



Causal Inference for Scoliosis and Strabismus: A 2-Sample Mendelian Randomization Study

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Abstract

Background: Some studies have shown an association between spinal curvature and strabismus, but the genetic association has not been clarified. Therefore, the present study is proposed to be a Mendelian randomization study aiming to investigate the genetic causal association between spinal curvature and strabismus.

Purpose: Genetic causal associations between strabismus, convergent concomitant strabismus (Ccs), Divergent concomitant strabismus (Dcs), Other specified and unspecified strabismus (Osus), Other strabismus (Os) and spinal curvature were investigated by a bidirectional Mendelian randomization study to provide a basis for the prevention and treatment of spinal curvature.

Methods: Significant and independent single nucleotide polymorphisms (SNPs) in genome-wide association studies were selected as instrumental variables (IVs) for Mendelian randomization (MR) analysis. Inverse variance weighted (IVW), MR-Egger regression, weighted median (WME), simple mode (SM), and weighted mode (WM) were used to analyze causal association; Heterogeneity and multiplicity tests were also performed and analyzed using the leave-one-out method to assess the stability of the results.

Results: MR and reverse MR was utilized to assess the im-

pect of scoliosis on strabismus, revealing that the 95% confidence intervals of all instrumental variables' OR values spanned 1 and the P values were all above 0.05. These results indicate a lack of evidence supporting a causal relationship between scoliosis and strabismus.

Conclusion: There is currently no conclusive evidence of a genetic causal relationship between scoliosis and strabismus, including their subtypes. Further laboratory studies are needed to confirm these findings, and future research with larger sample sizes is necessary to provide more robust support.

Keywords: Spinal Curvature; Strabismus; Subgroup; Mendelian Randomization; Causal Association Analysis

Introduction

Scoliosis is a three-dimensional deformity of the spine characterized by abnormal curvature and vertebral rotation. Diagnosis typically involves a Cobb Angle exceeding 10° on the coronal plane of the spine orthography [1]. The deformity occurs during skeletal growth and affects approximately 1–4% of children. While the condition can have various causes, over 80% of cases are classified as idiopathic scoliosis [2]. Factors such as congenital or acquired vertebral structural diseases, brain stem asymmetry, sensory and balance issues, as well as platelet and collagen dysfunction can contribute to the development of scoliosis [3]. The resulting spinal curvature and deformation can lead to movement and proprioception issues, along with restricted thorax movement that can impact lung expansion and ventilation, affecting the physical and mental health of adolescents [4]. Severe cases of scoliosis may result in organ damage such as spinal cord compression, respiratory failure, and cardiovascular disease [5]. The pathogenesis of scoliosis may involve a combination of genetic, hormonal, endocrinological, and muscular factors [6], with a higher prevalence in females typically around the age of 10 [7]. The prevalence of scoliosis in children and adolescents ranges from 0.47% to 5.20% [8]. In recent years, the incidence of scoliosis has been increasing, making it a significant health concern alongside myopia and obesity. Scoliosis can be difficult to detect early on, and the progression tends to accelerate with greater angles, emphasizing the importance of timely intervention to avoid missing the optimal window for correction. Currently, scoliosis treatment options are categorized into non-

surgical and surgical approaches. Surgical treatment is known for its complexity, high risk, and resource-intensive nature. Non-surgical treatments are typically recommended for patients with mild scoliosis and include exercise therapy, breathing exercises, suspension therapy, chiropractic massage, electrical stimulation, traction therapy, and bracing. These methods are crucial for both preventing and managing scoliosis in most patients [9].

Strabismus, the misalignment of the eyes, encompasses various types such as esotropia and exotropia [10]. According to the 2017 clinical guidelines for esotropia and exotropia from the American Academy of Ophthalmology and the 'Expert Consensus on the Classification of Strabismus' by the Strabismus and Pediatric Ophthalmology Group of the Chinese Medical Association, esotropia includes infantile esotropia, acquired esotropia, and other types, while exotropia includes infantile exotropia, intermittent exotropia, convergence deficiency, and other types [10]. Classification based on eyeball and eye movement changes and strabismus angle includes Convergent concomitant strabismus (Ccs), Divergent concomitant strabismus (Dcs), Other specified and unspecified strabismus (Osus), and Other strabismus (Os) [11,12]. Treatment is recommended for all types of esotropia, with early detection and intervention being crucial for improving long-term visual, motor, and perceptual outcomes, as highlighted in the 2017 Preferred Practice Pattern. The guidelines also emphasize the impact of strabismus on children's quality of life and the negative effects of exotropia on children and parents' quality of life [13].

