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The causal relationship between hallux valgus and endogenous pathogenic factors

A 2-sample Mendelian randomization

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Abstract

Notably, several factors are associated with hallux valgus (HV); however, their causal relationship remains unclear. In this study, a 2-sample Mendelian randomization (MR) analysis was performed to investigate the casual relationship between 9 endogenous risk factors and HV, aiming to provide a foundation for the clinical management of HV. Exposure factors such as body mass index (BMI), BMI (male), BMI (female), acquired flatfoot, rheumatoid arthritis, gout, knee osteoarthritis, hip osteoarthritis, and Ehlers–Danlos syndrome were considered, with HV as the outcome. Exposure and outcome data were obtained from the IEU Open Genome-wide association study project, UK Biobank, and FinnGen project. Strongly correlated ($P < 5\times10^{-08}/5\times10^{-06}$) single nucleotide polymorphisms (SNPs) were selected from the exposure dataset, and those associated with exposure were selected from the HV dataset. The intersection of these SNPs was used as instrumental variables. Five modes were used for the analysis: inverse variance-weighted (IVW), MR-Egger regression, weighted median (WME), simple mode, and weighted mode. MR analysis results of BMI show that except for MR-Egger, the other 4 modes are significant ($P < .05$), and the β directions are consistent among the 5 methods. For the 4 BMI (male) methods, except for the simple mode, the *P*- and β-values of the other results all suggest a positive causal relationship between BMI (male) and HV. Flatfoot-IVW and WME results were <.05, indicating statistical significance, whereas MR-Egger, simple mode, and median mode had no statistical significance. However, their β-values were consistent with those of IVW and WME. Further mediation MR analysis suggested that the effect mediated by HV accounts for 13.33% [95% CI (0.03–0.24)] of the total causal effect between the BMI and flatfoot, indicating HV as a mediator of the causal relationship between the BMI and flatfoot. However, the remaining 6 factors had no direct causal association with HV ($P < .05$). Flatfoot in all patients and elevated BMI in males are directly associated with HV. Therefore, treating acquired flatfoot and controlling the BMI to prevent HV are recommended.

Abbreviations: BMI = body mass index, EDS = Ehlers–Danlos syndrome, GWAS = genome-wide association study, HOA = hip osteoarthritis, HV = hallux valgus, IVS = instrumental variables, IVW = inverse variance-weighted, KOA = knee osteoarthritis, MR = Mendelian randomization, RA = rheumatoid arthritis, SNP = single nucleotide polymorphism, WME = weighted median.

Keywords: casual association, etiology, hallux valgus, Mendelian randomization

1. Introduction

Hallux valgus (HV) is 1 of the most common forefoot deformities in which the big toe deviates outward from the normal range. It manifests primarily as misalignment of the big toe, medial bulge of the first metatarsophalangeal joint, and lateral toe deformity due to the squeezing of the big toe. In severe cases, hammertoe of the second toe, submetatarsal callus, pain, and metatarsophalangeal arthritis may occur because of the weight-bearing displacement of the first metatarsal bone.[1–3] Once a deformity is formed, it cannot be adjusted voluntarily, and localized inflammatory pain progressively worsens, eventually making it difficult for patients to walk. The etiology of HV remains unclear; however, it is currently believed to be associated with factors such as shoeing habits, inflammation, sex, gait, and genetically inherited structural abnormalities of the foot. To address this issue, we started from a genetic perspective and performed a 2-sample Mendelian randomization (MR) analysis using single nucleotide polymorphisms (SNPs) that are minimally affected by confounders as instrumental variables (IVs). We investigated the causal associations

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The GWAS analyzed during the current study are available in the UK Biobank-Nealelab (http://www.nealelab.is/uk-biobank/), FinnGen project (https://risteys.finregistry.fi/) and IEU OpenGWAS project (https://gwas.mrcieu.ac.uk/).

Data sharing not applicable to this article as no datasets were generated or analyzed during the current study.

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between HV and 9 endogenous risk factors, including body mass index (BMI), BMI (female), BMI, (male), acquired flatfoot, rheumatoid arthritis (RA), gout, knee osteoarthritis (KOA), hip osteoarthritis (HOA), and Ehlers–Danlos syndrome (EDS).[2,4] We aim to provide a basis for the clinical management of HV.

