

The association between cognitive performance and meniscal injuries: A Mendelian randomization analysis

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Abstract

Background

The causal relationship between cognitive performance and meniscal injuries is unclear. This study aims to elucidate the genetic causality between cognitive performance and meniscal injuries.

Methods

We conducted a two-sample Mendelian Randomization (MR) analysis utilizing summary-level data from extensive genome-wide association studies. Single nucleotide polymorphisms (SNPs) achieving genome-wide significance ($P < 5 \times 10^{-8}$) were employed as instrumental variables for each exposure. The inverse-variance weighted (IVW) method served as the principal statistical technique, complemented by the weighted median, MR-Egger regression, and MR-PRESSO methods for sensitivity analyses, accommodating some of the assumptions inherent in IVs.

Results

Genetically predicted cognitive performance was inversely correlated with the odds of meniscal injuries. However, the MR-Egger regression analysis did not corroborate this association. The inverse-variance weighting (IVW) method yielded a pooled odds ratio (OR) of 0.76 (95% CI 0.66–0.88; $P = 2 \times 10^{-4}$) per standard deviation increase in the prevalence of cognitive performance, a finding echoed by the weighted median method (OR: 0.81, 95% CI 0.67–0.98; $P = 3 \times 10^{-2}$). Additionally, we did not detect pleiotropy of effects in our investigation using the MR-Egger intercept and Cochran's Q test ($P > 0.05$). But there is heterogeneity between them ($P > 0.05$).

Conclusion

This study used MR analysis to analyze and explore the genetic data, which showed that cognitive decline is a risk factor for meniscal injuries, and further studies on the mechanisms of the role between the two are needed in the future.

1 Introduction

The knee joint is the primary weight-bearing joint in humans. The meniscus consists of two pieces of fibrocartilage located on the medial and lateral sides of the knee joint, situated between the femur and the tibia. Meniscal injuries are classified into traumatic and degenerative types. Traumatic injuries typically occur in young, active individuals, mainly due to major sports-related incidents or occupations

involving physical activity. Conversely, degenerative injuries are common in middle-aged and elderly individuals and are often associated with osteoarthritis.

Cognitive impairment is a common chronic disease associated with aging, characterized by memory loss, inattention, difficulty accessing new information, and problem-solving abilities. Recent studies have indicated that the decline in cognitive ability increases the risk of cardiovascular diseases[1], and patients with rheumatoid arthritis also exhibit significant cognitive decline[2]. However, research on the relationship cognitive performance and meniscal injuries is lacking, and the causal relationship between them remains uncertain, necessitating further investigation.

Mendelian randomization (MR) examines whether observed correlations between exposure variables and outcomes are compatible with causal effects by utilizing genetic variation as an instrumental variable (IV)[3]. This method helps avoid confounding variables and reverse causation, and minimizes bias since genetic variation is unaffected by external environmental, social, behavioral, or other factors[4]. Therefore, the aim of this study was to determine the causal link cognitive performance and meniscal injuries using a two-sample MR analysis.

2 Materials and Methods

2.1 Study Overview

This MR study utilized published single nucleotide polymorphisms (SNPs) from the Genome-wide Association Studies (GWAS) database as instrumental variables to assess the impact of cognitive performance on the risk of meniscal injuries. The Inverse Variance Weighted (IVW) method was primarily employed to infer the causal relationship between these exposures and the injury. For the MR analysis to be valid, three fundamental assumptions must be met: First, the selected SNPs should be significantly associated with cognitive performance. Second, these SNPs must not be linked to any potential confounders that could affect the association between cognitive performance and meniscal injuries. Finally, the SNPs should not be directly associated with the injury itself, ensuring that any causal inference is mediated exclusively through cognitive performance.

2.2 Data source

The largest publicly accessible GWAS dataset, which includes 257,841 participants of European ancestry, provides summary data on cognitive performance. The summary dataset for the associations between SNPs and meniscal derangement was retrieved by searching GWAS ID: finn-b-M13_MENISCUSDERANGEMENTS on the website <https://gwas.mrcieu.ac.uk/> (accessed on June 6, 2024). This GWAS is the latest regarding meniscal derangement and was updated in 2021. It includes 13,568 cases of meniscal derangement and 147,221 controls, with a total of 16,380,200 SNPs tested. All participants are of European ancestry.