Recent clinical observational studies have indicated a potential association between visual and spinal curvature. The prevalence of scoliosis among both congenitally and acquired blind individuals has been reported to range from 42.9% to 59% [14]. A recent meta-analysis of literature involving a large sample of nearly 20,000 individuals demonstrated a 2.91 times increased risk of scoliosis in the visually impaired population. Subgroup analyses revealed that the risk of scoliosis was over 7 times higher in individuals with complete blindness, with three studies in the hyporefractive subgroup showing an elevated risk of scoliosis [15]. Two additional studies involving subjects with strabismus reported a 3.09-fold increased risk of scoliosis [15]. However, the causal relationship between strabismus and scoliosis remains uncertain, highlighting the need for further research to elucidate a potential link between these conditions.

Traditional observational epidemiological studies have faced challenges in identifying disease causes and making causal inferences, including issues like reverse causal association, potential confounders, microexposure factors, and multiple tests. Randomized control trials (RCTs) are often difficult to implement due to ethical constraints and experimental limitations when trying to establish a direct correlation between exposure factor X and disease outcome Y. Mendelian Randomization (MR) design, inspired by instrumental variable (IV) concepts from econometrics, uses gene variation as an instrumental variable for studying exposure factors [16]. This approach aims to estimate potential causal relationships between exposures and outcomes, offering a solution to the aforementioned challenges [17]. Genetic variation, randomly assigned during meiosis, is free from confounding and reverse causality, mimicking the effects of randomized controlled trials [18] and providing more accurate insights into causality [19]. In this study, strabismus and its subtypes were considered as exposure factors, scoliosis as outcome variables, and a two-sample MR Analysis was conducted to assess the causal relationship between strabismus and scoliosis, followed by reverse MR Validation analysis.

Materials and Methods

Research Design

This study utilized strabismus as the exposure factor, and single nucleotide polymorphisms (SNPs) significantly associated with it as instrumental variables (IVs).

Scoliosis was selected as the outcome variable, and genetic causal association analysis was conducted using the Two Sample MR package in R. The reliability of the results was verified through Cochran Q heterogeneity test, pleiotropy test, and sensitivity analysis. The study methodology adhered to three instrumental variable assumptions [20]: (1) significant association between instrumental variables and strabismus; (2) instrumental variables are unrelated to any potential confounding factors; (3) instrumental variables are not significantly associated with scoliosis (Figure 1). Q heterogeneity test, multiplicity test, and sensitivity analysis.

Data Sources

In this study, genome-wide association study data for scoliosis and strabismus and strabismus related subtyping were obtained from the website "<https://gwas.mrcieu.ac.uk/>". The included population was the European population.

Instrumental Variables

First, SNPs closely related to both strabismus and scoliosis with genome-wide significance ($P < 5 \times 10^{-5}$). Subsequently, SNPs strongly associated with strabismus were integrated with scoliosis data as instrumental variables, harmonizing the data with the effect allele frequency, while removing palindromic SNPs with intermediate allele frequencies and SNPs associated with confounding factors. Finally, the strength of the instrumental variable was evaluated by calculating the F value, with $F > 10$ indicating no weak instrumental variables. Ultimately, SNPs that are mutually independent and significantly associated with strabismus were obtained as the final instrumental variables [21]. The process of selecting strabismus-associated subtype's instrumental variables is consistent with the above.

MR Analysis

Statistical software R 4.3.1 and a significance level of $\alpha = 0.05$ were utilized in this research. Five MR Analyses were conducted to assess the causal relationship between strabismus and scoliosis. These analyses included inverse variance weighted (IVW), MR-Egger regression, weighted median (WME), simple mode (SM), and weighted mode (WM) [22]. IVW, the primary analysis model, utilized the inverse variance of each instrumental variable as weights and estimated the overall effect using the ratio method and weighted regression. MR-Egger regression method differs from IVW by considering an inter-

cept term and using the inverse of the outcome variance as weights. WME required at least 50% effective instrumental variables, and after sorting SNPs by weight, the median was used to estimate causal effects with good consistency. SM and

WM are modal-based estimation models that group SNPs with similar causal effects and provide estimates for most clustered SNPs. WM, in particular, assigns weights to each SNP based on the inverse variance of its effect.

