. **Results:** The IVW analysis indicated a statistically significant association between hypertension and diabetic foot ulcers (OR = 2.107, 95% CI = 1.2028–3.692, P = 0.009). Sensitivity analyses confirmed the stability of these findings, with no significant heterogeneity (Cochran's Q test) or evidence of horizontal pleiotropy detected. **Conclusion:** These findings suggest that hypertension may contribute to an elevated risk of diabetic foot ulcers, supporting a potential causal relationship between the two conditions.

**Keywords:** Hypertension; Diabetic Foot Ulcer; Mendelian Randomization.

## 1. Introduction

Diabetic foot ulcers (DFUs) represent among the most frequent complications of the lower extremities in patients with diabetes. Globally, they affect 6.3% of diabetic patients, while in China, the prevalence is approximately 4.1% [1]. From 2003 to 2020, the incidence of newly diagnosed DFUs increased from 20.7‰ to 33.1‰ [2]. DFUs are typically easy to diagnose but difficult to treat, characterized by prolonged treatment duration, high amputation and mortality rates, heavy economic burden, and poor prognosis [3]. With an aging population, the impact of DFUs extends beyond individual patients, substantially diminishing quality of life while creating socioeconomic burdens for families and communities [4].

DFUs have multiple risk factors. Established ones include neuropathy, vascular disease, smoking, and poor glycemic control [5–6]. However, due to the incomplete understanding of DFU pathogenesis, inter-individual differences, and multifactorial interactions, its prevention, diagnosis, and prognosis remain challenging. Therefore, identifying the risk factors and etiological mechanisms of DFU is an urgent issue that needs to be addressed.

As a highly prevalent chronic condition, hypertension poses significant threats to human health and has emerged as the foremost contributor to the global disease burden in recent years. Epidemiological studies indicate that in 2000, approximately one-quarter (26.4%) of the global population was affected by this condition, with projections suggesting an increase to 29.2% by 2025 [7].

The interplay between hypertension and DFU involves multiple pathophysiological mechanisms. Existing longitudinal research suggests that elevated blood pressure may exacerbate peripheral arterial disease, thereby potentially contributing to DFU development [8-9]. Nevertheless, conventional clinical investigations frequently encounter methodological constraints that may compromise the validity of causal conclusions.

Mendelian randomization (MR) offers an alternative

approach by leveraging genetic variants from GWAS datasets to simulate randomized controlled trial conditions [10-11]. This methodology has gained prominence in establishing causal associations between risk factors and clinical outcomes, effectively addressing limitations inherent in observational studies. Prior MR analyses have successfully demonstrated causal effects of smoking and hyperglycemia on DFU occurrence, confirming their role in diabetic complications [12].

Notably, the potential causal influence of hypertension on DFU remains unexplored through MR techniques. To address this knowledge gap, our investigation employs a two-sample MR framework utilizing genetically independent cohorts for exposure (hypertension) and outcome (DFU) data. This approach aims to elucidate the etiological connection between hypertension and DFU pathogenesis, offering novel insights for clinical understanding and management.

## 2. Materials and Methods

### 2.1. Study Design

The present research utilized hypertension as the exposure factor, with significantly correlated SNPs serving as instrumental variables, while diabetic foot ulcers represented the outcome measure, applying a two-sample Mendelian randomization methodology to investigate their possible causal association.

### 2.2. Data Sources

**Exposure Data:** The exposure dataset exclusively included individuals of European descent. Genetic association summary statistics for hypertension were derived from the FinnGen consortium, encompassing a total of 420,473 European-ancestry participants (137,312 hypertension cases and 316,345 control subjects).

**Outcome Data:** The outcome dataset similarly comprised exclusively European-ancestry individuals, with diabetic foot ulcer (DFU) genetic association data sourced from the 2020 Pan-UK Biobank initiative. This dataset included 420,473

participants of European descent (130 DFU cases and 420,343 controls). All original study protocols had received approval from respective institutional review boards, with participants providing informed consent. Since the current

analysis utilized de-identified, publicly accessible data, neither additional ethical clearance nor participant consent was necessary (Table 1).