2. Methods

2.1. Data sources

BMI, BMI (female), BMI (male), acquired flatfoot, RA, Gout, KOA, HOA, and EDS were used as the exposure factors. HV was the primary outcome of this study. Genome-wide association study (GWAS) data were obtained from the IEU GWAS, UK Biobank, and the FinnGen project. All the data were obtained from European populations (Table 1).

2.2. Filtering IVs

Strongly related SNPs ($P < 5\times10^{-08}/5\times10^{-06}$) were extracted from the exposure dataset. To ensure that the SNPs were independent of each other, the linkage disequilibrium was removed using the *clump_data* function, and the linkage disequilibrium coefficient was set ($r^2 < 0.001/0.01$). To limit the scope of the analysis, the region width was set to 10,000 kb/5000 kb to reduce the effect of gene pleiotropy on the results. The intersection of exposure data with outcome data was taken. Missing SNPs were replaced with proxy SNPs. The final IVs were used for MR analysis after searching and deleting duplicated and palindromic SNPs (Table 2).

2.3. MR analysis methods

This study aimed to utilize selected SNPs as IVs to substitute exposure and regress with outcomes to ultimately verify the causal relationship between the reported 9 risk factors and HV. Specific analysis methods included inverse variance-weighted (IVW), MR-Egger regression, weighted median (WME), simple mode, and weighted mode. IVW is a weighted linear regression of IVs on exposure and outcome effects. It strictly adheres to 3 key assumptions and is recognized for its superior statistical efficiency compared with other methods. However, because of the potential bias in its analysis results when IVs demonstrate horizontal pleiotropy,[5] the MR-Egger intercept method was additionally employed to detect the presence of such pleiotropy and enhance the reliability of the outcomes of IVW analysis. IVW can also not provide consistent estimates when invalid IVs are present. Therefore, WME was added to combine data from multiple genetic variants into a single dataset for causal estimation. The WME can provide unbiased results when at least 50% of the valid IVs are present in the data.[6–8]

Table 1

The specific information of genome-wide association study data.

GWAS ID	Trait	Year	Sample size	nSNPs
ukb-b-19953 (21001_both sex)	Body mass index	2018	461,460	9,851,867
21001_irnt	Body mass index (female)	2018	193,570	13,791,467
21001_irnt	Body mass index (male)	2018	166,413	13,791,467
ebi-a-GCST90018910	Rheumatoid arthritis	2021	417,256	24,175,266
finn-b-M13_FLATFOOT	Flatfoot	2021	148,480	16,380,142
finn-b-M13_GOUT	Gout	2021	150,797	16,380,152
finn-b-Q17_EHLER_SYNDR	Ehlers–Danlos syndrome	2021	218,792	16,380,466
ebi-a-GCST005813	Knee osteoarthritis	2018	22,347	15,708,690
ebi-a-GCST007091	Hip osteoarthritis	2019	393,873	29,771,219
finn-b-M13_HALLUXVALGUS	Hallux valgus	2021	155,757	16,380,195

Abbreviations: GWAS = genome-wide association study, nSNPs = number of single nucleotide polymorphisms.

2.4. Heterogeneity test

The Cochran *Q* test was used to assess statistical heterogeneity among SNPs, with a *P* value < .05, indicating statistical heterogeneity among SNPs. This suggests that researchers should concentrate primarily on IVW results.

2.5. Sensitivity analysis

The MR-Egger intercept method was used to assess horizontal pleiotropy. If the difference between this intercept and 0 is large, it indicates the existence of horizontal pleiotropy. Sensitivity analysis was conducted using leave-one-out analysis to estimate the robustness of the IVW results.[9]

2.6. Statistical methods

RStudio (4.3.2) was used to facilitate the analysis. The *TwoSampleMR* package (0.5.9) was used for the MR analysis. Funnel plots were used to examine the impact of individual SNPs on outcomes.

3. Results

3.1. Instrumental variables

After screening and harmonization, the numbers of SNPs were as follows: BMI = 432, BMI (female) = 131, BMI (male) = 124, flatfoot = 14, RA = 23, gout = 7, KOA = 13, HOA = 23, and EDS = 7.

