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Original Article

Exploring the Association between Childhood Intelligence and Vestibular Function: A Mendelian Randomization Study

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Abstract

Background: Childhood intelligence is a critical developmental milestone influenced by genetic and environmental factors. The interplay between intelligence and vestibular function, which is increasingly recognized for its relevance to cognitive abilities, has not been extensively studied. This study aims to investigate the potential association between childhood intelligence and vestibular dysfunction.

Methods: Utilizing a two-sample Mendelian randomization (MR) approach, we analyzed data from publicly available genome-wide association studies (GWAS) of European ancestry. Genetic instruments were selected based on GWAS significance, independence, and F-statistics. We employed MR Egger, Weighted median, Inverse variance weighted (IVW), Simple mode, and Weighted mode methods for robustness checks.

Results: Our analysis identified a significant inverse association between childhood intelligence and the risk of vestibular dysfunction (IVW: OR= 0.907, 95% CI = 0.843 - 0.976, p= 0.009). The MR Egger intercept test did not indicate horizontal pleiotropy, and heterogeneity analysis suggested consistency in the results.

Conclusion: The study provides preliminary evidence of a negative correlation between childhood intelligence and vestibular dysfunction risk, suggesting that higher intelligence may be associated with a lower likelihood of vestibular issues. This finding underscores the importance of vestibular function in cognitive development and offers insights for early intervention strategies.

Keywords: Childhood intelligence; Vestibular function; Mendelian randomization; Cognitive development; Genetic epidemiology

Introduction

The development of childhood intelligence is a complex process influenced by both genetic and environmental factors (1). In recent years, an increasing number of studies have found that intelligence plays a crucial role in the developmental process of children, such as the degree of social participation(2), early decision-making(3), and emotional state (4). Intelligence, as an important indicator of cognitive ability, is usually closely related to learning ability, problem-solving ability, and logical reasoning ability (5). The correlation between vestibular function and cognitive function has become increasingly clear (6-8). However, no studies have yet explored the correlation between vestibular function and childhood intelligence. Abnormal vestibular function is not un-

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common in children and may lead to balance disorders, dizziness, inattention, and other issues, which may indirectly affect children's learning and development(9). Therefore, understanding the correlation between children's intelligence and vestibular function is beneficial for us to provide early, precise, and personalized prevention of potential related diseases in children during the growth process, enabling children to achieve more effective and comprehensive growth and development.

This study will provide new perspectives for future research and promote our in-depth understanding of the development mechanism of childhood intelligence. However, it is a pity that although existing studies have explored the relationship between vestibular function and cognitive ability, most of these studies are based on observational data and are susceptible to the influence of confounding factors, making it difficult to determine causal relationships(6-8). Moreover, most current studies aim to explore the correlation between vestibular function and cognitive function, and there are fewer studies exploring the impact of children's intelligence on vestibular function(10). In addition, the development of childhood intelligence is influenced by a variety of factors, including genetics, environment, nutrition, and education(11, 12), and the interaction of these factors makes the research more complex. Therefore, we need more accurate methods to explore the causal relationship between the two.

Mendelian randomization (MR) analysis has been used in association disease studies to explore diseases related to vestibular function(13, 14). In this study, we plan to use a two-sample MR method to clarify the correlation between childhood intelligence and vestibular function. MR, as an emerging epidemiological tool, uses genetic variations as instrumental variables to assess the potential causal relationship between exposure factors and outcomes(15). This method can reduce the confounding factors in traditional observational studies and clarify the impact of the causal relationship between the two, providing us with a more reliable method to explore the connection between vestibular function and childhood intelligence.

Methods

Research Design

In this study, we conducted a two-sample MR analysis of childhood intelligence and vestibular dysfunction using genome-wide association studies (GWAS) datasets. The principles of MR analysis are as follows: (1) the genetic instrumental variable is strongly correlated with the exposure; (2) the genetic instrumental variable is related to the outcome only through the exposure; (3) the genetic instrumental variable is independent of other confounding factors(15).