**Table 1.** Data information

Trait report name	Ancestry	Year	Case(n)	Control(n)	Sample(n)	Database
Hypertension	EUR	2021	137312	316345	453657	Finn Gen
Disease	EUR	2020	130	420343	420743	UK-Biobank

### 2.3. Instrumental Variable Selection

The selection of SNPs as instrumental variables strictly adhered to the three core MR assumptions through rigorous screening criteria: (1) For genetic relevance, we identified hypertension-associated SNPs meeting genome-wide significance thresholds ( $P < 5 \times 10^{-8}$ ) through comprehensive GWAS [14]; (2) To ensure independence, we performed LD pruning ( $R^2 < 0.001$  within 10,000 kb windows) to eliminate correlated variants [14]; (3) Instrument strength was validated by computing F-statistics ( $F = \beta^2 / SE^2$ ), excluding all SNPs with  $F < 10$  to prevent weak instrument bias; (4) Potential pleiotropic effects were mitigated by systematically screening for confounding variants through PhenoScanner (<http://www.phenoscanter.medschl.cam.ac.uk/>), a curated database of genotype-phenotype associations.

### 2.4. Mendelian Randomization Analysis

The assessment of causal relationships between hypertension and DFU was performed utilizing the "TwoSampleMR" package (R version 4.4.1). Our primary analytical approach employed the inverse variance weighted (IVW) method [15], which yields reliable effect estimates when instrumental variables meet validity assumptions. To ensure result robustness, supplementary analyses were conducted using weighted median (WM) and MR-Egger regression approaches.

### 2.5. Sensitivity Analysis

The robustness of our findings was evaluated through comprehensive sensitivity analyses assessing potential pleiotropy, heterogeneity, and individual SNP influence. First,

we examined horizontal pleiotropy via MR-Egger regression, where an insignificant intercept term ( $P > 0.05$ ) suggested the absence of pleiotropic effects [16]. Second, Cochran's Q statistic ( $P > 0.05$ ) indicated minimal between-SNP heterogeneity. Third, we systematically evaluated each SNP's individual impact through leave-one-out analysis to identify potential influential variants [17]. Finally, we implemented MR-PRESSO to detect and adjust for pleiotropic outliers (significance threshold  $P < 0.05$ ), thereby enhancing the validity of our causal estimates.

