Sports Medicine and Health Science 7 (2025) 214–223

Contents lists available at ScienceDirect

Sports Medicine and Health Science

journal homepage: www.keaipublishing.com/smhs

Original Article

Future risk of falls induced by ankle-foot sprains history: An observational and mendelian randomization study

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ARTICLE INFO

Keywords:
Leg injuries
Accidental falls
Postural balance
Mendelian randomization analysis
UK biobank
FinnGen

ABSTRACT

Background: Ankle-foot sprains are the most common musculoskeletal injuries, which can impair balance and theoretically increase the risk of falls, but still, there is a lack of evidence supporting the direct association between ankle-foot sprains and the future risk of falls.
Methods: UK Biobank cohort was utilized to measure the association between ankle-foot sprains and fall risk with covariates adjusted. Then, the two-sample Mendelian randomization (MR) analysis was applied based on the genetically predicated ankle-foot sprains from FinnGen to validate causal relationship. Finally, genetically predicated cerebellar neuroimaging features were used to explore the mediating role of maladaptive neuroplasticity between ankle-foot sprains and falls by two-step MR analyses.
Results: Patients with ankle-foot sprains history exhibited a slightly increased risk of falls than the matched controls before and after adjustment for covariates (odd ratio [*OR*] ranged from 1.632 to 1.658). Two-sample MR analysis showed that ankle-foot sprains led to a higher risk of falls ($OR = 1.036$) and a lower fractional anisotropy of superior cerebellar peduncle (SCP) (left, $\beta = -0.052$; right, $\beta = -0.053$). A trend of mediating effect was observed for the fractional anisotropy of right SCP in the causal effects of ankle-foot sprains on falls ($\beta = 0.003$).
Conclusion: The history of ankle-foot sprains is associated with a slightly increased risk of falls. These findings improve our understanding of the clinical consequences of ankle-foot sprains in terms of fall risk and suggest the importance of adopting more efficient strategies for managing residual functional deficits after the injuries.

1. Introduction

The ankle-foot complex is the only part of the human body that touches the ground in the upright position, and our balance relies on the function of the ankle and foot.[1] Unfortunately, ankle-foot sprains are the most prevalent musculoskeletal injuries, constituting 7 per 1 000 person-years of emergency department visits.[2,3] Although often discharged as relatively innocuous injuries, about 1 out of 3 individuals fail to fully recover from the first-time sprain and develop chronic instability of ankle-foot complex, suffering from prolonged balance deficits.[2–4] Till now, numerous therapeutic strategies, such as external supports, sports rehabilitation, and even surgical reconstruction of ruptured ligaments, have been adopted for both acute and chronic sprains, but the clinical outcomes were still far from satisfying.[5,6] Additionally, as an injury that mostly occurs in youth, residual balance deficits can also influence middle-aged and older individuals, indicating a lifelong health burden after the sprains.[7,8]

Falls are the second leading cause of unintentional injury-related death worldwide, with an annual prevalence of about 9% and 28% among middle-aged and older individuals, respectively.[9–11] Numerous environmental and physiological risk factors, particularly balance deficit,

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https://doi.org/10.1016/j.smhs.2024.05.002
Received 7 July 2023; Received in revised form 6 May 2024; Accepted 17 May 2024
Available online 21 May 2024

Abbreviations

CI	confidence interval
FA	fractional anisotropy
GWAS	genome-wide association study
ICD-10	International Classification of Diseases, Tenth Revision
ICP	inferior cerebellar peduncle
IVs	instrumental variables
IVW	inverse-variance weighted
MCP	middle cerebellar peduncle
MR	Mendelian randomization
OD	orientation dispersion
OR	odd ratios
PSM	propensity-score matching
SCP	superior cerebellar peduncle
SNP	single nucleotide polymorphism

can result in falls.[12,13] With the recent boom in the sport's popularity, the ankle-foot injury, especially its subsequent residual balance deficits, also received much attention.[12,14,15] The proprioceptive sense from the ankle-foot complex can be disrupted by swelling, inflammation, and mechanoreceptor blockade after the sprain, and then, the disrupted balance control system can cause functional instability.[12,16] Furthermore, the most recent neuroimaging evidence suggested that prolonged lack of proprioception of ankle-foot after injury may lead to maladaptive neuroplasticity in the cerebellum.[17–19] However, the relationship between falls and ankle-foot injuries has primarily been inferred from small, cross-sectional studies with limited sample sizes.[20] As a result, the direct relationship between ankle-foot sprains and falls remains an unaddressed research gap, restricting our understanding of the clinical consequences of ankle-foot sprains.

Assessing the direct relationship between ankle-foot sprains and falls needs large-sized studies with comprehensive measurements that consider various factors contributing to falls. Such studies need high cost and long duration that can hardly be afforded by single-center studies.[21,22] Large-scale open databases can help fill this knowledge gap and explore the potential links between sprain history and fall with increased statistical power. For example, the large population-based UK Biobank with approximately a half-million adult participants, their detailed demographic characteristics, and disease records can be used to assess the association between an ankle-foot sprain and risk of falls.[23] In addition, the recent development of Mendelian randomization (MR) based on genome-wide association study (GWAS) can be employed to strengthen the causal relationship. It randomly allocates single nucleotide polymorphisms (SNPs) as instrumental variables (IVs) for the exposure of interest, reducing the risk of confounding and reverse causation.[24] Among the open GWAS data, the FinnGen Database that provided the integrated genetic association of recorded diseases can be used to predict ankle-foot sprains and establish the causal association between ankle-foot sprains and falls.[25,26] The integration of these approaches can help overcome the limitations of traditional studies on fall-related balance deficits in ankle-foot sprains, filling the gap in understanding the direct relationship between ankle-foot sprains and falls.

Thus, this study aimed to (1) assess the association between the history of ankle-foot sprains and risk of falls through an observational cohort; (2) validate the causal effect of ankle-foot sprains on falls through two-sample MR analysis; (3) explore the potential pathways among previously demonstrated balance-related maladaptive neuroplasticity pathways in the cerebellum mediating the higher risk of falls after ankle-foot sprains. We hypothesized that the history of ankle-foot sprains increases the risk of falls, and maladaptive cerebellar features are the potential mediators of this effect.

2. Material and methods

2.1. Overall study design

The design of this study is shown in Fig. 1, incorporating retrospective cohorts and MR analyses. All analyses were performed on publicly available individual-level data and summary-level GWAS statistics from the UK biobank and FinnGen database. Ethics approval was obtained from the North West Multi-centre Research Ethics Committee and the Steering and Scientific Committee of the University of Helsinki; participants' informed consent was provided in these open databases.[23,25] This study followed the guideline of the Strengthening the Reporting of Observational Studies in Epidemiology for both observational study and MR study.[24,27]

2.2. Data sources and samples

2.2.1. Individual-level data for observational cohort

The individual-level data were extracted from the UK Biobank (Application No. 62721). The baseline data at the initial recruitment were used in this study. Exposure was defined as a binary variable by the medical records of the International Classification of Diseases, Tenth Revision (ICD-10), and individuals with ankle-foot sprains at least one year before the recruitment were included as patients, and others were classified as healthy controls. Wrist-hand sprains (the corresponding injuries in upper limbs) were used for the sensitivity analysis to demonstrate that the higher risk of falls was caused by ankle-foot sprains, instead of just joint sprains. The outcome was also defined according to the following question during the baseline investigation "*Have you had any falls during the last year?*", and the participants were then classified as "fallers" and "non-fallers". A list of covariates, including basic demographic factors (i.e., age, sex, BMI, and ethnicity), lifestyle factors (i.e., smoking status, alcohol consumption, and physical activity), and socioeconomic factors (i.e., education and Townsend deprivation index), were adjusted. Full descriptions of exposure, outcome, and covariates are presented in Supplementary appendix A. The diagram of cohort design is provided in Supplementary appendix B.