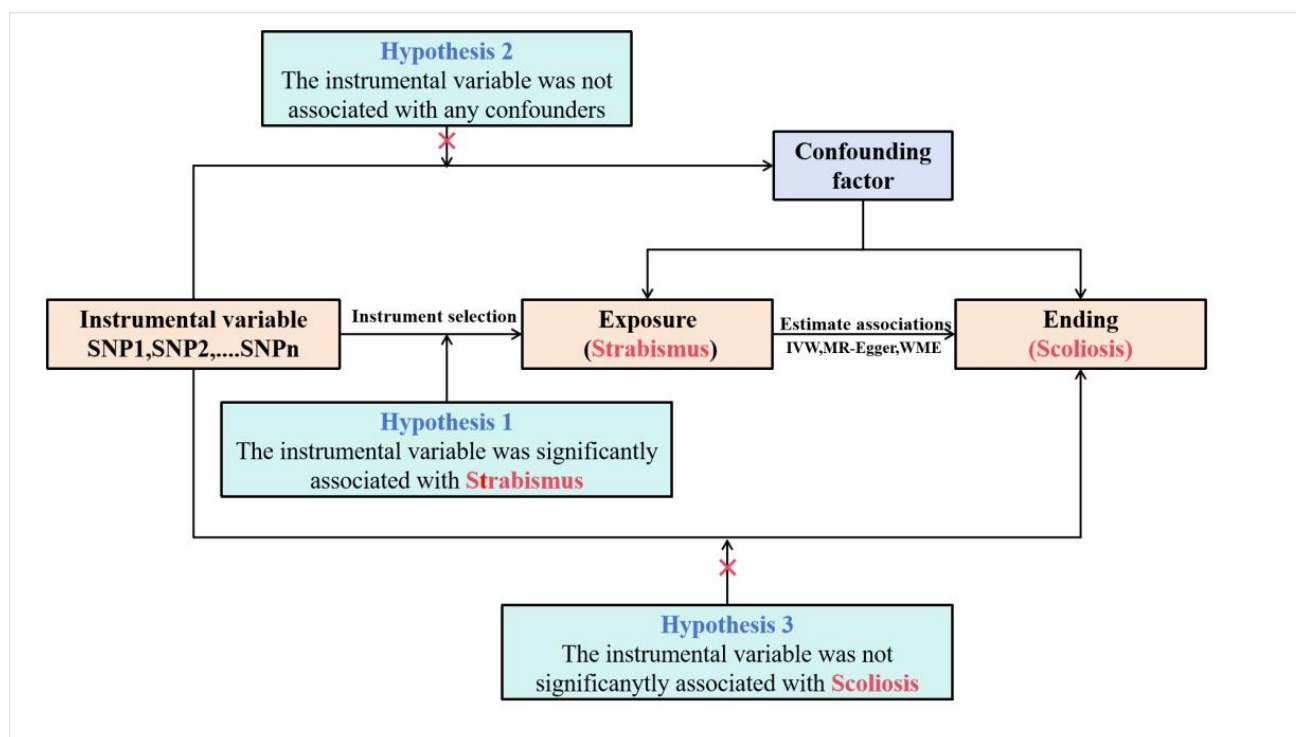


Figure 1: Design of the two-sample Mendelian randomization study

Sensitivity Analysis

Cochran Q test, MR-Egger regression, and leave-one-out analysis were employed to assess the robustness of the findings [23]. Cochran Q was utilized to evaluate differences among SNPs, with a significance level of $p < 0.05$ indicating heterogeneity. A MR-Egger regression intercepts term with $p < 0.05$ suggests potential horizontal pleiotropy among the instrumental variables. The leave-one-out method involved systematically removing SNPs one by one to assess the collective impact of the remaining SNPs on the results, thus examining the influence of individual SNPs.

Results

Population characteristics and SNP information for instrumental variables

There were six strabismus-related datasets including the UK Biobank (UKB) Finn Gen (Finn) databases Convergent concomitant strabismus (Ccs), Divergent concomitant strabis-

mus (Dcs), Other specified and unspecified strabismus (O-sus), and Subtype classification of Other strabismus (Os). . The UKB dataset focused on patients undergoing surgical correction of strabismus and had the largest sample size, consisting of 6117 patients, 456,816 controls, and 9.8 million SNPs. Additionally, a scoliosis dataset from the Finnish database comprised 1,168 individuals with the disease and 164,682 controls, with a total of 16.38 million SNPs. All datasets represented European populations and included both male and female individuals, with reference genomes of HG19/GRCh37 (Table 1).