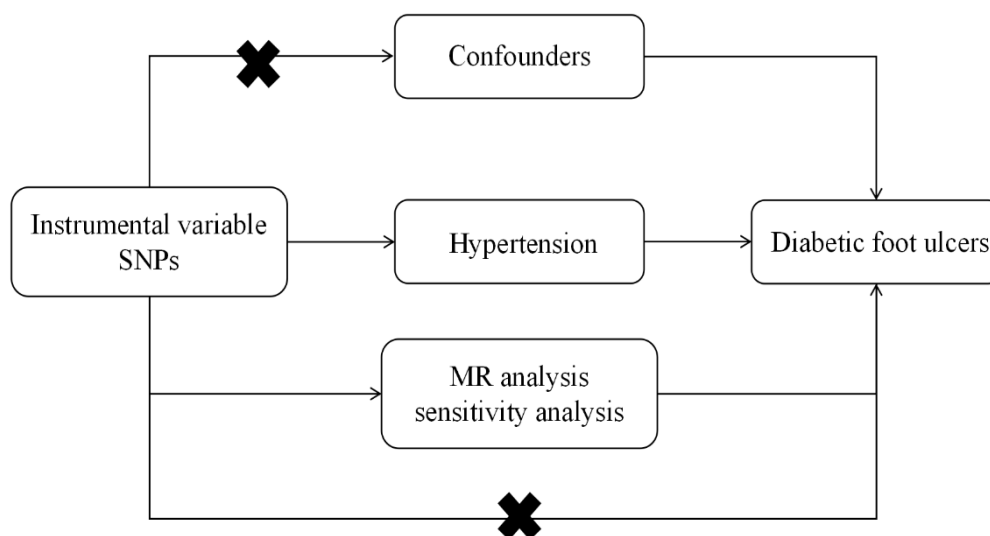
### 2.6. Statistical Analysis

The statistical analyses were conducted in R software (v4.4.1), primarily utilizing the TwoSampleMR and MR-PRESSO packages. Results quantifying the hypertension-DFU association were expressed as odds ratios (OR) accompanied by 95% confidence intervals. Statistical significance was determined at  $P < 0.05$ , suggesting evidence for a potential causal link between these variables.

## 3. Results

### 3.1. Instrumental Variable Selection

The present Mendelian randomization investigation evaluating the hypertension-DFU causal association (illustrated in Figure 1) incorporated 234 hypertension-related SNPs as instrumental variables following stringent quality control procedures. Each selected genetic variant demonstrated F-statistics exceeding the threshold of 10, confirming their robustness as instruments and minimizing potential weak instrument bias (Table 2).



**Figure 1.** Research process

**Table 2.** List of SNPs and associations

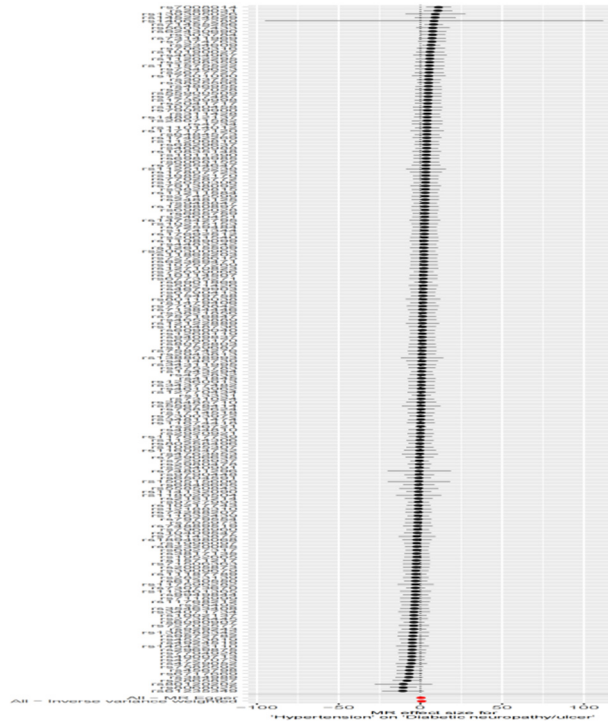
SNP	P	F
rs1002137	7.77E-09	33.331
rs10048736	3.75E-08	30.277
rs1011390	1.18E-09	36.995
.....		
rs9727993	5.45E-13	52.036
rs9790448	1.37E-08	32.235
rs9949844	1.07E-09	37.193

Note: SNP: single nucleotide polymorphism.

### 3.2. Mendelian Randomization Analysis

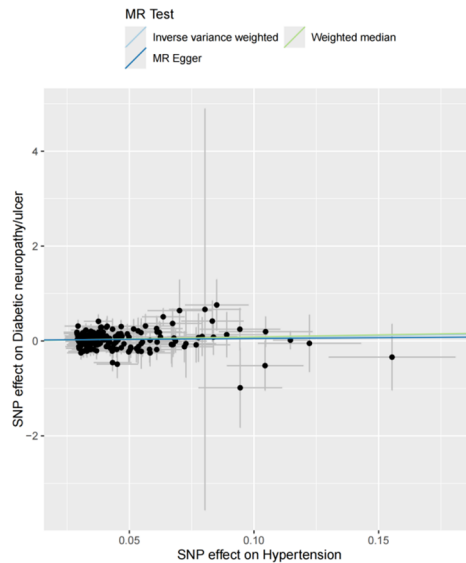
The Mendelian randomization results demonstrated