Participants with complete data on falls and covariates were included in this study. The exclusion criteria were as follows: (1) selecting "prefer not to answer" about the falls; (2) having diseases that might interfere with the effect of ankle-foot injuries on falls (e.g., Alzheimer's disease, disorders of vestibular function, transport accident); (3) To avoid the mixture of exposure and outcome, patients having ankle-foot sprains or wrist-hand sprains during "the last year" before the investigation were also excluded. The inclusion criterion was the presence of ankle-foot sprains or wrist-hand sprains such as dislocation, recurrent injury, and ligament instability. The ICD-10 codes as criteria for exclusion and inclusion were determined by three experienced researchers on orthopedics, kinesiology, and neurosciences (Supplementary Appendix C).

2.2.2. Summary-level GWAS statistics for MR

The ankle-foot sprain-related SNPs were obtained from the GWAS data of the FinnGen database.[25] Ankle-foot sprains were defined as the binary variable collected from hospital discharge records of ICD-10 diagnostic code: participants with S93 (Dislocation, sprain, and strain of joints and ligaments at ankle and foot level) as cases ($n = 7\ 223$), and participants without S90–S99 (Injuries to the ankle and foot) as controls ($n = 245\ 598$). The average age in the first ankle sprain event was 39.71 years old. The wrist-hand-related SNPs were similarly extracted to replicate the sensitivity analysis in part 1. Fall-related statistics were referred to the latest GWAS of *Trajanoska* et al. in 2021 which was built by the recalled baseline fall histories of the UK biobank. Participants were classified as "fallers" ($n = 89\ 076$) and "non-fallers" ($n = 362\ 103$).[28]

Previous studies suggested that dysfunction of the cerebellum might be associated with a higher risk of falls, and patients with ankle-foot

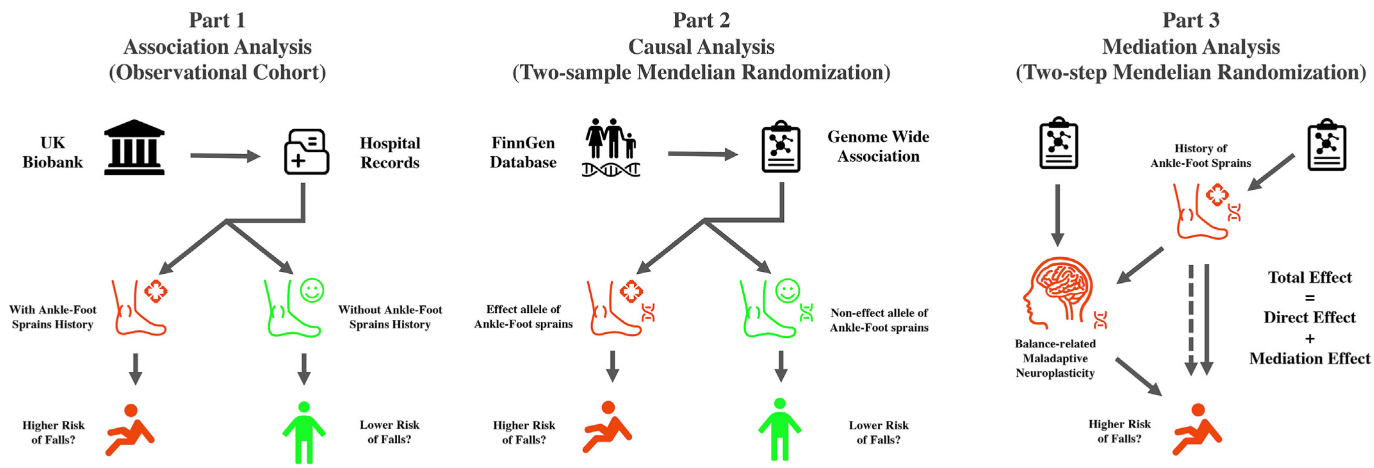

Fig. 1. Analytical workflow of the study. First, we integrated hospital records data derived from UK Biobank to compare the risk of falls between participants with and without ankle-foot sprains. Second, we replicated the causal effect of genetically predicted ankle-foot sprains obtained from the FinnGen database on falls. Finally, we explored the potential mediating role of balance-related maladaptive neuroplasticity in the causal effect of ankle-foot sprains on falls.

sprain may have maladaptive neuroplasticity of cerebellar pathways.[28] Therefore, the GWAS data of cerebellar peduncles were obtained from the latest GWAS on neuroimaging to reduce the risk of bias. This included the sub-cohort of the UK Biobank (n = 31 356, average age 64.3 years) that minimized overlap with both FinnGen and the whole cohort of UK Biobank (<10%).[29–31] The extracted neuroimaging features were set as continuous variables. According to previous observational studies, the fractional anisotropy (FA) values of the superior cerebellar peduncle (SCP) and inferior cerebellar peduncle (ICP), and the orientation dispersion (OD) values of ICP were set as the primary outcomes, while the effects of ankle-foot sprains on other outcomes of the ICP, SCP, and middle cerebellar peduncle (MCP) were set as the secondary outcomes.[18,19] The details of the imaging are presented in Supplementary Appendix D.

The genetic instruments were selected according to the three-core instrumental variable assumptions of MR: (1) relevance, the IVs are strongly associated with the exposure; (2) independence, the IVs are not associated with any potential confounder of the exposure-outcome association; (3) exclusion restriction, the IVs do not affect outcome independently of exposure (Supplementary Appendix E/F). Regarding the relevance assumptions, the genome-wide significance threshold was set to $p < (5 \times 10^{-6})$ for sprains-related SNPs and $< (5 \times 10^{-6})$ for cerebellum-related SNPs.[32] A strict linkage disequilibrium clumping cut-off of $R^2 < 0.001$ and a window of 10 000 kb was performed using the European reference panel to obtain independent SNPs.[33] To minimize weak instrumental bias, F-statistics were calculated to assess the strength of individual SNP, and a value of more than 10 was deemed sufficient.[34] Regarding the independence assumption, each selected SNP was investigated in the PhenoScanner database (www.phenoscanner.medschl.cam.ac.uk) to assess any previous associations ($p < [1 \times 10^{-5}]$) with plausible confounders (i.e. fatal illness, vital signs, and the aforementioned excluded diseases in the observational cohort).[35] Regarding the exclusion restriction assumption, outcome-related SNPs with a threshold of 1×10^{-5} were removed, and the Mendelian randomization pleiotropy residual sum and outlier tests were applied to identify the underlying horizontal pleiotropic outliers.[36] Finally, the utilized SNPs were harmonized to the same effect alleles and the palindromic or missed SNPs were removed. For two-step MR analysis, the cerebellum-related SNPs that were duplicated with the ankle/fall sprain-related SNPs were removed to avoid overlapped SNPs in MR-based mediation analysis.[37]