Data Sources

All data used for MR analysis come from publicly available GWAS of European ancestry. Each GWAS data source has obtained ethical approval and informed consent. We obtained the GWAS data related to childhood intelligence(1) from the IEU GWAS database (https://gwas.mrcieu.ac.uk/), which is a genome-wide association study conducted by the Social Science Genetic Association Consortium on 12,441 subjects. Additionally, we obtained the data set of vestibular dysfunction from the R12 version of the FinnGen database (16), which includes data from 21,139 cases and 474,839 European ancestry controls.

Selection of Genetic Instruments

We selected single nucleotide polymorphisms (SNPs) that meet the following criteria from the GWAS datasets: 1. Significant in the genome-wide study (Due to the limited number of SNPs included, we set the significance threshold at $P < 5\times10^{-5}$); 2. Ensure that there is no linkage disequilibrium between each SNP to preserve the independence of the SNPs ($r2 < 0.001$ and within 10,000KB); 3. The F-statistic of the SNPs should be greater than 10. We then attempted to infer the positive strand allele using the allele frequency of the palindrome.

Statistical Analysis

We conducted a two-sample MR analysis for childhood intelligence and vestibular dysfunction, using five methods: MR Egger, Weighted median, Inverse variance weighted (IVW), Simple mode, and Weighted mode to assess the results. IVW is the most important analytical method. The non-zero intercept value shown by MR-Egger is mainly used to check for horizontal pleiotropy(17). The other three methods are used to further verify the reliability and stability of the results(18). If the OR values of the five methods are consistent in direction, it indicates that the results are reliable. We also performed heterogeneity analysis and pleiotropy analysis to understand the reliability of the results.

Finally, to further evaluate the robustness of the MR results, we conducted single-SNP analyses and leave-one-out analyses. The single-SNP analysis assessed the effect of each individual genetic instrumental variable on the outcome, while the leave-one-out analysis evaluated the stability of the MR results by excluding one SNP at a time.

Results

We conducted a MR analysis for the exposure (childhood intelligence) and the outcome (vestibular dysfunction), where we selected SNPs that were strongly associated with the exposure (P < 5×10^-5), and all SNPs had an F-statistics greater than 10. A total of 22 SNPs met the screening criteria. The results indicated that childhood intelligence (IVW: OR= 0.907, 95% CI = 0.843 - 0.976, *P*= 0.009) had a significantly meaningful result in the MR analysis with vestibular dysfunction (Fig. 1).

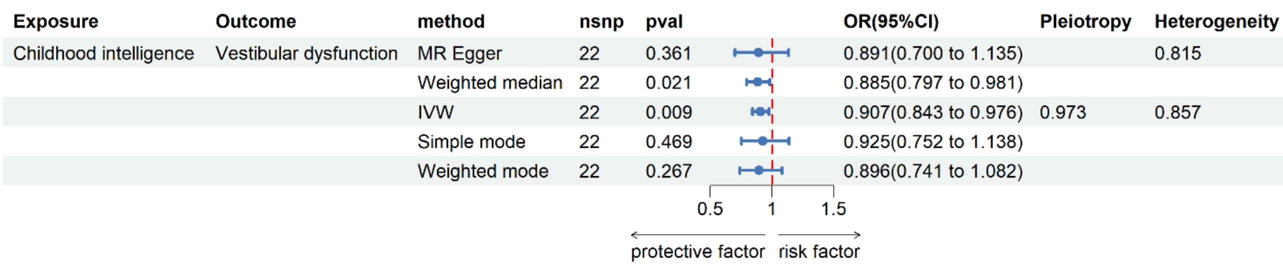

Fig. 1: Forest plot of results from MR analysis of exposure (childhood intelligence) and outcome (vestibular dysfunction)

The causal relationship between childhood intelligence and vestibular dysfunction can be intuitively demonstrated through the scatter plot (Fig. 2). The MR Egger intercept test did not suggest the presence of horizontal pleiotropy. Heterogeneity analysis indicated that the MR results were not heterogeneous. Single SNP analyses (Fig. 3) and leave-one-out analyses (Fig. 4) did not identify any SNPs with significant effects.