2.3 Instrumental selection

From the pooled GWAS datasets, we first identified SNPs strongly associated with cognitive performance ($P < 5 \times 10^{-8}$). We then used a reference set of 1000 genomes from a European population to rule out linkage disequilibrium between these SNPs ($r^2 < 0.001$ and clump window $> 10,000$ kb). Palindromic SNPs were manually eliminated. Following these procedures, the remaining SNPs were used as instrumental variables. To reduce weak instrument bias ($F > 10$), we also employed the F-statistic ($F = \beta^2 / \text{se}^2$) to assess the statistical efficacy of the SNPs and exclude those with poor statistical efficacy[5].

2.4 Mendelian Randomization Analyses

All statistical analyses were conducted using R software (version 2024.04.1) with the Two Sample MR (0.6.3)[6] and Mendelian Randomization (0.6.3)packages[7], along with the MR-PRESSO package[8]. P-values were two-tailed throughout. Odds ratios (ORs) and the corresponding 95% confidence intervals (95% CIs) for meniscal injuries were scaled per one-unit increase in genetically predicted exposure levels to cognitive performance. F-statistics for each exposure were calculated using the previously outlined approximation method[9].

Our primary analytical strategy employed the standard IVW method under a random-effects model, assuming the validity of each SNP as an IV. While the IVW method synthesizes Wald ratios within a meta-analytic framework to yield precise association estimates, it remains susceptible to pleiotropic effects from invalid IVs[10]. Variance among genetic variants was assessed using Cochran's Q-statistic[10].

For sensitivity analysis, we used methods that relax certain IV assumptions, including the weighted median, MR-Egger regression, and MR-PRESSO. The weighted median method provides consistent estimates assuming that the majority of the analysis weight comes from valid instruments [9]. MR-Egger regression helps identify and adjust for directional pleiotropy, offering a pleiotropy-corrected causal estimate, though at a loss of statistical power[9]. The P-value for the MR-Egger intercept was used to indicate the presence of pleiotropy[9]. The MR-PRESSO method identifies outliers through a global test and recalculates estimates after outlier removal [8]. The P-value from the MR-PRESSO distortion test indicated significant deviations in estimates before and after outlier adjustment [8].

3 Results

Following thorough screening, we identified 136 SNPs as IVs for meniscal derangement outcomes. There was no evidence of weak instrument bias, as indicated by the F-statistics, all of which were greater than 10. The MR results of cognitive performance on meniscal derangement are presented in Table 1. Genetically predicted cognitive performance was inversely associated with the odds of meniscal derangement. However, this association was not supported by the MR-Egger regression analysis. The inverse-variance weighting (IVW) method produced a pooled odds ratio (OR) of 0.76 (95% CI 0.66–0.88; $P = 2 \times 10^{-4}$) per standard deviation increase in cognitive performance, a finding corroborated by the weighted median method (OR: 0.81, 95% CI 0.67–0.98; $P = 3 \times 10^{-2}$). Additionally, no pleiotropic effects were detected in our investigation using the MR-Egger intercept and Cochran's Q test ($P > 0.05$).

However, there was heterogeneity among the results ($P > 0.05$). Figure 1 illustrates the scatter plots showing the associations between genetically predicted cognitive performance and the risk of meniscal injuries. The causal associations depicted in the forest plots are presented in Fig. 2. To further validate these findings, the symmetry of the causal effect distribution was assessed through a funnel plot, which indicated no apparent bias from potential confounders, as shown in Fig. 3.

Table 1. Causal effects of cognitive performance on meniscus derangement using MR analysis

Exposure	MR method	OR(95%CI)	P
cognitive performance: 136 SNPs	MR Egger	0.95(0.47,1.91)	0.89
	Weighted median	0.81(0.67,0.98)	3*10-2
	Inverse variance weighted	0.76(0.66,0.88)	2*10-4
	Simple mode	0.86(0.48,1.52)	0.61
	Weighted mode	0.88(0.53,1.48)	0.65

4 Discussion

The prevalence of meniscal injuries is said to be on the rise[11]. Both conservative and surgical approaches are commonly employed for treatment[12]. In the case of minor meniscus injuries, conservative methods like rest, application of cold packs, pain relievers, and physical therapy can prove effective[13]. These techniques aid in alleviating pain and inflammation while promoting self-healing of meniscal injuries. Surgical intervention may become necessary for severe meniscal injuries characterized by extensive tears or limited joint functionality[14]. Surgery aims to repair or remove damaged meniscal tissue in order to restore normal joint function. Various factors contribute to the occurrence of meniscal injuries, making it crucial to identify these risk factors in clinical practice[15]. Recognizing the risk factors associated with meniscal injuries assists physicians in evaluating patient susceptibility and devising personalized treatment plans. Previous research has highlighted several risk factors linked to meniscal injuries including age, male gender, type of physical activity undertaken, higher body mass index, as well as delayed repair of accompanying anterior cruciate ligament injuries[16–20].