3.2. Mendelian randomization analysis results

The BMI analysis results were statistically significant ($P < .05$) for all 4 methods except for MR-Egger regression, and the direction of the β-value is consistent for all 5. The P-values and β-values of the results of the 4 analyses, except for Simple mode, for BMI (male), suggest a positive causal relationship between BMI (male) and HV deformity. Flatfoot-IVW and WME results were all statistically significant ($P < .05$), whereas MR-Egger, simple mode, and median mode were not statistically significant. However, their β-values were in the same direction as IVW and WME. The Finngen Endpoint Browser suggests that flatfoot has a high sample overlap with HV (29% > 10%); therefore, the *F*-statistic for the 14 SNPs was calculated.[10] The *F*-statistics of all SNPs were > 10, with a mean value of 23.45, suggesting that the sample overlap rate had little effect on the analysis results.[11] The results of this analysis suggest a direct and positive causal association among acquired flatfoot, elevated BMI (male), and HV. The MR analysis results of 6 risk factors for HV, including BMI (female), RA, gout, EDS, KOA, and HOA, were not statistically significant (IVW_Pval > .05), suggesting no direct causal relationship between any of these 6 factors and HV (Figs. 1 and 2). Body weight and flatfoot do have a clinical correlation, and some studies have found that patients with flatfoot are more likely to develop HV deformity[2]; therefore, a 2-step mediated MR analysis[12] was performed with BMI as the exposure, flatfoot as the mediator, and HV as the outcome. The results showed that flatfoot did not play a mediating role in the casual relationship between the

Table 2

The SNP selection thresholds and *F*-statistics.

GWAS ID	Setting range of *P*	Setting for removing LD	*F*-statistics (average)	*F*-statistics (minimum)
ukb-b-19953 (21001_both sex)	$<5\times10^{-08}$	$r^2 = 0.001$, kb = 10,000	63.71	29.76
21001_irnt (female)	$<5\times10^{-08}$	$r^2 = 0.001$, kb = 10,000	49.92	29.77
21001_irnt (male)	$<5\times10^{-08}$	$r^2 = 0.001$, kb = 10,000	50.89	29.74
ebi-a-GCST90018910	$<5\times10^{-08}$	$r^2 = 0.001$, kb = 10,000	134.77	30.72
finn-b-M13_FLATFOOT	$<\times10^{-06}$	$r^2 = 0.01$, kb = 5000	23.45	21.24
finn-b-M13_GOUT	$<5\times10^{-08}$	$r^2 = 0.001$, kb = 10,000	88.70	30.99
finn-b-Q17_EHLER_SYNDR	$<5\times10^{-06}$	$r^2 = 0.01$, kb = 5000	22.29	20.84
ebi-a-GCST005813	$<5\times10^{-06}$	$r^2 = 0.01$, kb = 5000	22.24	15.16
ebi-a-GCST007091	$<5\times10^{-08}$	$r^2 = 0.001$, kb = 10,000	45.10	29.94

Abbreviations: GWAS = genome-wide association study, LD = linkage disequilibrium, SNP = single nucleotide polymorphism.

BMI and HV ($P < .05$). However, when analyzed using HV as a mediator, the mediated proportion was 13.33%, consistent with the view that HV is a pathological manifestation of arch collapse (Table 3).

3.3. Heterogeneity test

Cochran *Q* test results suggested heterogeneity in BMI-HV, BMI (female)-HV, BMI (male)-HV, flatfoot-HV, and HOA-HV, whereas the rest of the analyses showed no significant heterogeneity (Fig. 2). The random effects model (Random effect-IVW) in IVW analysis is commonly favored when the number of SNPs exceeds 3; therefore, this model exhibits a degree of tolerance towards heterogeneity and offers greater statistical power compared with MR-Egger regression and WME. Thus, emphasis is primarily placed on the outcomes derived from the IVW analysis.

3.4. Sensitivity analysis

The MR-Egger intercept method was used for 9 datasets. These results suggest that none of the studies reported significant levels of pleiotropy (Fig. 2). The MR analysis results were verified as reliable and robust. The leave-one-out analysis showed that when the SNPs for BMI, RA, EDS, BMI (male), BMI (female), Flatfoot, and Gout were excluded individually, the remaining SNPs were still located on the same side of the null line, and the odds ratio and its 95% CI did not change significantly. The results of the leave-one-out analysis of KOA and HOA showed that several SNPs crossed the null line (KOA: rs115336006, rs77639587, and rs10190094; HOA: rs80287694 and rs2396502). Therefore, SNPs with inconsistent directions were excluded. IVW analysis was performed again, which showed that the results after exclusion were consistent with those before, suggesting that the MR results were still robust (Fig. 3).