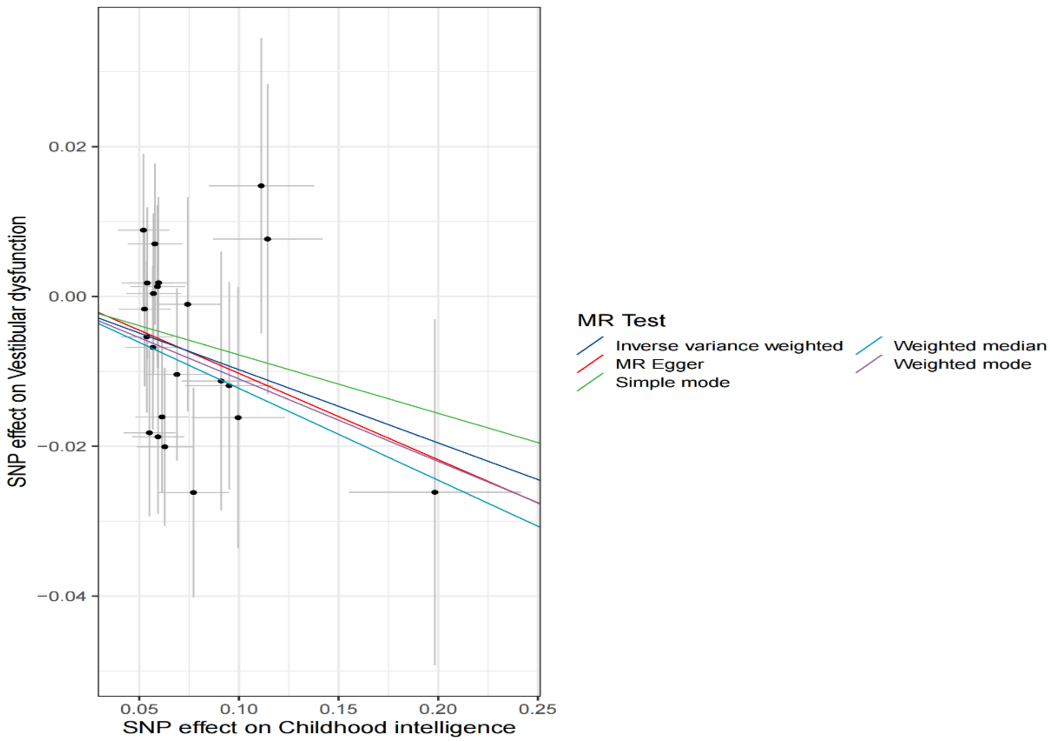

Fig. 2 : Summary view of MR findings for exposure (childhood intelligence) and outcome (vestibular dysfunction). MR analysis results were summarized using IVW, MR-Egger, simple mode, weighted median and weighted mode