Cognitive impairment predominantly affects the population over 65 years of age, with Alzheimer's disease and vascular disease being the leading causes in the West[21]. With an estimated 135 million people worldwide expected to have dementia by 2050[22], cognitive impairment poses a significant challenge to global health and social care[23].

It is known that a significant decline in cognitive performance may be an observational risk factor for meniscal injuries, but the causality of this association is unclear. Our MR study aimed to elucidate the causal relationship between cognitive performance and meniscal injuries. The results of the two-sample MR showed a causal association between cognitive performance and meniscal injuries with an OR (95%

CI) of 0.76 (0.66–0.88), $P = 2 \times 10^{-4}$, suggesting that individuals with significant cognitive decline have a higher risk of meniscal injuries compared to the general population. Furthermore, statistical evidence from sensitivity analyses strongly supports our findings. Therefore, raising awareness of the dangers of cognitive impairment is important. Screening for meniscal injuries should be increased among individuals with cognitive impairment, enabling timely detection and treatment of meniscal injuries, which is beneficial for patient prognosis. For patients with meniscal injuries, improving cognitive ability should be advocated.

The underlying mechanism linking cognitive performance and meniscal injuries is unclear. This study is the first to examine the causal relationship between cognitive performance and meniscal injuries, concluding that a decline in cognitive performance increases the risk of meniscal injuries. Possible reasons include: First, cognitive decline may reduce athletic capacity and activity levels, increasing the risk of accidental falls and athletic injuries leading to meniscal injuries[24]. Second, cognitive impairment often accompanies a decline in balance and coordination, raising the risk of injury during daily activities, particularly to the meniscus[25]. Third, cognitive impairment may cause delays in attention and reaction time[26], elevating the risk of injuries in sports and daily activities. Fourth, cognitive impairment is often associated with other health problems, such as cardiovascular disease or diabetes[27–28], which may increase the risk of meniscus injury. Additionally, some cognitive impairment treatments may affect physical abilities and balance. Fifth, cognitive impairment may lead to unhealthy lifestyles and behaviors[29–31], such as physical inactivity and poor diet, indirectly increasing the risk of meniscus injury. Understanding the relationship between meniscus injuries and cognitive performance can enhance prevention strategies for meniscus injuries and mitigate the impact of cognitive impairment.

Our study has several limitations. First, due to data limitations, we did not stratify by age or sex. Second, the exposure and outcome analyses were confined to European populations. The generalizability of these findings to other populations needs further investigation. Significant GWAS data including participants from diverse ethnic groups is required. Finally, due to data source restrictions, we were unable to investigate different subtypes of cognitive impairment. Future research would benefit from larger, more comprehensive datasets.

5 Conclusions

In conclusion, this study utilized Mendelian randomization (MR) analysis to explore genetic data, revealing that cognitive decline is a risk factor for meniscal injuries. Further research is needed to understand the underlying mechanisms linking these two conditions.

Declarations

Data availability statement

The original contributions presented in the study are included in the article/Supplementary material, further inquiries can be directed to the corresponding author.

Author contributions

Conceptualization, C.L.; Data curation, Y.Z.; Formal analysis, D.C.; Funding acquisition, B.Y.; Investigation, Y.Z.; Methodology, C.L.; Software, D.C.; Supervision, J.Y.; Validation, B.Y.; Visualization, C.L.; Writing—original draft, C.L.; Writing—review and editing, Y.Z.,B.Y.

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Conflict of interest

The authors declare no conflicts of interest.

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Supplementary material

The Supplementary material for this article can be found online.

References

1. Duan L, Xiao R, Liu S, Shi Y, Feng Y. Causality between cognitive performance and cardiovascular disease: A bidirectional Mendelian randomization study. *Gene*. 2024;891:147822. doi:10.1016/j.gene.2023.147822.