2.3. Statistical analysis

All analyses were conducted using R, version 4.2.2 (R Foundation). Continuous variables are described as means (standard deviations[SD]) and binary/categorical variables are presented as numbers (percentages). Our hypothesis was that ankle-foot sprains lead to a higher risk of falls via balance-related maladaptive neuroplasticity (instead of preventing falls); therefore, we performed one-tailed analyses and evaluated the β values with 90% confidence intervals (CI) for all of the estimates. A p-value of less than 0.05 was considered significant, while a p-value of between 0.05 and 0.1 was considered marginally significant.

2.3.1. Observational analyses

To reduce the effect of confounders caused by different numbers of patients and uninjured controls, propensity-score matching (PSM) with the nearest neighbors method was used to identify uninjured controls with the most similar covariates in a 1:4 ratio. Two-tailed chi-square tests, and independent two-sample t-tests were used to measure the covariate balance between the cohorts before and after matching. Logistic regression models were adopted to evaluate the relationship between joint sprains and the risk of falls (measured by odd ratio [OR]). First, we implemented a univariable regression as model 0 to estimate the relationship between the history of ankle-foot sprains (exposure) and the risk of falls, without controlling for potential confounders. Then, three models of multivariable regression were used to adjust confounders. Model 1 was adjusted for basic demographic information, including age, sex, BMI, and ethnicity. In addition to confounders in model 1, model 2 was further adjusted for lifestyle factors, including alcohol consumption, smoking status, and summed minutes of activity. Model 3 was further adjusted for socioeconomic factors, including education score and Townsend deprivation index. Sensitivity analyses were conducted for the effect of wrist-hand sprains on falls, and the regressions were also replicated in the full cohort.

2.3.2. Two-sample MR analyses

The random-effects inverse-variance weighted (IVW) method was used as the primary approach for assessing the causal effect (i.e. "exposure-on-outcome" effects) of ankle-foot sprains (primary analysis) and wrist-hand sprains (sensitivity analysis) on falls. We considered that the aforementioned core IVs assumptions were not violated, and all IVs were valid.[32] Furthermore, MR-Egger and weighted median methods were applied, assuming that all IVs were invalid or at least half of the IVs were valid, respectively.[38,39] The conclusion should be interpreted with caution if the direction (i.e., positive or passive effect) of the results from these 3 methods were inconsistent. Cochran's Q statistic was used to evaluate the heterogeneity caused by different SNPs in the fixed-effect variance-weighted analysis, with $p \leq 0.05$ indicating the presence of heterogeneity. Then, MR-Egger regression was used to explore the presence of horizontal pleiotropy, with $p \le 0.05$ considered to provide evidence for directional pleiotropic bias.[40]

2.3.3. Two-step MR mediation analyses

Since both our exposure and outcome were binary variables, the 2-step MR was supposed to produce a less-biased mediating effect compared with other methods.[37] Two-sample MR analyses were also performed to measure the causal effect of ankle-foot sprains on cerebellar features (Step 1, exposure on mediator), and the causal effect of cerebellar features on falls (Step 2, mediator on outcome). Notably, since the left-side and right-side neuroimaging features were provided separately, only features that were significantly associated with ankle-foot sprains on both sides in Step 1, were used in Step 2. The beta values and the corresponding standard errors calculated by the IVW method were used to estimate the indirect effect of ankle-foot sprains on the risk of falls through maladaptive neuroplasticity in the cerebellum. Sobel test was used to quantitatively calculate the mediating effect and its confidence intervals.

3. Results

3.1. Observational cohort

Of 314 932 participants with complete data on falls and covariates, 560 participants who reported "prefer not to answer" questions about the falls, and 38 762 participants who had the confounding diseases before recruitment were excluded. For the primary analyses, 11 participants with ankle-foot sprains during the last year before the recruitment were excluded. We identified 98 patients (duration [5.53 ± 2.95] years) and 392 matched controls, with 25 (25.5%) and 68 (17.3%) participants classified as fallers, respectively. For the sensitivity of upper limb injury, 16 participants were excluded. We identified 136 patients (duration [6.00 ± 3.12] years) with 544 matched controls, with 23 (16.9%) and 111 (20.4%) participants classified as fallers, respectively (Fig. 2). Before matching, patients with ankle-foot sprains ([53.99 ± 8.69] years old, 66.3% males) were slightly younger and more likely male than control subjects ([55.98 ± 8.13] years old, 53.7% males). After matching, all baseline covariates were comparable ([53.92 ± 8.59] years old, 66.3% males in the control group). Baseline characteristics for the two cohorts are shown in Supplementary Appendix G.

Fig. 3 depicts the association between the history of joint sprains and the risk of falls. Ankle-foot sprains slightly increased the risk of falls before and after adjusting for covariates (*OR* ranged from 1.632 to 1.658, *p* value ranged from 0.032 to 0.037), while wrist-hand sprains did not significantly alter the risk of falls (*OR* ranged from 0.775 to 0.794, *p* value ranged from 0.161 to 0.181). By replicating the analyses in the whole cohort, only the univariable regression indicated a slightly increased risk of falls in patients with ankle-foot sprains (*OR* = 1.528, 90% *CI*: 1.030 to 2.214, $p = 0.034$), and the effect became marginally significant after adjustment for covariates (*OR* ranged from 1.441 to 1.458, *p* value ranged from 0.054 to 0.060). Full results of the regression models are presented in Supplementary Appendix H.

3.2. Two sample MR from ankle-foot sprains to falls

According to the core IV assumptions, we identified 106 SNPs associated with ankle-foot sprains, among which 92 SNPs were removed due to linkage disequilibrium. In addition, 1 palindromic SNP (rs6734538) and 1 SNP with incompatible alleles (rs11160728) were removed. After reviewing by PhenoScanner, 2 SNPs were removed due to genetic associations with fatal illnesses in previous GWAS. Ultimately, 8 SNPs were selected as potential genetic susceptibility factors involved in the relationship between ankle-foot sprains and the risk of falls. No fall-related SNPs were detected. The F values of the included SNPs ranged from 813 to 1 060, indicating the absence of weak instrument bias.