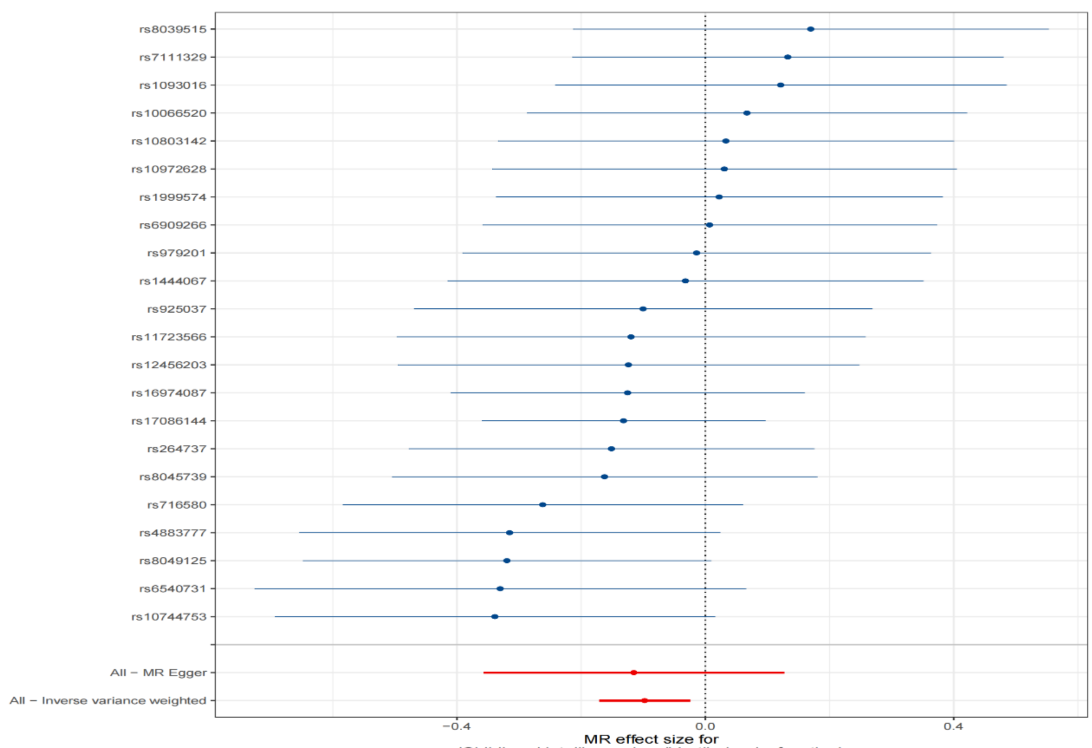

Fig. 3: Forest plot of MR sensitivity analysis. The IVM method showed a MR Effect size greater than 0, indicating a causal effect of childhood intelligence on vestibular dysfunction