2. Duan L, Li S, Li H, Shi Y, Xie X, Feng Y. Causality between rheumatoid arthritis and the risk of cognitive impairment: a Mendelian randomization study. *Arthritis Res Ther*. 2024;26(1):5. Published 2024 Jan 2. doi:10.1186/s13075-023-03245-x.
3. Emdin CA, Khera AV, Kathiresan S. Mendelian Randomization. *JAMA*. 2017;318(19):1925-1926. doi:10.1001/jama.2017.17219.
4. Ebrahim S, Davey Smith G. Mendelian randomization: can genetic epidemiology help redress the failures of observational epidemiology?. *Hum Genet*. 2008;123(1):15-33. doi:10.1007/s00439-007-0448-6.
5. Pierce BL, Ahsan H, Vanderweele TJ. Power and instrument strength requirements for Mendelian randomization studies using multiple genetic variants. *Int J Epidemiol*. 2011;40(3):740-752. doi:10.1093/ije/dyq151.
6. Hemani G, Zheng J, Elsworth B, Wade KH, Haberland V, Baird D, et al. The MR-Base platform supports systematic causal inference across the human phenome. *Elife*. 2018 May 30;7:e34408. doi: 10.7554/eLife.34408.
7. Yavorska OO, Burgess S. Mendelian Randomization: an R package for performing Mendelian randomization analyses using summarized data. *Int J Epidemiol*. 2017;46(6):1734-1739. doi:10.1093/ije/dyx034.
8. Verbanck M, Chen CY, Neale B, Do R. Detection of widespread horizontal pleiotropy in causal relationships inferred from Mendelian randomization between complex traits and diseases. *Nat Genet*. 2018 May;50(5):693-698. doi: 10.1038/s41588-018-0099-7.
9. Bowden J, Del Greco M F, Minelli C, Davey Smith G, Sheehan NA, Thompson JR. Assessing the suitability of summary data for two-sample Mendelian randomization analyses using MR-Egger regression: the role of the I² statistic. *Int J Epidemiol*. 2016 Dec 1;45(6):1961-1974. doi: 10.1093/ije/dyw220.
10. Burgess S, Bowden J, Fall T, Ingelsson E, Thompson SG. Sensitivity Analyses for Robust Causal Inference from Mendelian Randomization Analyses with Multiple Genetic Variants. *Epidemiology*. 2017 Jan;28(1):30-42. doi: 10.1097/EDE.0000000000000559.
11. Urhausen AP, Berg B, Øiestad BE, Whittaker JL, Culvenor AG, Crossley KM, et al. Measurement properties for muscle strength tests following anterior cruciate ligament and/or meniscus injury: What tests to use and where do we need to go? A systematic review with meta-analyses for the OPTIKNEE consensus. *Br J Sports Med*. 2022 Dec;56(24):1422-1431. doi: 10.1136/bjsports-2022-105498.
12. Wei Y, Sun H, Gui T, Yao L, Zhong L, Yu W, et al. The critical role of Hedgehog-responsive mesenchymal progenitors in meniscus development and injury repair. *Elife*. 2021 Jun 4;10:e62917. doi: 10.7554/eLife.62917.
13. Han Y. Application of Tissue Engineered Nanomaterials in Meniscus Sports Injury Repair. *Front Bioeng Biotechnol*. 2022 Jun 14;10:905869. doi: 10.3389/fbioe.2022.905869.