consistent evidence for hypertension's causal effect on DFU risk across multiple analytical approaches. The primary IVW analysis yielded an odds ratio of 2.107 (95% CI: 1.203-3.692, P=0.009), while the weighted median approach showed an OR of 2.367 (95% CI: 1.046-5.359, P=0.039). MR-Egger regression produced an OR of 1.424 (95% CI: 0.164-12.330, P=0.749), with all methods indicating concordant effect directions (OR>1). Visual inspection of scatter plots revealed stable regression trajectories without significant deviations. Based on IVW estimates, each standardized unit elevation in hypertension status corresponded to a 110.7% elevated DFU risk (see Figures 2-3 and Table 3).



**Figure 2.** Causal effect of instrumental variables on outcome

Notes: black data points indicate individual SNP effect estimates for hypertension's influence on DFU risk, while red points display the aggregated effect sizes derived from both MR-Egger and IVW analyses.



**Figure 3.** Scattergram for Mendelian stochastic analysis results

Note: the scatter plot illustrates the association between individual SNP effects on hypertension (x-axis) and their corresponding effects on diabetic foot ulcers (y-axis). The colored trend line depicts the overall causal relationship estimate between these two variables.

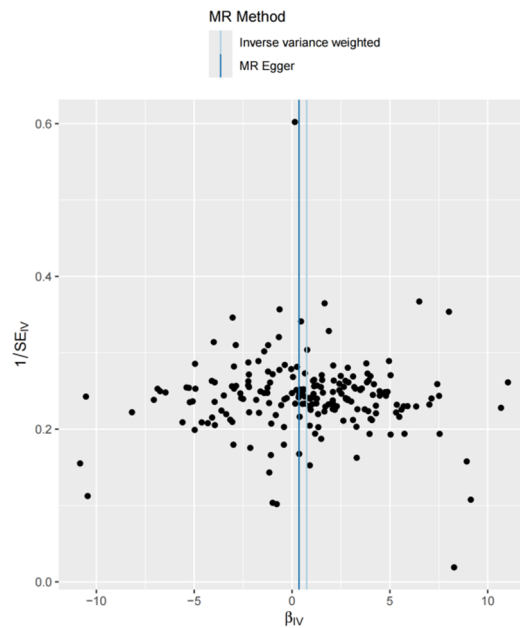
**Table 3.** High blood pressure and diabetic foot ulcers in a Mendelian randomization analysis

Exposure	Outcome	Method	P	OR	95%CI
Hypertension	Diabetic foot ulcers	IVW	0.009	2.107	1.203~3.692
		Weighted median	0.039	2.367	1.046~5.359
		MR-Egger	0.749	1.424	0.164~12.330

### 3.3. Sensitivity Analysis

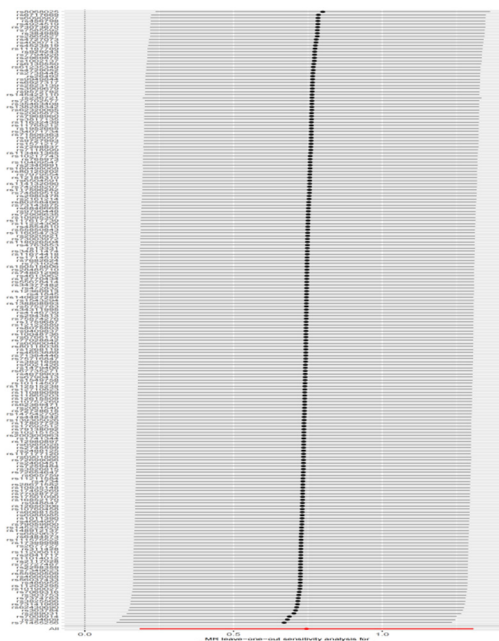
The sensitivity analyses consistently demonstrated the robustness of our findings. Both IVW (Cochran's  $Q=154.893$ ,  $P=0.990$ ) and MR-Egger ( $Q=154.757$ ,  $P=0.991$ ) approaches showed negligible heterogeneity. The MR-Egger intercept test ( $P=0.713$ ) and symmetrical funnel plot (Figure 4) provided no evidence of horizontal pleiotropy or SNP