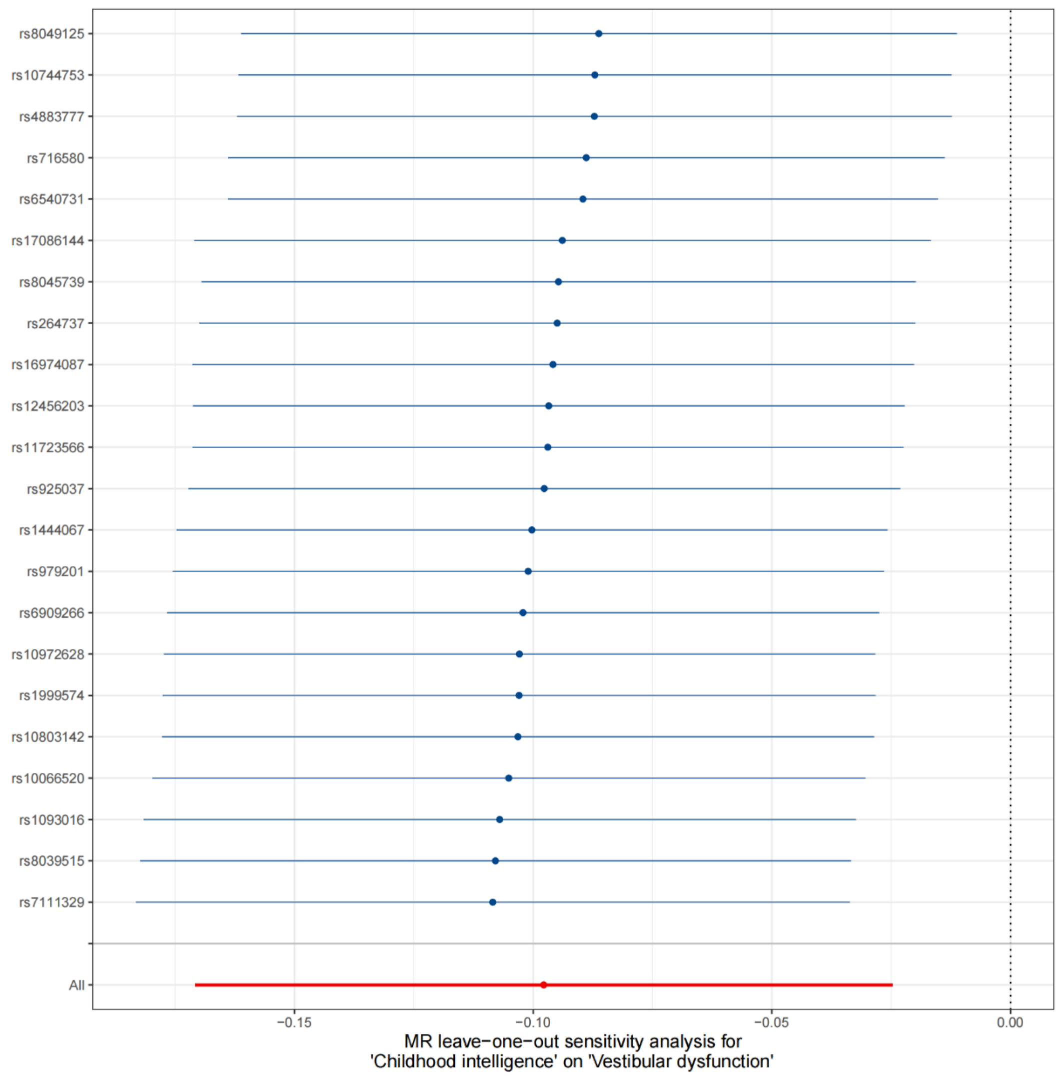

Fig. 4: A leave-one-out analysis of the estimations for childhood intelligence and vestibular dysfunction

Discussion

This study conducted an in-depth analysis of the relationship between childhood intelligence and vestibular dysfunction using the MR method. The results suggest that childhood intelligence may be negatively correlated with the probability of developing vestibular dysfunction, meaning that children with higher intelligence levels may have a lower risk of vestibular dysfunction. This finding provides a new perspective for understanding the role of the vestibular system in the development of childhood intelligence and offers important insights for future research and practice.

While our study provides evidence of a potential correlation between childhood intelligence and vestibular dysfunction, it is important to acknowledge that the biological mechanisms underlying this relationship remain largely unexplored. Understanding these mechanisms is crucial for developing targeted interventions and further elucidating the causal pathways.

First, we consider intelligence to be a manifestation of cognitive function, which is closely related to the development of vestibular function. Vestibular function reflects cognitive function to some extent, and some studies consider it an early predictor of cognitive dysfunction(19, 20). There is research that found children with cerebral palsy to have intact peripheral vestibular function but impaired central vestibular and oculomotor nerve function(21), and some reviews suggest that the sitting balance of children with cerebral palsy deserves our close attention(22). However, due to factors such as sample size and confounding factors, there is still no definitive prospective study that can prove the correlation between intelligence level and vestibular function. Our study emphasizes the potential impact of the vestibular system on the development of childhood intelligence. The analysis suggests that children with higher intelligence levels may have a more effective vestibular system, which helps them excel in learning and cognitive tasks.

Secondly, intellectual development indirectly reflects the degree of brain development. The vestibular system has extensive neural connections with other cognitive areas of the brain, which may provide a biological basis for the influence of intellectual development on vestibular function(23, 24). During childhood, the development of the prefrontal cortex is crucial for the cultivation of executive functions and problem-solving abilities, which are integral components of intelligence(25, 26). The maturation of the hippocampus is particularly key to spatial cognition and memory formation, which has profound implications for a child's learning and intellectual development(27). The development of the cerebellum is associated with the development of motor skills and certain cognitive functions, and the development of these functions is equally important for a child's overall intellectual performance(27). The close relationship between the vestibular system and these regions has been confirmed by research(28-31).