3.5. Funnel plots

The results of the funnel plot analysis showed that the distribution of SNPs for BMI-HV, BMI (female)-HV, BMI (male)-HV, flatfoot-HV, RA-HV, KOA-HV, HOA-HV, and EDS-HV were symmetrical, suggesting that inferred causality was relatively less affected by underlying factors when SNPs were used as IVs. Gout-HV did not have symmetry on the left and right sides of the funnel plot. However, the number of SNPs included in the study was too small; therefore, the results of the funnel plots had little reference value.

4. Discussion

Hallux valgus is a prevalent deformity affecting the forefoot. Conservative treatment may temporarily relieve patients' symptoms or slow the progression of the condition; however, it does not completely correct the deformity.[13–15] Therefore, surgical intervention offers notable advantages for addressing HV. Recent randomized controlled trial studies have demonstrated that surgery is more efficacious than conservative approaches in rectifying HV deformities and notably enhancing pain relief during ambulation.[16] Currently, over 200 surgical procedures[17] have been developed domestically and internationally to manage the various pathological alterations of HV. These procedures aim to restore normal foot function by removing the inflamed hallux bursa and proliferative osteophytes, correcting the increased intermetatarsal angle, reconstructing the function of the first metatarsophalangeal joint, and redistributing the load on the metatarsal head.[2] However, postoperative complications, including hallux rigidus, soft tissue pain, nonunion, and metatarsal shortening, can significantly affect patients' quality of life.[18,19] All categories of performed procedures, especially distal, shaft and proximal osteotomies of the first metatarsal (M1), exhibit elevated rates of deformity recurrence during postoperative follow-up, as documented in the existing literature.[20] This phenomenon significantly affects patient satisfaction with surgical outcomes.

4.1. Body mass index

A recent study showed that an above-normal BMI increases the risk of plantar pressure and foot pain.[21] Cho et al also found a strong relationship between high BMI and HV.[22] In contrast, Roddy et al and Abhishek et al did not find an obvious association between them. The results might have been affected by confounders such as race, lifestyle, and socioeconomic background.[23–25] In a study involving 3429 samples, the authors concluded there was an inverse relationship between BMI and HV.[26] However, given that HV is diagnosed using visual inspection instead of radiography, obesity might cause the incorrect estimation of HV. The research conducted by Golightly et al encountered a similar problem. A laminated foot diagram with 2 lines intersecting at 15° makes detecting false negative HV results difficult due to local fat thickening.[4] The MOBILIZE Boston study reported a sex difference in the correlation between BMI and HV. This supports the conclusion that BMI negatively correlates with the incidence of HV in females, whereas the opposite is true for males. This contrary inference may be associated with confounding factors such as shoe preferences.[27] The conclusion of our study supports the latter; that is, males with a higher BMI are more likely to suffer from HV deformities.

4.2. Flatfoot

Early research on the association between HV and flatfoot suggested that patients with high arches rarely suffer from HV, leading to the inference that patients with flatfoot may be more prone to developing HV deformity. Jung et al confirmed this viewpoint.[28,29] Blackwood et al believed that HV was a pathological manifestation of foot arch collapse. Except for the arch, posterior tibial tendon dysfunction, a prevalent pathology of flatfoot, seems to be associated with HV. The expansion of the posterior tibial tendon into the short flexor and oblique