14. de Roy L, Warnecke D, Hacker SP, Simon U, Dürselen L, Ignatius A, et al. Meniscus Injury and its Surgical Treatment Does not Increase Initial Whole Knee Joint Friction. *Front Bioeng Biotechnol*. 2021 Dec 10;9:779946. doi: 10.3389/fbioe.2021.779946.
15. Brophy RH, Gefen AM, Matava MJ, Wright RW, Smith MV. Understanding of Meniscus Injury and Expectations of Meniscus Surgery in Patients Presenting for Orthopaedic Care. *Arthroscopy*. 2015 Dec;31(12):2295-300.e5. doi: 10.1016/j.arthro.2015.05.003.
16. Dumont GD, Hogue GD, Padalecki JR, Okoro N, Wilson PL. Meniscal and chondral injuries associated with pediatric anterior cruciate ligament tears: relationship of treatment time and patient-specific factors. *Am J Sports Med*. 2012 Sep;40(9):2128-33. doi: 10.1177/0363546512449994.
17. Magnussen RA, Pedroza AD, Donaldson CT, Flanigan DC, Kaeding CC. Time from ACL injury to reconstruction and the prevalence of additional intra-articular pathology: is patient age an important factor? *Knee Surg Sports Traumatol Arthrosc*. 2013 Sep;21(9):2029-34. doi: 10.1007/s00167-013-2380-8.
18. Millett PJ, Willis AA, Warren RF. Associated injuries in pediatric and adolescent anterior cruciate ligament tears: does a delay in treatment increase the risk of meniscal tear? *Arthroscopy*. 2002 Nov-Dec;18(9):955-9. doi: 10.1053/jars.2002.36114.
19. Vaquero J, Vidal C, Cubillo A. Intra-articular traumatic disorders of the knee in children and adolescents. *Clin Orthop Relat Res*. 2005 Mar;(432):97-106. doi: 10.1097/01.blo.0000156002.16750.8d.
20. Vavken P, Tepolt FA, Kocher MS. Concurrent Meniscal and Chondral Injuries in Pediatric and Adolescent Patients Undergoing ACL Reconstruction. *J Pediatr Orthop*. 2018 Feb;38(2):105-109. doi: 10.1097/BPO.0000000000000777.
21. Iadecola C, Duering M, Hachinski V, Joutel A, Pendlebury ST, Schneider JA, et al. Vascular Cognitive Impairment and Dementia: JACC Scientific Expert Panel. *J Am Coll Cardiol*. 2019 Jul 2;73(25):3326-3344. doi: 10.1016/j.jacc.2019.04.034.
22. Ponjoan A, Garre-Olmo J, Blanch J, Fages E, Alves-Cabratos L, Martí-Lluch R, et al. Epidemiology of dementia: prevalence and incidence estimates using validated electronic health records from primary care. *Clin Epidemiol*. 2019 Mar 4;11:217-228. doi: 10.2147/CLEP.S186590.
23. Livingston G, Sommerlad A, Orgeta V, Costafreda SG, Huntley J, Ames D, et al. Dementia prevention, intervention, and care. *Lancet*. 2017 Dec 16;390(10113):2673-2734. doi: 10.1016/S0140-6736(17)31363-6.
24. Riva D, Fani M, Benedetti MG, Scarsini A, Rocca F, Mamo C. Effects of High-Frequency Proprioceptive Training on Single Stance Stability in Older Adults: Implications for Fall Prevention. *Biomed Res Int*. 2019 May 22;2019:2382747. doi: 10.1155/2019/2382747.
25. Xiao T, Yang L, Smith L, Loprinzi PD, Veronese N, Yao J, et al. Correlation Between Cognition and Balance Among Middle-Aged and Older Adults Observed Through a Tai Chi Intervention Program. *Front Psychol*. 2020 Apr 6;11:668. doi: 10.3389/fpsyg.2020.00668.

26. Sapsford TP, Johnson SR, Headrick JP, Branjerdporn G, Adhikary S, Sarfaraz M, et al. Forgetful, sad and old: Do vascular cognitive impairment and depression share a common pre-disease network and how is it impacted by ageing? *J Psychiatr Res.* 2022 Dec;156:611-627. doi: 10.1016/j.jpsychires.2022.10.071.
27. Sumbul-Sekerci B, Hanagasi HA, Bilgic B, Tufekcioglu Z, Gurvit H, Emre M. Medication management and treatment adherence in Parkinson's disease patients with mild cognitive impairment. *Acta Neurol Belg.* 2023 Jun;123(3):823-829. doi: 10.1007/s13760-022-01916-1.
28. Khandaker GM, Zuber V, Rees JMB, Carvalho L, Mason AM, Foley CN, et al. Correction: Shared mechanisms between coronary heart disease and depression: findings from a large UK general population-based cohort. *Mol Psychiatry.* 2021 Jul;26(7):3659-3661. doi: 10.1038/s41380-020-0857-7.
29. Coelho-Júnior HJ, Trichopoulou A, Panza F. Cross-sectional and longitudinal associations between adherence to Mediterranean diet with physical performance and cognitive function in older adults: A systematic review and meta-analysis. *Ageing Res Rev.* 2021 Sep;70:101395. doi: 10.1016/j.arr.2021.101395.
30. Scarmeas N, Luchsinger JA, Schupf N, Brickman AM, Cosentino S, Tang MX, et al. Physical activity, diet, and risk of Alzheimer disease. *JAMA.* 2009 Aug 12;302(6):627-37. doi: 10.1001/jama.2009.1144.
31. Damluji AA, Ijaz N, Chung SE, Xue QL, Hasan RK, Batchelor WB, et al. Hierarchical Development of Physical Frailty and Cognitive Impairment and Their Association With Incident Cardiovascular Disease. *JACC Adv.* 2023 May;2(3):100318. doi: 10.1016/j.jacadv.2023.100318.