distribution bias. Furthermore, leave-one-out analysis (Figure 5) confirmed the stability of effect estimates across all SNP iterations, eliminating concerns about disproportionate influence from any individual variant. These comprehensive sensitivity assessments validate the reliability of our MR results and strengthen the evidence for hypertension's causal role in DFU development.



**Figure 4.** The funnel plot

Note: the black dots represent a single SNP, and it can be seen that the funnel map SNP is basically symmetrical, and the research results are less affected by bias.



**Figure 5.** Leave-one-out analysis

Note: (1) black markers representing the causal effect estimates of hypertension on DFU following sequential SNP exclusion, and (2) red markers showing the overall causal estimate using all selected SNPs. The x-axis quantifies the effect size after each SNP removal, while the y-axis lists all sequentially excluded SNPs (single nucleotide polymorphisms).

## 4. Discussion

This research employed extensive GWAS (genome-wide association study) datasets sourced from both the UK Biobank and FinnGen repositories to perform a two-sample Mendelian randomization investigation. The primary objective was to elucidate the genetic mechanisms linking hypertension (the exposure factor) with diabetic foot ulcer (DFU, the outcome measure). Analysis outcomes demonstrated notable genetic associations between hypertension and DFU, indicating potential common genetic determinants. Additional sensitivity testing consistently supported a causal association between these medical conditions.

China has a large diabetic population, among whom diabetic foot ulcer (DFU) represents one of the most serious disease-related complications [18]. Previous studies have shown that hypertension is both a common comorbidity and an established risk factor for DFU [19, 20]. A report from Barcelona indicated that, in 2019, the prevalence of hypertension in the region was 20%, while diabetes prevalence was 7% [21]. Clinically, hypertension is considered a predictive factor for amputation in DFU patients [22], and blood pressure control is recognized as a fundamental component of medical management for DFU [23].

Basic research also supports the role of hypertension in DFU pathophysiology. Blood pressure regulation has been shown to improve healing by modulating biological pathways such as increasing exosomal miR-125b-1-3p and miR-126-3p levels in DFU patients [24] and inhibiting pathological angiogenesis [25]. Hypertension has been identified as a potential risk factor for diabetic foot ulcer (DFU), making the investigation of their association crucial for improving clinical strategies in early detection, management, and outcome prediction. The Mendelian randomization (MR) results revealed a significant causal effect, indicating that hypertension contributes to a higher DFU risk. These discoveries provide meaningful implications for further scientific exploration.

This research benefits from employing a two-sample Mendelian randomization approach, an effective method for reducing biases from unmeasured confounding factors and reverse causation, thereby strengthening causal conclusions. Nevertheless, certain limitations merit consideration: (1) The genomic data were derived exclusively from European populations. Considering well-documented ethnic variations in genetic architecture and the distinct epidemiological patterns of these disorders between East Asian and European populations, future investigations incorporating diverse ethnic cohorts would enhance the external validity of our results. (2) Both the hypertension and DFU GWAS samples exhibited constrained sizes, with particularly limited DFU case numbers. Consequently, more extensive epidemiological studies with adequate statistical power are required to corroborate these findings.

This investigation systematically assessed the causal influence of hypertension on DFU pathogenesis, with analytical results substantiating a significant causative association between these conditions. Hypertension is considered the risk factor for DFU, providing new perspectives for prevention, intervention, and therapeutic strategies. Furthermore, our findings offer valuable clues for

understanding the pathogenic mechanisms underlying DFU. Nonetheless, additional scientific investigations are necessary to confirm and extend these results.