Forward MR Analysis Results

Genetic causal relationship analysis between Strabismus and Scoliosis

This study utilized two datasets on strabismus (UKB-b-15527, finn-b-H7_STRABISMUS) as exposure variables and scoliosis (finn-b-M13_SCOLIOSIS) as the outcome to perform MR analyses on two separate samples. Following the screening for SNP sites with genome-wide significance and re-

removal of palindromic SNPs with intermediate allele frequencies, 44 and 15 SNPs were identified as instrumental variables, respectively. Various methods were employed to estimate the causal relationship between strabismus and scoliosis, with the results depicted in Figure 2 and Figure 3. The data analysis of ukb_Strabismus and finn_Scoliosis revealed

odds ratio (OR) values for the MR-Egger, WME, IVW, SM, and WM methods, with corresponding p-values of 0.101, 0.825, 0.791, 0.966, and 0.830, respectively. The IVW method suggested no causal link between strabismus and scoliosis, as all p-values > 0.05. Similar results were observed in the analysis of finn_Strabismus and finn_Scoliosis.

Table 1: Basic information about the data set

ID	Trait	Case(n)	Control(n)	SNPs(n)	Population	Build	Year
UKB-b-15527	Strabismus	6117	456816	9851867	European	HG19/GRCh37	2018
Finn-b-M13-SCOLIOSIS	Scoliosis	1168	164682	16380270	European	HG19/GRCh37	2021
Finn-b-H7-CONVERSTRAB	Ccs	967	210931	16380461	European	HG19/GRCh37	2021
Finn-b-H7-STRABISMUS	Strabismus	4620	214172	16380466	European	HG19/GRCh37	2021
Finn-b-H7-DIVERGSTRAB	Dcs	1348	210931	16380456	European	HG19/GRCh37	2021
Finn-b-H7-STRABISMUS	Osus	140	210931	16380456	European	HG19/GRCh37	2021
Finn-b-H7-STRABOTH	Os	3829	210931	16380463	European	HG19/GRCh37	2021

Note: Convergent concomitant strabismus (Ccs); Divergent concomitant strabismus(Dcs); Other specified and unspecified strabismus (Osus);Otherstrabismus(Os).

Heterogeneity tests were conducted on MR-Egger and IVW results. In the dataset analysis model of ukb_Strabismus, finn_Strabismus, and scoliosis, all heterogeneity test results were $p > 0.05$ (Table S1 and Figure S1), indicating the absence of heterogeneity. The intercept of the MR-Egger regression was utilized to assess pleiotropy in the study. The results revealed that the Egger-intercept values were all close to 0, with the re-

gression intercept term $p > 0.05$, suggesting no horizontal pleiotropy and no interference effects in the MR results (Table S2). A 'Leave-one-out' sensitivity analysis demonstrated that excluding a specific SNP did not significantly alter the IVW analysis results of the remaining SNPs, indicating no SNPs had a substantial impact on the estimated causal association (Figure S2).