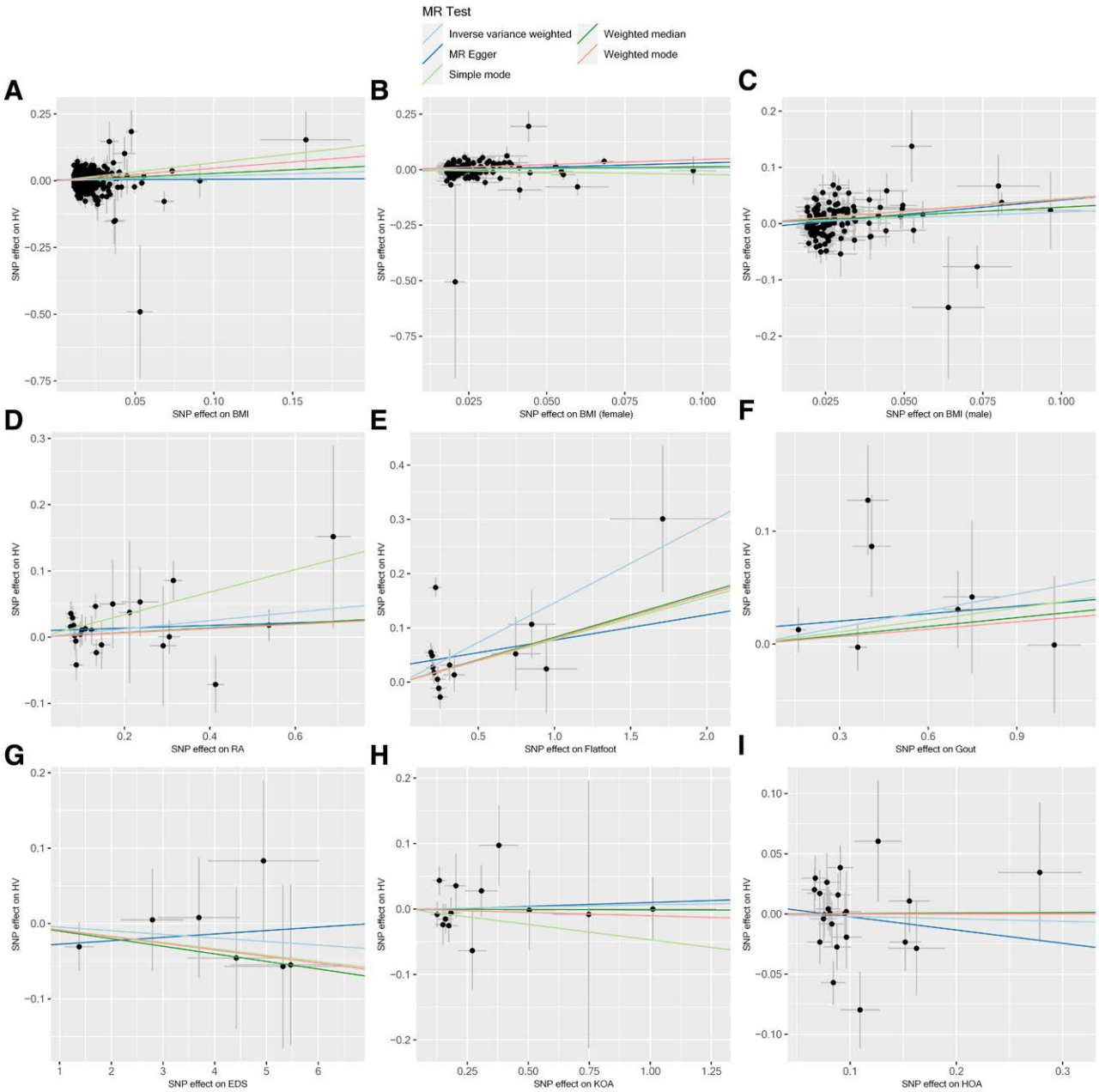

Figure 1. Scatter plots showing MR analysis of 9 endogenous risk factors and HV. (A) BMI-HV; (B) BMI (female)-HV; (C) BMI (male)-HV; (D) RA-HV; (E) Flatfoot-HV; (F) Gout-HV; (G) EDS-HV; (H) KOA-HV; (I) HOA-HV. BMI = body mass index, EDS = Ehlers–Danlos syndrome, HOA = hip osteoarthritis, HV = hallux valgus, KOA = knee osteoarthritis, MR = Mendelian randomization, RA = rheumatoid arthritis.

adductor of the big toe may be the mechanism underlying this link.[30] Similarly, some studies have indicated no apparent pertinence between them based on different statistical methods and evaluation indicators.[27]

4.3. Rheumatoid arthritis

As a symmetrical and inflammatory musculoskeletal disorder, RA may cause hindfoot instability through local inflammation and changes in the integrity of bones and ligaments, resulting in forefoot deformities such as HV, calluses, lesser toe deformities, and subluxation of the metatarsophalangeal joint.[31,32] Notably, several recent studies have determined the relationship between RA and HV; however, most were observational and had weak controls for confounding factors. The negative results of our study suggest that HV pathogenesis due to RA is multifactorial. Other diseases may induce the correlation between RA and HV, as some studies have found that patients with RA are more likely to develop flatfoot with age,[32,33] and flatfoot is a direct risk factor for HV, as clearly indicated in our study.