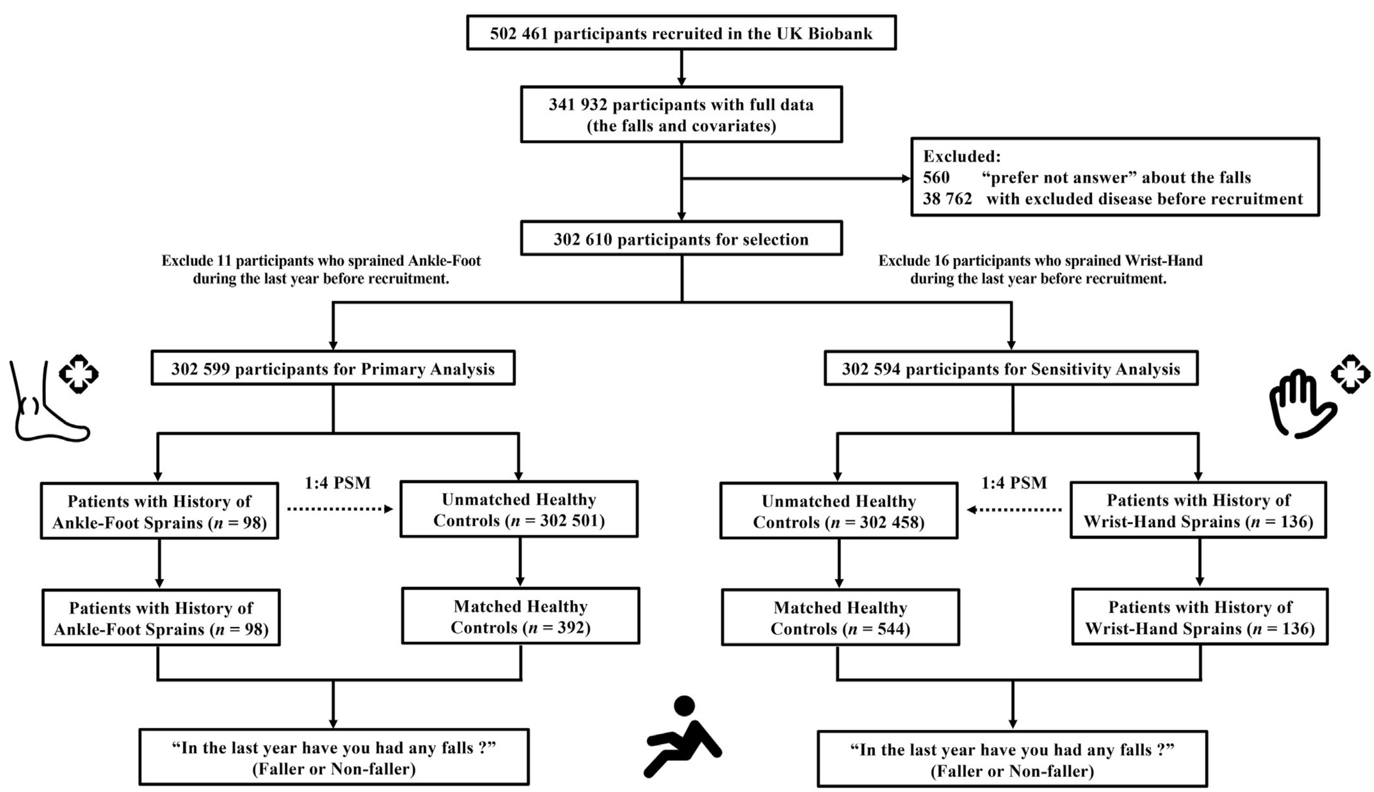

Fig. 2. Flow chart of participant selection process and study design for the observational cohort in UK Biobank. Patients with a history of ankle-foot sprains and matched controls were included in the primary analysis. Wrist-hand was considered as the counterpart of ankle-foot in the upper limbs in the sensitivity analysis. PSM, Propensity Score Matching.

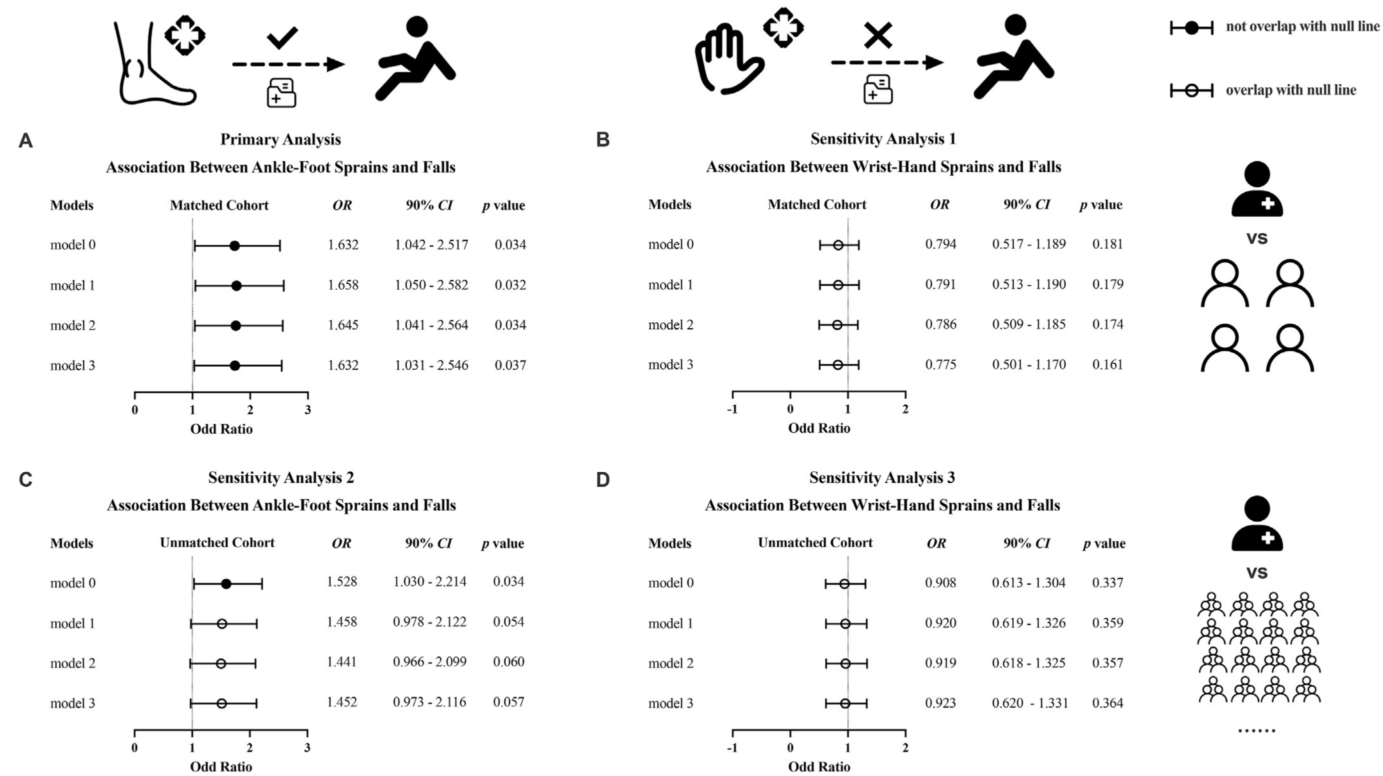

Fig. 3. Forest plots of the logistic regression models for the association between history of ankle-foot or wrist-hand sprains and risk of falls in matched (A, B) or unmatched cohorts (C, D). Model 0, without adjusting for potential confounders: Model 1 adjusted for demographic characteristics, including age, sex, BMI, and ethnicity; Model 2 further adjusted for lifestyle factors, including alcohol consumption, smoking status, and summed minutes activity; Model 3 additionally adjusted for socioeconomic factors, including education score and Townsend deprivation index. *CI*, confidence interval; *OR*, odd ratio.