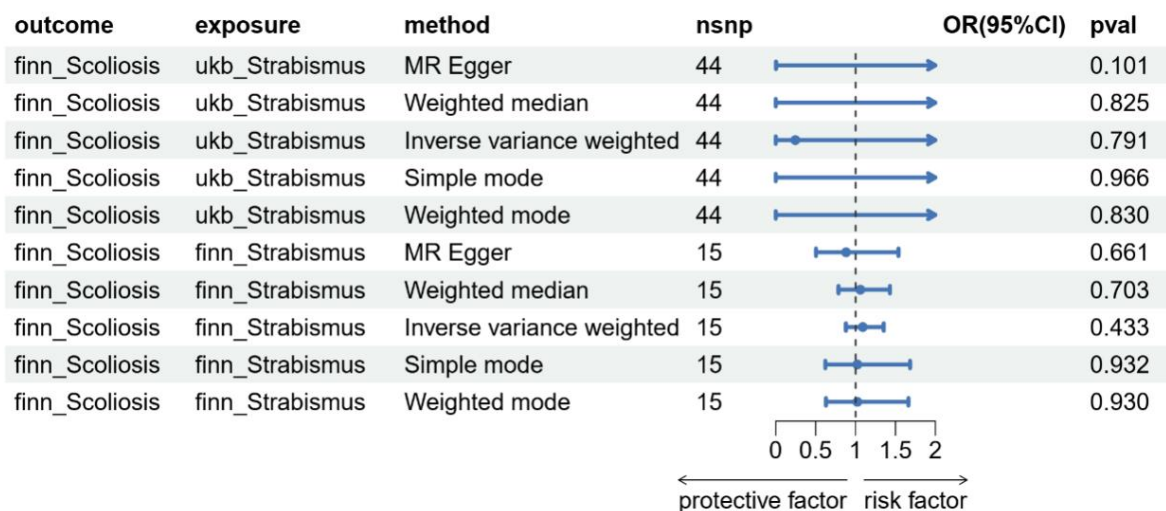


Figure 2: MR results of Strabismus and Scoliosis

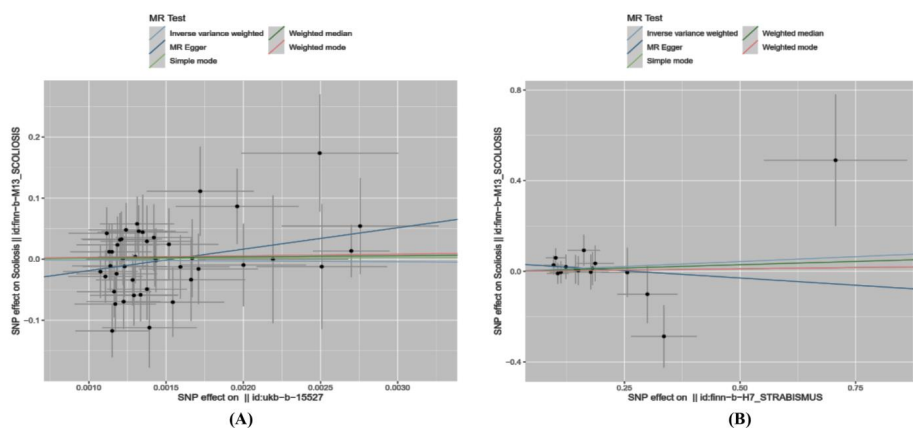


Figure 3: Mendelian randomized scatterplot of strabismus and scoliosis

((A) Mendelian randomized scatterplot of finn_Scoliosis and ukb_Strabismus; (B) Mendelian randomized scatterplot of finn_Scoliosis and finn_Strabismus.)

Genetic causal relationship between strabismus subtypes and scoliosis

The genetic causal relationship between Ccs, Dcs, Os, Osus, and scoliosis in strabismus subtypes was further analyzed. MR results for Ccs and scoliosis are presented in Figure 4 and Figure 5A. The P-values for the five MR inspection methods (MR-Egger, WME, IVW, SM, and WM) are 0.184, 0.422, 0.208, 0.651, and 0.617, respectively. Based on the IVW and MR-Egger models, it is concluded that there is no causal relationship between Ccs and scoliosis. Similarly, MR results for Dcs and scoliosis are shown in Figure 4 and Figure 5B. The P-values for the five test methods are 0.599, 0.109, 0.104, 0.083, and 0.698, respectively. Again, based on the IVW and MR-Egger models, it is concluded that there is no causal relationship between Dcs and scoliosis.

The MR results for Os and scoliosis are illustrated in Figure 4 and Figure 5C. The P-values for the five test methods were 0.682, 0.930, 0.735, 0.853, and 0.827, respectively. Based on the IVW and MR-Egger models, it can be inferred that there is no causal relationship between Os and scoliosis. The MR results for Osus and scoliosis are presented in Figure 4 and Figure 5D. The P-values for the five test methods were 0.285, 0.822, 0.560, 0.776, and 0.952, respectively. Similarly, the IVW and MR-Egger models suggest no causal relationship between Osus and scoliosis.