Figures

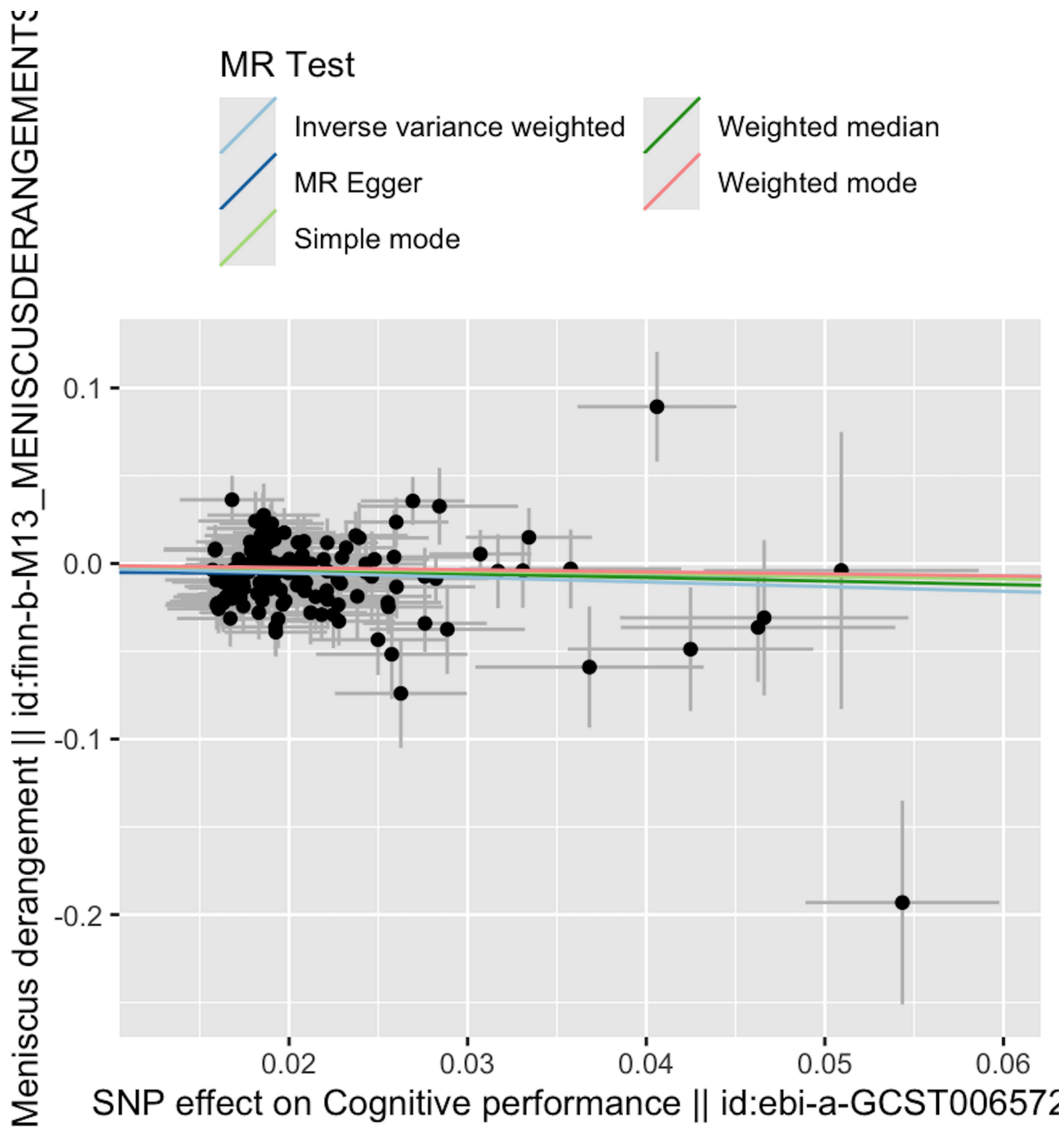


Figure 1

Scatter plots showing the effects of cognitive performance on the risk of meniscus derangement. Each point represents the per allele association with exposure plotted against per allele association with meniscus derangement.