Intelligence is a concentration of multiple functions of the human body, and we believe that the degree of brain development during childhood may indirectly reflect its impact on vestibular function through the manifestation of intelligence. In addition, we believe that the development of children's intelligence is a multifactorial and multidimensional process that is influenced by multiple factors such as genetics, environment, education, and socioeconomic status(11, 12). Therefore, it is difficult for a single biological factor such as vestibular function to fully explain the differences in intelligence level.

The results of this study have important implications for the early intervention and educational practice in the development of childhood intelligence. Understanding the relationship between vestibular dysfunction and the development of childhood intelligence can help educators and parents take targeted intervention measures, such as earlier vestibular function training, balance training, and attention training. At the same time, it also highlights the importance of considering vestibular function in the assessment of childhood intelligence and educational interventions. This study used genetic variation as an instrumental variable for MR analysis, allowing us to more accurately assess the causal relationship between vestibular function and childhood intelligence, reducing the impact of confounding factors and reverse causality in traditional observational studies. Previous studies have shown that vestibular dysfunction is associated with a variety of cognitive deficits, including visuospatial skills, attention, executive function, and memory(6, 32). These studies suggest that the vestibular system plays a crucial role in overall cognitive health, especially in the context of aging and neurodegenerative diseases. Our study extends these findings by focusing specifically on childhood intelligence, which is a key developmental milestone influencing lifelong cognitive and academic outcomes. However, the MR method also has its limitations. First, due to the specific genetic background, environmental factors, and disease manifestations of the European population used in this study, the generalizability of our findings may be limited. These factors may vary significantly across different ethnicities and populations, which could affect the applicability of our results to other groups. Future studies should strive to include more diverse cohorts to enhance the external validity of the findings. Second, the significance threshold for selecting genetic instruments in this study was set at $P < 5\times10^{-5}$, which is less stringent than the traditional genome-wide significance threshold ($P < 5\times10^{-8}$). Given the limited number of available SNPs, this decision was necessary but may have led to the inclusion of some SNPs that do not fully meet the strict criteria for valid instrumental variables. This could introduce bias and affect the robustness of our results. Finally, our study relied solely on publicly available GWAS datasets and MR analysis. While this approach provides valuable insights into potential causal relationships, it does not allow for the exploration of other factors that may mediate or modify these relationships. For example, environmental factors such as socioeconomic status, nutrition, and educational opportunities can influence both childhood intelligence and vestibular function. Moreover, MR methods cannot completely rule out potential residual confounding factors, such as environmental influences and population stratification. Future studies should aim to address these limitations by including more diverse cohorts and using more sophisticated statistical techniques to control for potential residual confounding factors. Longitudinal cohort studies following children from birth through adolescence could provide valuable insights into the temporal relationships between vestibular function and cognitive development. Additionally, integrating neuroimaging data and detailed environmental assessments could help elucidate the biological mechanisms underlying the observed associations.

Conclusion

We conducted a two-sample MR analysis and found preliminary evidence of the relationship between vestibular dysfunction and childhood intelligence. Although our results need further verification and expansion, they provide a new perspective for understanding the role of the vestibular system in the development of childhood intelligence and offer important insights for future research and practice. We look forward to future research that can more deeply explore the complex relationship between childhood intelligence and the development of vestibular function, and provide more scientific evidence for the comprehensive development of children.

Journalism Ethics considerations

Ethical issues (Including plagiarism, informed consent, misconduct, data fabrication and/or falsification, double publication and/or submission, redundancy, etc.) have been completely observed by the authors.

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Conflict of interests

The authors declare no competing interest.

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List of abbreviations

nsnp = Number of Single Nucleotide Polymorphisms,
pval = *P*-value,
or = Odds Ratio,
or_lci95 = Odds Ratio Lower Confidence Interval 95%,
or_uci95 = Odds Ratio upper Confidence Interval 95%,
MR = Mendelian randomization,
GWAS = Genome-wide association studies,
IVW = Inverse variance weighted,
SNPs = Single nucleotide polymorphisms

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