Model evaluation of causality between strabismus sub-

typing and scoliosis

Heterogeneity tests were conducted on MR-Egger and IVW, with all results indicating no heterogeneity between models (Table S3 and Figure S3). The intercept of MR-Egger regression was utilized to assess pleiotropy in the study. The Egger-intercept values were all near 0, with regression intercept $t_{\text{term}} > 0.05$, suggesting no horizontal pleiotropy and no interference in the MR results (Table S4). The 'Leave-one-out' sensitivity analysis demonstrated that excluding a specific SNP did not significantly alter the IVW analysis results of the remaining SNPs, indicating no single SNP had a substantial impact on the estimated causal association (Figure S4).

Results of Reverse MR Analysis

Based on the reverse MR analysis results (Figure 6-7), the IVW OR for ukb_Strabismus is 0.99 with a 95% CI of 0.998-1.000 and a P-value of 0.265. For finn_Scoliosis, the IVW OR is 1.010 with a 95% CI of 0.967-1.056 and a P-value of 0.630. It is currently inconclusive to state a clear association between scoliosis and strabismus. No significant causal relationship was found between the subtypes Ccs and Dcs of scoliosis and strabismus (Figure 8-9). Furthermore, no SNPs related to scoliosis were identified in Os and Osus. Cochran's IVW and MR-Egger's Q tests indicate no significant heterogeneity in the model (Tables S4, S7 and Figures S5, S7). MR-Egger regression intercept analysis (Tables S5, S6) and MR-PRESSO analysis also did not reveal significant horizontal pleiotropy (Figures S6, S8).

outcome	exposure	method	nsnp	OR(95%CI)	pval
Scoliosis	Concomitant Strabismus	MR Egger	25	1.0	0.184
Scoliosis	Concomitant Strabismus	Weighted median	25	1.0	0.422
Scoliosis	Concomitant Strabismus	Inverse variance weighted	25	1.0	0.208
Scoliosis	Concomitant Strabismus	Simple mode	25	1.0	0.651
Scoliosis	Concomitant Strabismus	Weighted mode	25	1.0	0.617
Scoliosis	Divergent concomitant strabismus	MR Egger	22	1.0	0.559
Scoliosis	Divergent concomitant strabismus	Weighted median	22	1.0	0.109
Scoliosis	Divergent concomitant strabismus	Inverse variance weighted	22	1.0	0.104
Scoliosis	Divergent concomitant strabismus	Simple mode	22	1.0	0.083
Scoliosis	Divergent concomitant strabismus	Weighted mode	22	1.0	0.698
Scoliosis	Other strabismus	MR Egger	19	1.0	0.682
Scoliosis	Other strabismus	Weighted median	19	1.0	0.930
Scoliosis	Other strabismus	Inverse variance weighted	19	1.0	0.735
Scoliosis	Other strabismus	Simple mode	19	1.0	0.853
Scoliosis	Other strabismus	Weighted mode	19	1.0	0.827
Scoliosis	Other specified and unspecified strabismus	MR Egger	11	1.0	0.285
Scoliosis	Other specified and unspecified strabismus	Weighted median	11	1.0	0.822
Scoliosis	Other specified and unspecified strabismus	Inverse variance weighted	11	1.0	0.560
Scoliosis	Other specified and unspecified strabismus	Simple mode	11	1.0	0.776
Scoliosis	Other specified and unspecified strabismus	Weighted mode	11	1.0	0.952