4.4. Gout

The first metatarsophalangeal joint is the region most affected by monosodium urate.[34] Chronic and long-term gouty tophi deposition erodes bones, resulting in joint injury and deformity.[35] A case-control study that contained 164 cases found that HV may be more likely to occur in patients with gout,[36] but another study that included 1184 patients concluded that there was no statistically significant difference in the prevalence of HV between patients with gout and the general population.[37] Both studies collected sample data using questionnaires,

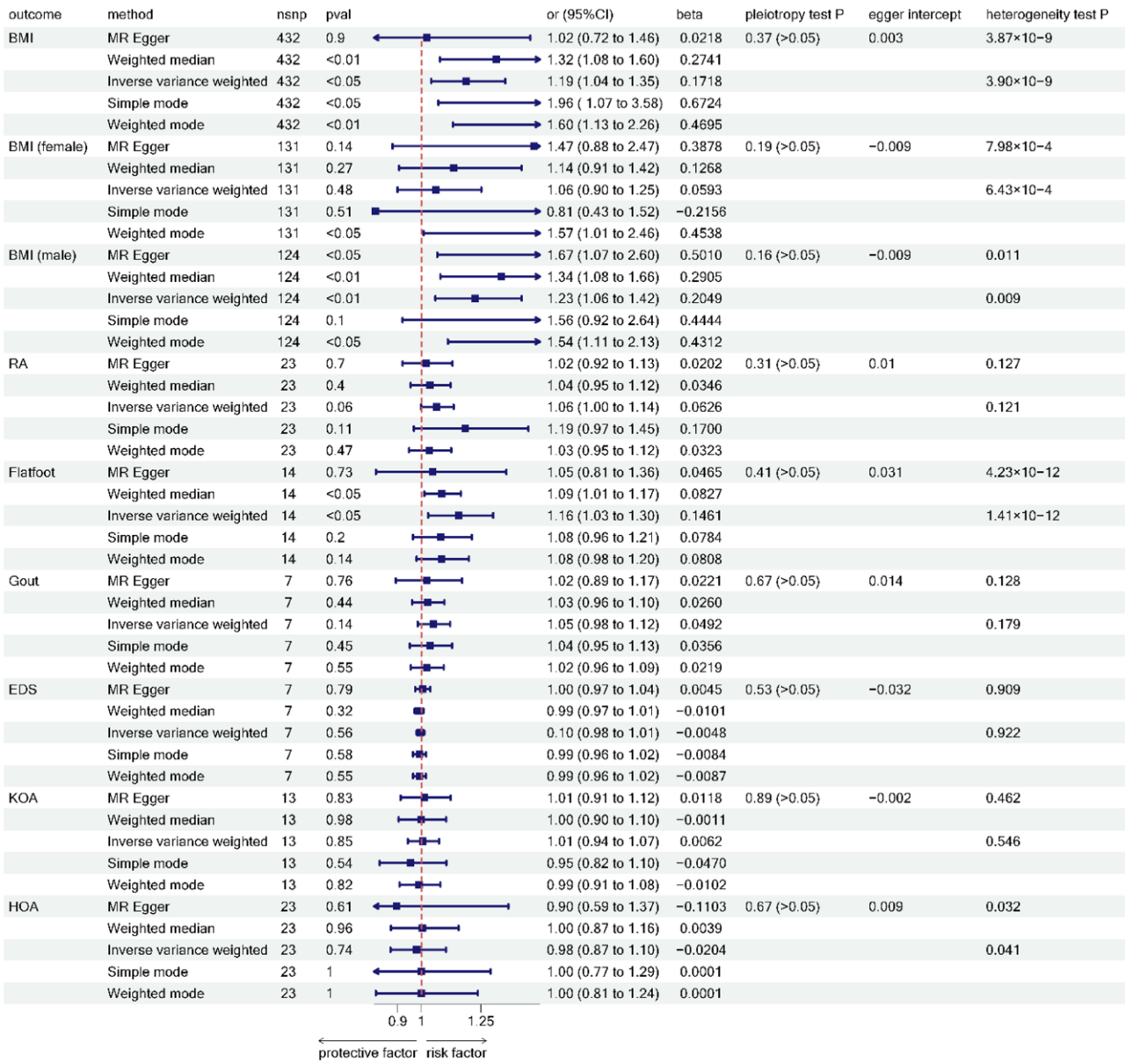

Figure 2. Forest plots showing MR analysis of HV and 9 endogenous risk factors. BMI = body mass index, CI = confidence interval, EDS = Ehlers–Danlos syndrome, HOA = hip osteoarthritis, HV = hallux valgus, KOA = knee osteoarthritis, MR = Mendelian randomization, RA = rheumatoid arthritis.