The IVW revealed the causal effect of ankle-foot sprains on falls ($OR = 1.036$, 90% $CI = 1.008$, 1.065, $p = 0.017$). The MR egger and WM methods consistently indicated the slightly increased risk of falls in ankle-foot injured patients. For sensitivity analysis, 10 SNPs were obtained for genetically predicted wrist-hand sprains, and the result showed no significant effect of wrist-hand injuries on the risk of falls ($OR = 1.020$, 90% $CI = 0.987$, 1.054, $p = 0.162$). No horizontal pleiotropic outliers, significant pleiotropy or heterogeneity was observed in MR analyses (Fig. 4). Detailed information on SNPs for genetically predicted ankle-foot and wrist-hand sprains and their causal effect on falls are provided in Supplementary Appendix I.

3.3. Two-step MR for detecting the mediator

The same IVs of the genetically predicted ankle-foot sprains were used to estimate the causal effect of ankle-foot sprains on cerebellar features. Among the primarily analyzed outcomes, only the lower FA of SCP had a causal relationship with ankle-foot sprains consistently on both sides of the cerebellum (left, $\beta = -0.052$, 90% $CI = -0.102$, -0.002, $p = 0.041$; right, $\beta = -0.053$, 90% $CI = -0.103$, -0.003, $p = 0.040$). As supplementary analyses, only the higher Lambda 2 values of bilateral SCP exhibited a significant association with ankle-foot sprains (Fig. 5). Detailed information on SNPs related to ankle-foot strains and their causal effects on neuroimaging features of the cerebellum are provided in Supplementary Appendix J.

After removing 9 SNPs with genetic associations with fatal illnesses, alcohol assumption, pulse rate, and diabetes, 22 and 19 SNPs were selected to predict the FA of left and right SCP, respectively. No fall-related SNPs were detected, and the F values of the included SNPs ranged from 24 to 31, indicating a low risk of bias due to weak instrument. According to the IVW methods, the FA of the right SCP significantly increased the risk of falls ($OR = 0.953$, 90% CI: 0.916 to 0.992, $p = 0.025$), while no association was observed for the left side ($OR = 1.020$, 90% CI: 0.982 to 1.050, $p = 0.217$). No horizontal pleiotropic outliers, significant pleiotropy or heterogeneity was observed in MR analyses. Detailed information on SNPs for genetically predicted FA of SCP and their causal effects on falls are provided in Supplementary Table 31-35. Regarding the results of the Sobel test, only the FA of right side SCP marginally mediated the causal effects of ankle-foot sprains on falls (β-mediator $= 0.003$, 90% $CI = -0.001$, 0.006, $p = 0.096$) (Fig. 6).

4. Discussion

Observational and MR-based causal evidence both indicated that a history of ankle-foot sprains increased the risk of falls. Furthermore, maladaptive neuroplasticity in SCP caused by ankle-foot sprains may partly mediate the increased risk of falls. To the best of our knowledge, this study is the first one providing direct evidence of the higher risk of falls in ankle-foot sprains. The authors hope these findings could deepen our understanding of the clinical consequence of ankle-foot sprains in terms of fall risk and suggest the need to establish more efficient strategies for the management of residual balance deficits after ankle-foot sprains.

4.1. Risk of falls caused by ankle-foot sprains

Falling occurs due to intrinsic, behavioral, or environmental factors.[13] Considering the key role of the ankle-foot complex in maintaining upright balance and preventing falls, particular attention should be paid to ankle-foot sprains.[1] Several age-related ankle-foot problems (e.g. toe bunion, nail deformity, and foot ulcer) were proven to be associated with falls, while regular examination and improved nursing care properly improved them.[14,41] Nevertheless, the prevalence of sport-related ankle-foot injuries increased alongside the popularity of sports, and the