Figure 4: Mendelian randomized Results of strabismus Subtyping and Scoliosis

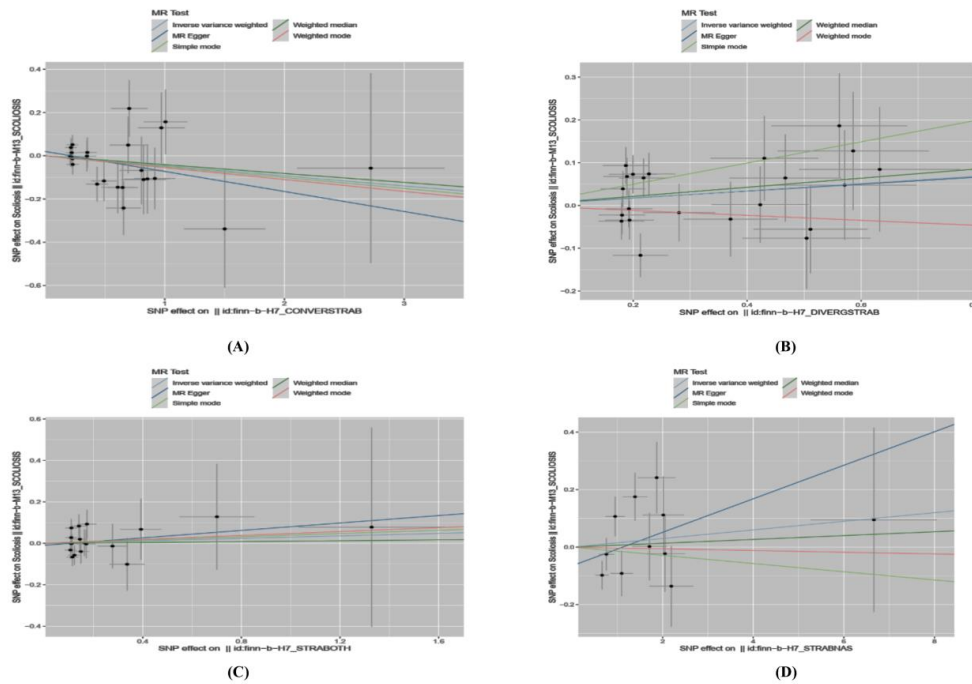


Figure 5: Mendelian randomized scatterplot of strabismus subtyping and scoliosis

((A)Mendelian randomized scatterplot of Ccsand scoliosis; (B) Mendelian randomized scatterplot of Dcsand scoliosis; (C)Mendelian randomized scatterplot of Osand scoliosis; (D)Mendelian randomized scatterplot of Osusand scoliosis.)