Table 3

The mediation effect of hallux valgus between body mass index and flatfoot.

	Total effect	Direct effect A	Direct effect B	Mediation effect		Mediated proportion (95% CI)
Mediator	β	β	β	β (95% CI)	*P*	
HV	0.6	0.2	0.4	0.08 (0.02–0.14)	.01	0.13 (0.03–0.24)

Abbreviation: HV = hallux valgus.

which may have introduced subjective biases into the methodology. HV diagnosis in both studies was based on patient self-reporting. The latter study used a line-drawing instrument to validate HV, whereas the diagnostic criteria of the former study were not clearly stated. An observational study involving only 87 participants, using objective grouping based on the levels of uric acid in the blood, concluded that patients with gout are more likely to have severe HV.[38] Therefore, based on our study's MR analysis, we believe there is a specific correlation between gout and HV, but no direct causal relationship exists between them.

4.5. Knee osteoarthritis and hip osteoarthritis

Osteoarthritis is a chronic disease characterized by degeneration and loss of joint cartilage and bone tissue regeneration at the joint's edge and beneath the cartilage.[1] Notably, multiple studies have indicated a statistically significant correlation among HV, KOA, and HOA.[4,24,25] This correlation seems to be bidirectional, where the HV may develop the progression of OA by altering the joint load and torque.[39] However, our study did not find evidence to support the conclusion that KOA and HOA have direct causal associations with HV, suggesting that both, along with other factors, collectively contribute to the occurrence of HV.[40,41] Moreover, inflammation in the metatarsophalangeal joint is more closely associated with HV; however, further research is required to confirm this correlation owing to the lack of corresponding GWAS.