MR Method

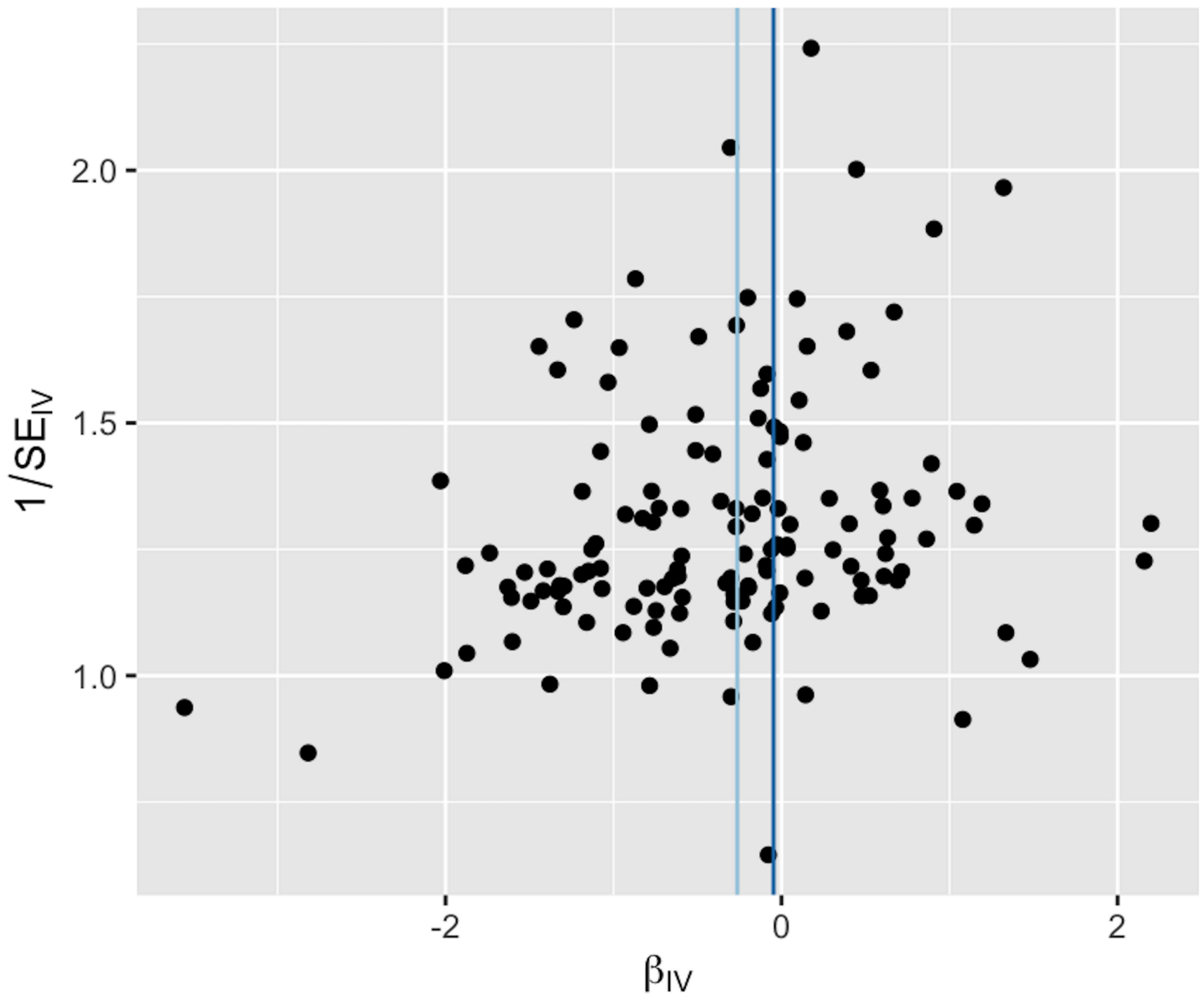
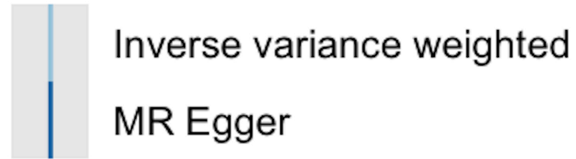


Figure 3

Funnel plots of Mendelian randomization effect sizes for causal associations. cognitive performance on the risk of meniscus derangement.

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