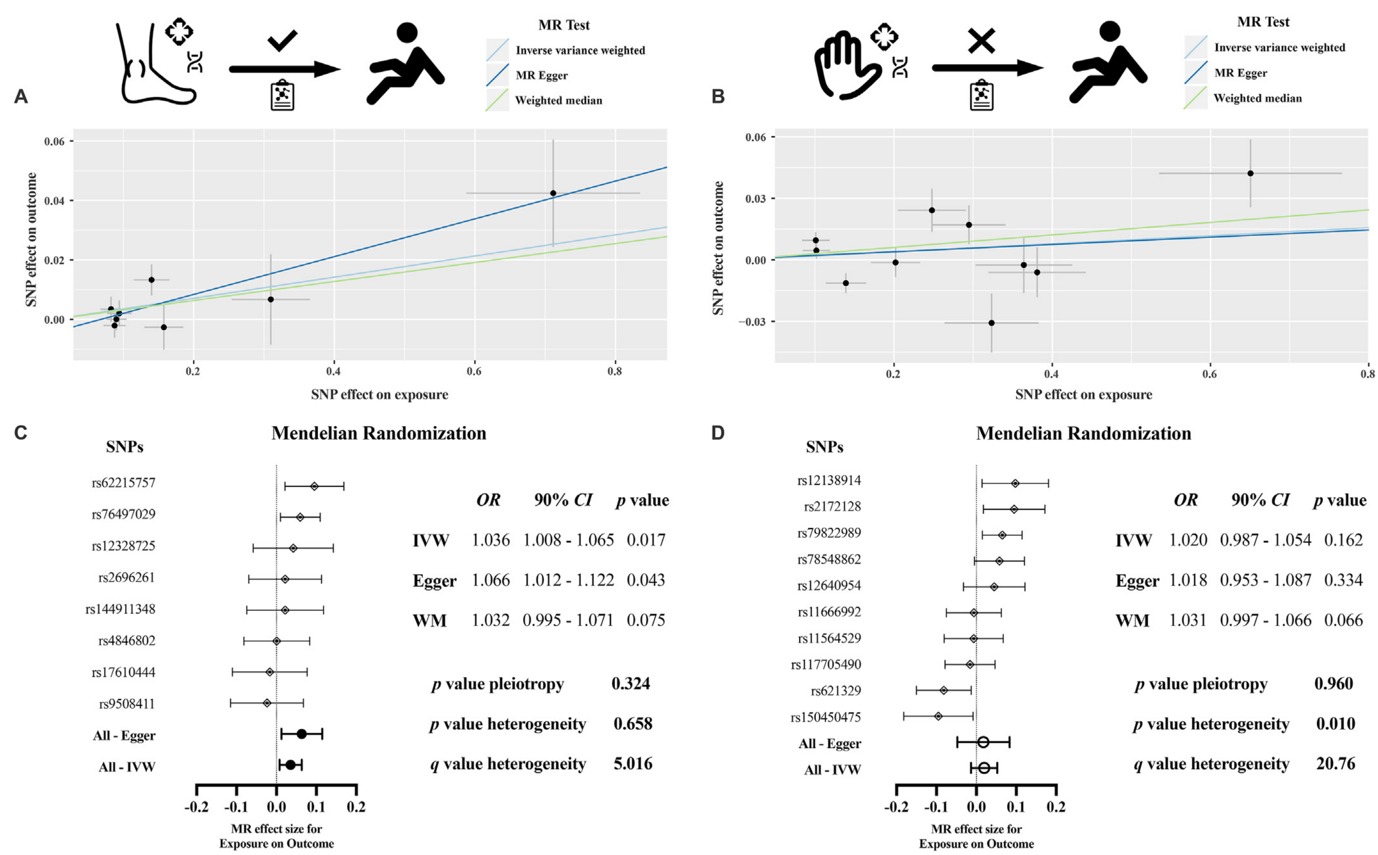

Fig. 4. MR analysis of the causal effect of ankle-foot or wrist-hand sprains on falls with 90% *CI*. Scatter plots depict the “SNP-ankle-foot sprains effect” (A), “SNP-wrist-hand sprains effect” (B), and the “SNP-fall effect”. Forest plots depict the causal effect of single SNPs and the pooled causal effect size of ankle-foot sprains (C) and wrist-hand sprains (D) on the risk of falls. *CI*, confidence interval; IVW, inverse variance weighted; MR, mendelian randomization; *OR*, odd ratio; SNPs, single nucleotide polymorphisms; WM, weighted median.

management of residual balance deficits is still troublesome.[42,43] Residual balance deficits were mostly investigated through cross-sectional functional performance and short-term reinjury rates, and the long-term effect of balance deficits on future falls was mainly speculative.[8,44] Although the association between ankle sprains and falls is not particularly novel given the growing evidence on the consequences of ankle-foot sprains, we used population-based data to establish a direct link between ankle-foot sprains and falls, contributing to the literature and underscoring the importance of addressing residual balance deficits after sprains.

In this study, we explored the association between ankle-foot injuries and the higher risk of falls through observational studies and MR causality analysis. Regarding its mechanism, fall-related balance deficits have been well documented in patients with ankle-foot sprains.[3,45,46] In the 1960s, Freeman et al. for the first time, proposed the theory that the mechanoreceptors in the ligaments are damaged along with joint injuries, thereby leading to functional instability of the ankle-foot complex.[47] After that, numerous studies have been performed to unfold the mechanism of balance deficit after ankle-foot sprains. Recent findings suggest that prolonged proprioceptive de-afferentation can lead to a series of alterations in the balance center of the brain, thereby leading to persistent dysfunction of postural muscles.[17,48] In addition, these alternations may be amplified by age-related impairment of balance, and further increase the risk of falls in middle-aged and older adults.[7,8] Our findings supported the theory of deficits and indicated that patients with foot-ankle sprain have a slightly increased risk of falls even after 5 years of sprain. We also showed that the genetically predicted sprains at about 40 years of age (recorded by FinnGen) can increase the risk of fall at about 60 years of age among UK Biobank participants. However, this study only focused on the epidemiological associations between ankle-foot sprains and falls, and physiological studies are needed to explore the mechanism of balance deficits after ankle-foot sprains.

4.2. Potential mediators increase the risk of falls after ankle-foot sprains

Finding potential mediators that increase the risk of falls after ankle sprains can help design more efficient interventions to prevent falling. As mentioned previously, the neuroimaging features of the balance canter have been applied in this study to determine the association between their alterations and ankle-foot sprains.[18,19] According to the anatomical structure of the balance center in the cerebellum, proprioceptive signals from joints are transferred into the cerebellum via the ICP and SCP. Then, processed sensorimotor information will be transferred from the cerebellum to the cortex via SCP, and from the cortex to the cerebellum via MCP.[49,50] For the first time, Terada et al. in 2019 indicated that adult patients with a history of ankle sprain have SCP impairments related to postural instability.[19] Then, Xue et al. revealed that adolescents with chronic ankle instability have dysfunctional ICP compared to controls.[18] In this study, MR analysis indicated abnormal SCP (i.e., lower FA) in middle-aged and older individuals with ankle sprain. Although lambda 2 of SCP was associated with ankle-foot sprains in supplementary analysis, it lacked physiological significance because the association was only observed in half of the radial diffusion coefficient of neural tracts (averaged lambda 2/3).[51] More neurological studies are needed to clarify the mechanism of central balance impairments after ankle-foot injuries.

Regarding the mediating effect of maladaptive neuroplasticity in SCP, only the right side of SCP showed a statistically significant effect on the slightly increased risk of falls. There may be several reasons for this unilateral association, including: (1) hemisphere of the cerebellum is ipsilaterally dominant, (2) most humans are right-footers, (3) the