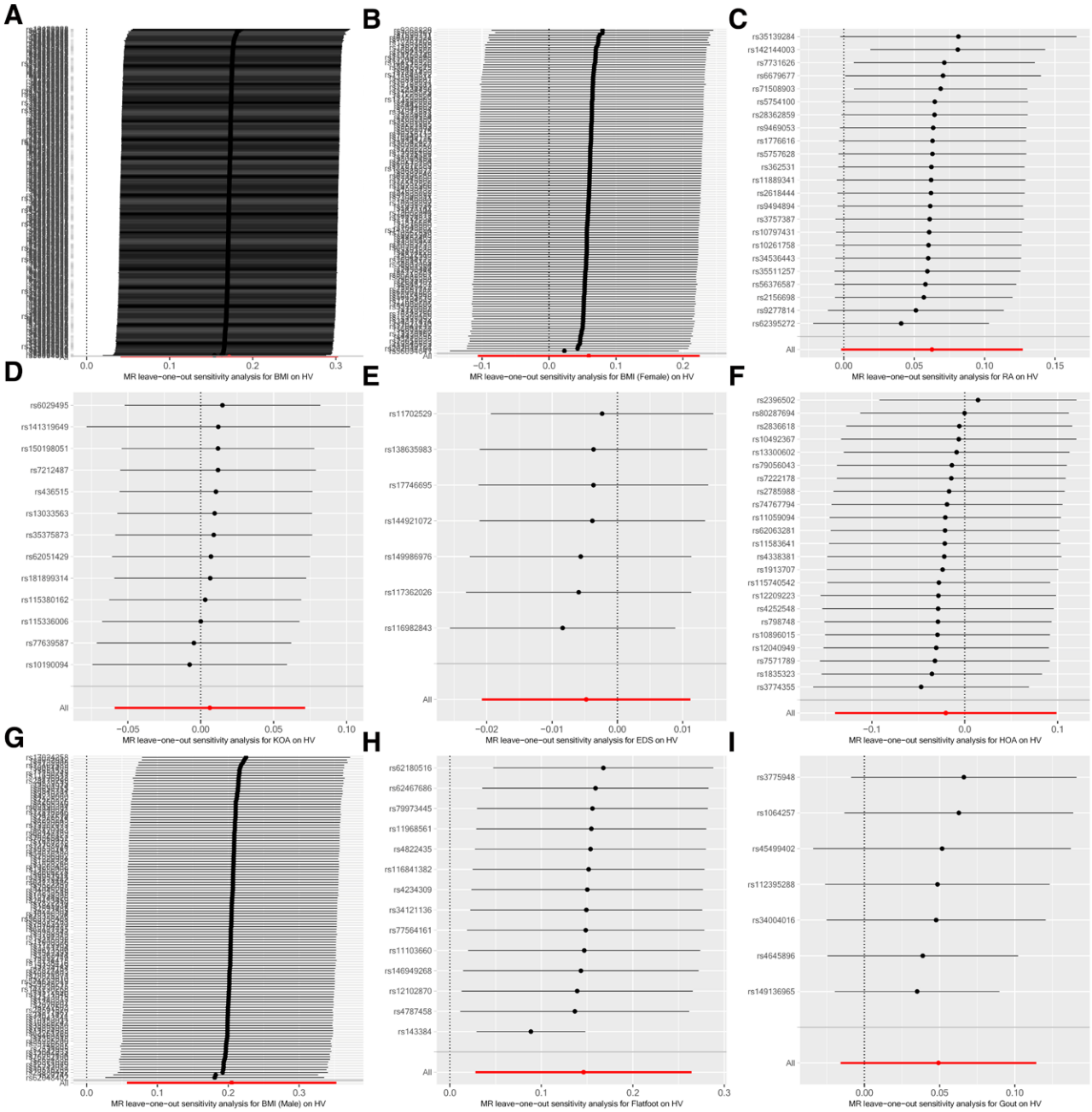

Figure 3. Leave-one-out analysis showing the robustness of our results. (A) BMI-HV; (B) BMI (female)-HV; (C) RA-HV; (D) KOA-HV; (E) EDS-HV; (F) HOA-HV; (G) BMI (male)-HV; (H) Flatfoot-HV; and (I) Gout-HV. BMI = body mass index, EDS = Ehlers–Danlos syndrome, HOA = hip osteoarthritis, HV = hallux valgus, KOA = knee osteoarthritis, MR = Mendelian randomization, RA = rheumatoid arthritis.

4.6. Ehlers–Danlos syndrome

Ehlers–Danlos syndrome, as a heterogeneous group of heritable connective tissue disorders, is characterized by atrophic scars, generalized tissue fragility, excessive skin elasticity, and joint hypermobility.[42,43] The mechanism that leads to HV deformity may be overactive joint movement and local ligament laxity, resulting in changes in the foot's biomechanical structure.[2] In the EDS classification formulated by the International Consortium on EDS in 2017, HV was only considered a minor criterion for cardiac valvular EDS, Classical-Like EDS, and brittle cornea syndrome, which means its diagnostic specificity is relatively low.[44,45] However, this study's conclusions did not support a direct causal relationship between the 2. Therefore, further evidence is required to support the association between EDS and HV.

Based on this background, we can clearly identify the intrinsic risk factors that have a direct causal relationship with HV and take targeted measures that can effectively avert the occurrence and development of this deformity. As mentioned earlier, previous studies on the etiology of HV have not been clear owing to the influence of confounding factors and research methods. MR, as a causal inference method based on genetic variation, can more effectively evaluate causal relationships owing to the random allocation of individual genetic variations and the natural control of confounding factors, that is, as a quasi-RCT.[46–48]

This study has some limitations. First, most of the data sample population came from Europe; therefore, extrapolating to other populations still requires reference to local lifestyle and dietary habits. Second, due to the limitations

of GWAS, not all endogenous pathogenic factors associated with HV can be validated, such as sesamoid displacement and metatarsophalangeal arthritis, which require further research in the future.

In conclusion, BMI in males and acquired flatfoot are endogenous risk factors for HV. Furthermore, HV plays a mediated role in the casual association between the BMI and flatfoot. BMI in females, gout, RA, KOA, HOA, and EDS have no direct causal association with HV. Therefore, controlling BMI, reducing plantar pressure, preventing arch collapse, and avoiding the occurrence of acquired flatfoot are recommended ways of preventing HV deformities.

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