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## References

- [1] Zhang P, Lu J, Jing Y, Tang S, Zhu D, Bi Y. Global epidemiology of diabetic foot ulceration: a systematic review and meta-analysis †. *Ann Med*. 2017 Mar;49(2):106-116. doi: 10.1080/07853890.2016.1231932. Epub 2016 Nov 3. PMID: 27585063.
- [2] Armstrong DG, Tan TW, Boulton AJM, Bus SA. Diabetic Foot Ulcers: A Review. *JAMA*. 2023 Jul 3;330(1):62-75. doi: 10.1001/jama.2023.10578. PMID: 37395769; PMCID: PMC10723802.
- [3] Xia F. Effect of Traditional Chinese Medicine Fumigation on Patients with Diabetic Foot. *Chin J Min Health Med*. 2022;34(17):96-99.
- [4] Wang XY. Study on Quality of Life and Its Influencing Factors Among Caregivers of Patients with Diabetic Foot Ulcer Amputation [D]. Qingdao University, 2023. DOI:10.27262/d.cnki.gqda.2023.000058.
- [5] Boyko EJ, Ahroni JH, Stensel V, Forsberg RC, Davignon DR, Smith DG. A prospective study of risk factors for diabetic foot ulcer. The Seattle Diabetic Foot Study. *Diabetes Care*. 1999 Jul;22 (7):1036-42. doi: 10.2337/diacare.22.7.1036. PMID: 10388963.
- [6] Singh N, Armstrong DG, Lipsky BA. Preventing foot ulcers in patients with diabetes. *JAMA*. 2005 Jan 12;293(2):217-28. doi: 10.1001/jama.293.2.217. PMID: 15644549.
- [7] Kearney PM, Whelton M, Reynolds K, Muntner P, Whelton PK, He J. Global burden of hypertension: analysis of worldwide data. *Lancet*. 2005 Jan 15-21;365(9455):217-23. doi: 10.1016/S0140-6736(05)17741-1. PMID: 15652604.
- [8] Guidelines for the Prevention and Treatment of Diabetic Foot in China (2019). *Chin J Diabetes*. 2019;11(2):92-108.
- [9] Wei HR, Ma L. Research Progress on Risk Factors of Diabetic Foot Ulcer. *J Tradit Chin Med*. 2024;42(02):145-148.
- [10] Smith GD, Ebrahim S. Mendelian randomization: prospects, potentials, and limitations. *Int J Epidemiol*. 2004 Feb;33(1):30-42. doi: 10.1093/ije/dyh132. PMID: 15075143.
- [11] Sekula P, Del Greco M F, Pattaro C, Köttgen A. Mendelian Randomization as an Approach to Assess Causality Using Observational Data. *J Am Soc Nephrol*. 2016 Nov;27 (11): 3253-3265. doi: 10.1681/ASN.2016010098. Epub 2016 Aug 2. PMID: 27486138; PMCID: PMC5084898.
- [12] Yin K, Qiao T, Zhang Y, Liu J, Wang Y, Qi F, Deng J, Zhao C, Xu Y, Cao Y. Unraveling shared risk factors for diabetic foot ulcer: a comprehensive Mendelian randomization analysis. *BMJ Open Diabetes Res Care*. 2023 Nov;11(6):e003523. doi: 10.1136/bmjdr-2023-003523. PMID: 37989345; PMCID: PMC10660165.
- [13] Skrivankova VW, Richmond RC, Woolf BAR, Yarmolinsky J, Davies NM, Swanson SA, VanderWeele TJ, Higgins JPT, Timpson NJ, Dimou N, Langenberg C, Golub RM, Loder EW, Gallo V, Tybjaerg-Hansen A, Davey Smith G, Egger M, Richards JB. Strengthening the Reporting of Observational Studies in Epidemiology Using Mendelian Randomization:

- The STROBE-MR Statement. *JAMA*. 2021 Oct 26;326 (16): 1614-1621. doi: 10.1001/jama.2021.18236. PMID: 34698778.
- [14] Ma J, Li J, Jin C, Yang J, Zheng C, Chen K, Xie Y, Yang Y, Bo Z, Wang J, Su Q, Wang J, Chen G, Wang Y. Association of gut microbiome and primary liver cancer: A two-sample Mendelian randomization and case-control study. *Liver Int*. 2023 Jan;43(1):221-233. doi: 10.1111/liv.15466. Epub 2022 Nov 8. PMID: 36300678.
- [15] Ru X, Huang L, Su Z, Ye C, Guo Y. Exploring the causal relationship between asthma in the metabolic syndrome: a Mendelian randomization study. *J Asthma*. 2024 Aug 20:1-38. doi: 10.1080/02770903.2024.2394143. Epub ahead of print. PMID: 39163002.
- [16] Wang YZ, Shen HB. [Challenges and factors that influencing causal inference and interpretation, based on Mendelian randomization studies]. *Zhonghua Liu Xing Bing Xue Za Zhi*. 2020 Aug 10;41(8):1231-1236. Chinese. doi: 10.3760/cma.j.cn.112338-20200521-00749. PMID: 32867428.
- [17] Zhu X, Huang S, Kang W, Chen P, Liu J. Association Between Polyunsaturated Fatty Acids and Parkinson's Disease: A Two-Sample Mendelian Randomization Study. *Front Aging Neurosci*. 2023 Feb 22;15:1123239. doi: 10.3389/fnagi.2023.1123239. PMID: 36909950; PMCID: PMC9992541.
- [18] Chinese Diabetes Society. Chinese Guidelines for the Prevention and Treatment of Type 2 Diabetes (2020 Edition, Part II). *Chin J Pract Intern Med*. 2021;41(9):757-784.
- [19] Zaki SM, El Karsh DS, Faden TM, Almghamsi LT, Fathaldin JO, Alhazmi OA. Diabetic Foot Complications in Saudi Arabia: A Retrospective Study. *Cureus*. 2024 Feb 3;16(2):e53531. doi: 10.7759/cureus.53531. PMID: 38445149; PMCID: PMC 1091 2821.
- [20] Luo Y, Liu C, Li C, Jin M, Pi L, Jin Z. The incidence of lower extremity amputation and its associated risk factors in patients with diabetic foot ulcers: A meta-analysis. *Int Wound J*. 2024 Jul;21(7):e14931. doi: 10.1111/iwj.14931. PMID: 38972836; PMCID: PMC11227953.
- [21] La salut a Barcelona 2019. Agència de Salut Pública de Barcelona. 2020. [consultado 22 Mar 2022]. Disponible en: <https://www.aspb.cat/noticies/informe-salut-barcelona-2019/>.
- [22] Jeon BJ, Choi HJ, Kang JS, Tak MS, Park ES. Comparison of five systems of classification of diabetic foot ulcers and predictive factors for amputation. *Int Wound J*. 2017 Jun;14 (3): 537-545. doi: 10.1111/iwj.12642. Epub 2016 Oct 10. PMID: 27723246; PMCID: PMC7949506.
- [23] Chen ZJ, Pan XY, Deng P, et al. Advances and Prospects in Local Wound Treatment for Diabetic Foot Ulcers. *Chin J Foot Ankle Surg (Electronic Edition)*. 2022;9(04):95-100.
- [24] Wang L, Zeng N, Xie WP, et al. Effects of Intensive Glycemic and Blood Pressure Control on Exosomal microRNAs in Patients with Diabetic Foot. *Youjiang Med J*. 2021;49(02):97-102.
- [25] Zhang Y, Zhou DM, Li W, et al. Risk Factors of Diabetic Foot and the Impact of Ulcer Severity on Prognosis. *Chin J Gerontol*. 2021;41(22):4911-4914.