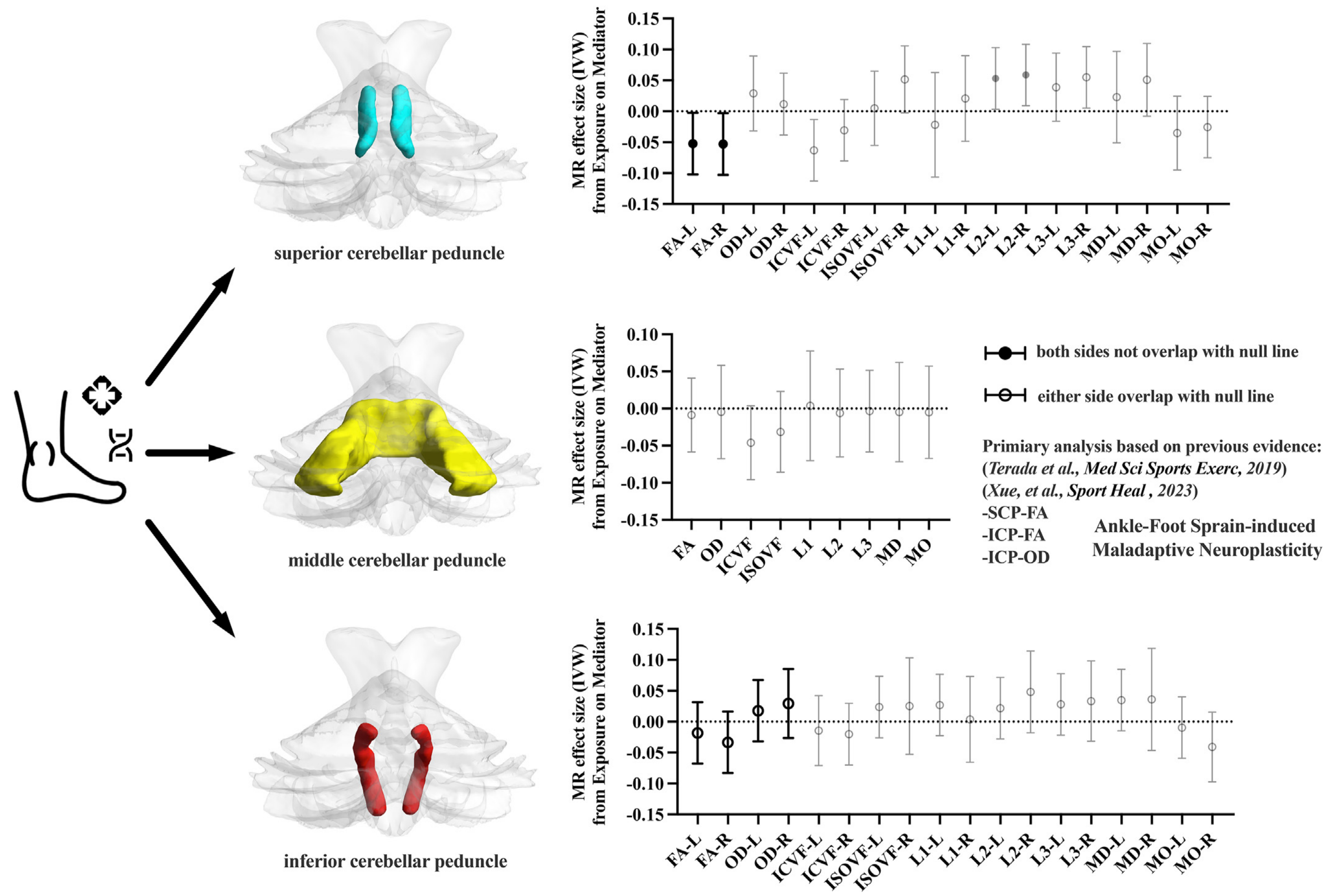

Fig. 5. MR analysis of the causal effect of ankle-foot sprains on cerebellar neuroimaging features by IVW method with 90% *CI*. The primary analyses included the FA of SCP that have been previously reported to be different between patients with ankle-foot sprains and healthy controls in observational studies. Other analyses are provided as supplementary results. *CI*, confidence interval; FA, fractional anisotropy; ICP, inferior cerebellar peduncle; ICVF, intracellular volume fraction; ISOVF, isotropic volume fraction; IVW, inverse variance weighted; L, left; L1/2/3, lambda 1/2/3; L, left; MD, mean diffusivity; MO, diffusion tensor mode; OD, orientation dispersion index; *OR*, odd ratio; R, right; SCP, superior cerebellar peduncle.

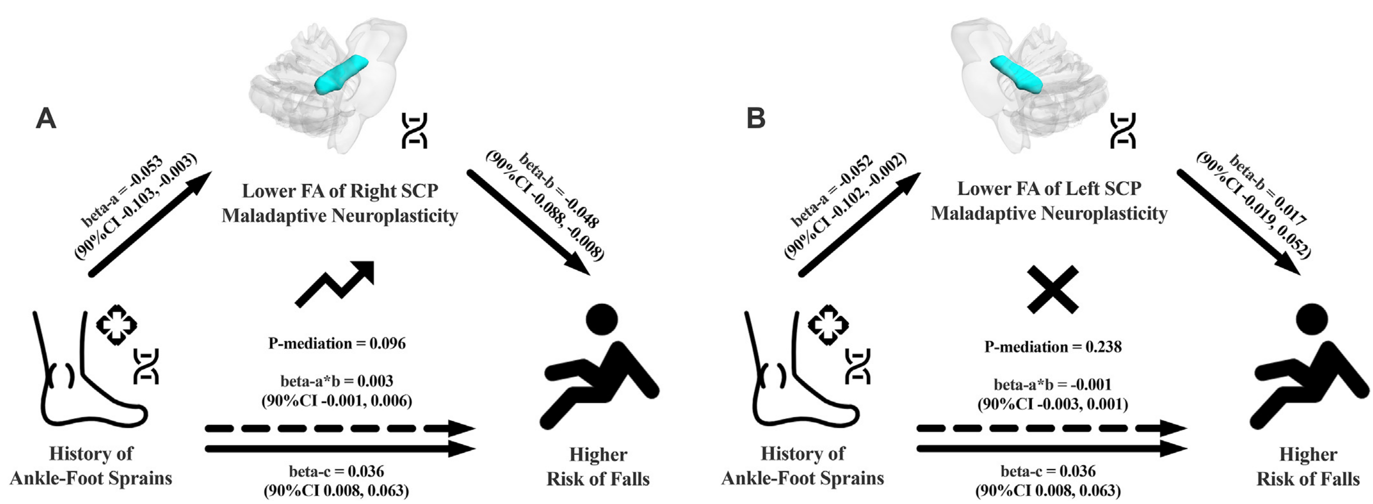

Fig. 6. The mediating role of lower FA of right (A) and left (B) SCP in the causal effect of ankle-foot sprains on the risk of falls. Pathway a is the effect of the exposure (history of ankle-foot sprains) on the mediator (lower FA of SCP); Pathway b is the effect of the mediator (lower FA of SCP) on the outcome (higher risk of falls); Pathway c is the total effect of the exposure (history of ankle-foot sprains) on the outcome (risk of falls). The indirect path a*b shows whether lower FA of SCP mediates the causal effect of ankle-foot sprains on the risk of falls. *CI*, confidence interval; FA, fractional anisotropy; SCP, superior cerebellar peduncle.

dominant side is more important for maintaining the upright position.[52–54] Weak imaging-function association (i.e., the impaired imaging feature does not necessarily mean functional deficit) may be responsible for the marginal mediating effect. In addition, there may be other pathways that can mediate the effect of ankle-foot sprains on falls. Furthermore, the balance deficits after ankle-foot injuries can be attributed to low tactile sensitivity of the planter surface, persistent pain, and reduced flexibility/strength from the ankle to the toes.[13–15,55] Apart from balance impairment, other fall-related factors can also happen after ankle-foot sprains. For instance, fear of movement (kinesophobia) after joint sprains can reduce confidence in balance and alter gait patterns, which has been shown to increase the risk of falls.[56–58] Future studies are needed to elucidate the complex interplay between these factors and their contribution to falls in individuals with a history of ankle-foot sprains.

4.3. Clinical implications

Several clinical implications can be obtained from our study. Previous studies reported postural and balance deficits following ankle-foot injuries and showed poor outcomes (e.g., reinjuries). Additionally, our study suggested the history of sprain might be a contributing factor to the increased risk of falls. It is consistent with the well-known theory that falling history is a significant risk factor for future falls. Identification of the history of ankle-foot sprains as a potential risk factor for future falls may promote the development of more efficient prevention and treatment strategies for falls.[13] Strength training, proprioceptive exercises, and gait retraining are needed for both patients with ankle-foot injuries and fallers to improve residual balance deficits and reduce the risk of falls.[59,60] Additionally, maladaptive neuroplasticity in the cerebellum indicates that particular attention should be paid to central control during treatment. Consistently, neuromodulation techniques could partly restore balance deficits, although further studies are needed before clinical application.[61,62] Last but not least, considering the high prevalence of ankle-foot sprains, post-sprain rehabilitation should be launched not only in laboratories or first-class hospitals but also in community-oriented primary care to fully benefit patients with residual functional deficits.

4.4. Research implications

Our study constructed a foundation for future investigation of the causal relationship between ankle-foot sprains and falls. First, although the increased risk of falls was validated in both retrospective cohorts and MR analyses, prospective cohorts that follow patients from the initial sprains, and use monthly fall calendars or instrumented-based assessments of falls are needed to reduce potential recalling biases and reverse causality.[55] Due to the characteristics of the dataset, we pooled ankle and foot sprains based on the medical records. More detailed information on the severity (e.g. partial ligament torn, complete joint dislocation), location (e.g. toes, mid-foot, ankle), and chronicity (e.g. acute, chronic, recurrent) of injuries can explain the heterogeneous effect of ankle-foot sprains on fall-related balance deficits. In addition, information on the treatment of joint sprains should be included in future modeling, since patients who undergo systematic rehabilitation may have minor residual functional deficits. Cerebellar imaging features may be related to balance deficits, but more comprehensive data on biomechanical, physiological, and psychological variables (e.g. proprioception, strength/flexibility, and kinesophobia) are needed to explain how ankle-foot sprains increase the risk of falls.[3] Finally, the loss of balance normally occurs in older age, and the combination of ankle-foot injuries and age-related decline in balance may warrant the increased risk of falls in middle-aged and older adults. Further studies of this interaction with longer follow-up duration from adolescence to older age can answer this dilemma.

4.5. Limitation

Several limitations should be acknowledged for this study. First, we highlighted the mediating role of residual balance deficits after sprains in this study; however, the direct measurements of balance and other kinesiological parameters were lacking in almost all of the existing open datasets. Although accumulating evidence supports this link, future cohorts should record the functional outcomes for more specific analysis. Second, the relatively weak effect size and wide confidence interval should be concerned for the history of ankle-foot sprains, compared to other well-known risk factors of falls.[3,44,45] Several reasons could lead to this problem: (a) Ankle symptoms and resulting falls can arise from various conditions. Considering the age range, different injuries beyond ankle-foot sprains, such as ankle instability, osteoarthritis, muscle shortening, tenosynovitis/tendinopathies sequelae, neural deficits from prior trauma, referred pain, or widespread pain, may also contribute to falls, potentially obscuring the specific impact of ankle-foot sprains. (b) Due to the natural limitation of open databases, we had to merge the heterogeneous injuries in the ankle-foot complex for analysis. Most of the previous data were based on lateral ankle sprains and ankle instability. Whether other injuries (e.g., toe sprains) can cause fall-related deficits still need validation. (c) Most patients with ankle-foot sprains did not seek formal medical treatments, and the UK Biobank only included the medical records since 1990s.[4] Thus, the number of "patients" was underestimated, and some of our "uninjured controls" might also have injuries (misclassification). (d) UK Biobank mainly included middle-aged and older adults, and the prevalence of sport injuries among them might be lower than that among adolescents, which further restricted the number of "patients" and biased the sensitivity analysis on the complete dataset (<5 % of cases).[63] Third, sprains are frequently accompanied by fractures, but the open databases only provided primary diagnoses, making it difficult to distinguish between isolated sprains and those with fractures. Although we have excluded cases involving transport accidents and exposure to mechanical forces to reduce bias from severe trauma, this issue may still potentially affect the outcomes. Fourth, treatment options can influence patient outcomes, but the open databases also lacked detailed treatment records. This limitation prevented us from fully accounting for treatment variations in sprains. Future research should address these gaps to confirm our preliminary observations. Fifth, both the retrospective cohort and MR analyses measured falls based on a single, self-reported recall in the UK Biobank. A recall period of one year may be too long for participants to accurately remember all falls, especially minor or injury-free ones, which introduces potential recall bias and could compromise the results. Sixth, both ankle-foot sprains and falls were multifactorial phenomena; thus, despite adjusting for several confounding factors in observational cohorts and MR analyses, there might be unidentified confounders that were not included in the UK Biobank and FinnGen databases (e.g., there are unknown factors that will induce both ankle-foot sprains and falls, and then induce false association). Seventh, the selection of exposure-related SNPs were based on a relaxed significance level, because their multifactorial characteristics that made their association with SNPs were not strong enough. However, the selection of IVs met the lowest thresholds of 1×10^{-5}, and the F value of each SNP indicated the absence of weak instrument bias.[32] Finally, participants from the UK were mostly of European ancestry, limiting the generalizability of our findings to other ethnic groups. Since the UK Biobank and FinnGen databases were restricted to volunteers with European ancestry and a relatively high socioeconomic background, these databases may not represent the general population.

5. Conclusions

A history of ankle-foot sprains is associated with a slightly increased risk of falls, with maladaptive neuroplasticity in the superior cerebellar peduncle as a potential mediator. These findings improve our understanding of the clinical consequence of ankle-foot sprains in terms of fall risk and suggest the importance of adopting more efficient strategies for managing residual functional deficits after the injuries.

Ethical approval statement

All analyses were performed on publicly available individual-level data and summary-level GWAS statistics from the UK biobank (http://www.ukbiobank.ac.uk/) and FinnGen (https://www.finngen.fi/fi) database. Ethics approval was obtained from respective institutional review boards and participants' informed consent was provided in these cohort projects.

Funding

This work was supported by the National Natural Science Foundation of China [No. 81871823, 81971583, 81671652, 8207090113], National Key R&D Program of China [No. 2018YFC1312900], Natural Science Foundation of Shanghai [No. 20ZR1406400], Science and Technology Commission of Shanghai Municipality [No. 18JC1410403], Shanghai Municipal Science and Technology Major Project [No.2017SHZDZX01, 2018SHZDZX01], and Shanghai Science and Technology Committee [No. 22dz1204700].

Data statement

All data are publicly available, and the codes are available upon reasonable request corresponding to the authors.

CRediT authorship contribution statement

Xiao'ao Xue: Conceptualization, Formal analysis, Writing – original draft, Methodology. **Weichu Tao:** Conceptualization, Formal analysis, Writing – original draft, Methodology. **Qianru Li:** Conceptualization, Formal analysis, Methodology, Writing – original draft. **Yi Li:** Data curation, Methodology, Writing – review & editing. **Yiran Wang:** Data curation, Methodology, Writing – review & editing. **Le Yu:** Software, Visualization, Writing – review & editing. **Xicheng Gu:** Software, Visualization, Writing – review & editing. **Tian Xia:** Data curation, Resources, Writing – review & editing. **Rong Lu:** Data curation, Resources, Writing – review & editing. **Ru Wang:** Funding acquisition, Project administration, Supervision, Writing – review & editing. **He Wang:** Funding acquisition, Project administration, Supervision, Writing – review & editing. **Yinghui Hua:** Conceptualization, Funding acquisition, Supervision, Writing – review & editing.

Declaration of competing interest

The authors have no direct or indirect interests that are in direct conflict with the conduction of this study.

Acknowledgements

The authors would like to express their gratitude to EditSprings (https://www.editsprings.cn) for the expert linguistic services provided, and Dr. Aichen Xia from Shanghai Jiao Tong University for the help of downloading GWAS data.

Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.smhs.2024.05.002.

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