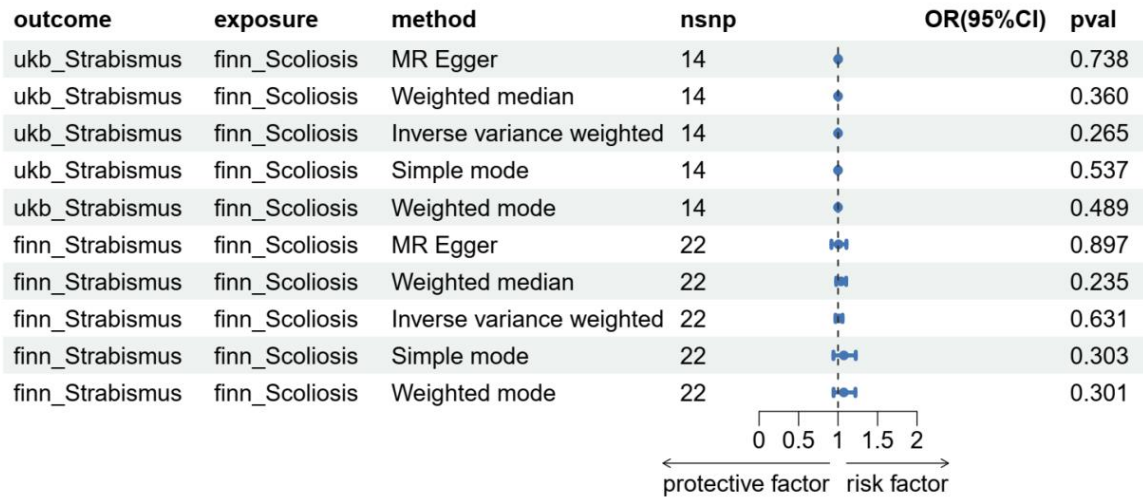


Figure 6: MR Results of strabismus and scoliosis

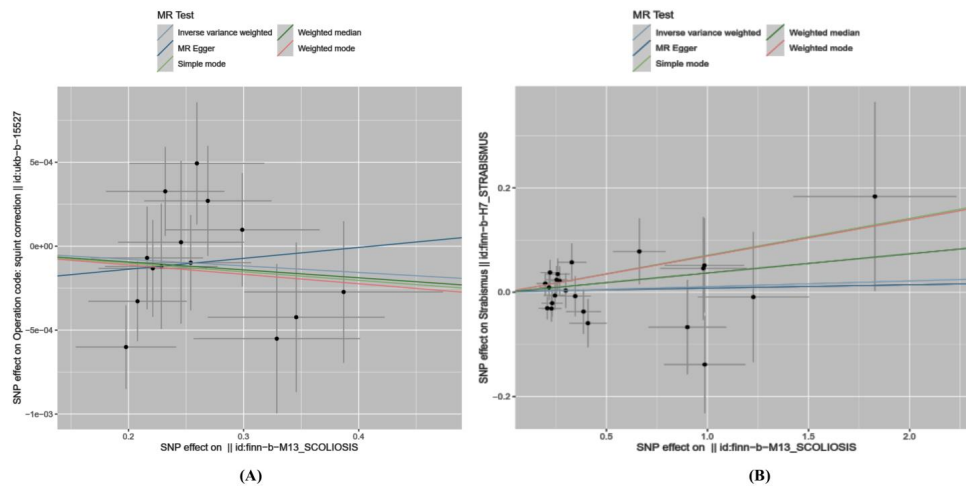


Figure 7: Mendelian randomized scatterplot of strabismus and scoliosis

((A) Scatterplot of ukb_Strabismus for finn_Scoliosis; (B) Scatter plot of finn_Strabismus for finn_Scoliosis.)

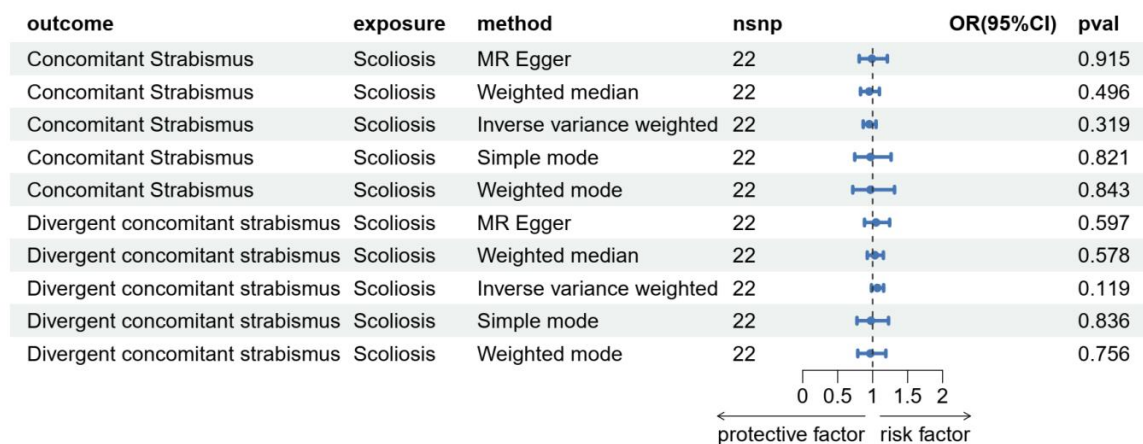


Figure 8: Mendelian randomized Results of strabismus subtyping and scoliosis

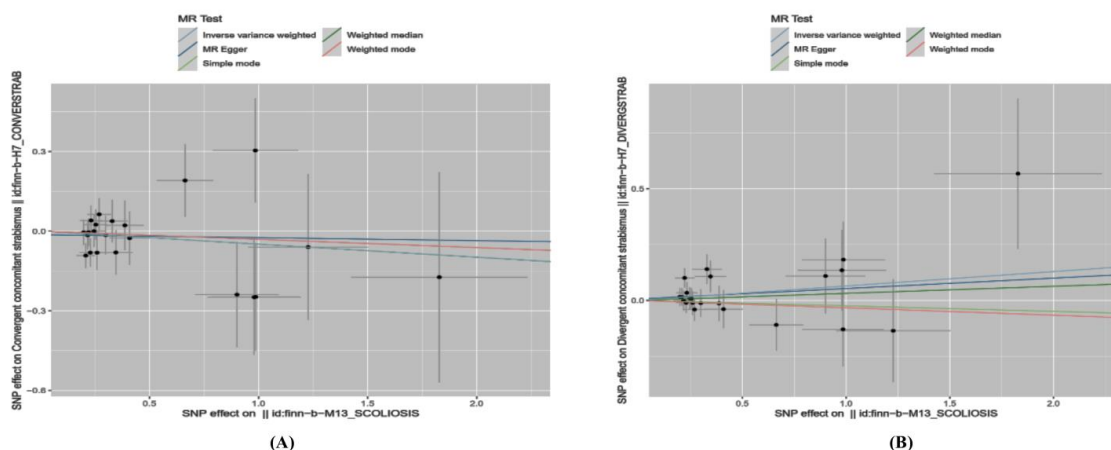


Figure 9: Mendelian randomized scatterplot of strabismus subtyping and scoliosis

((A) Scatterplot between Ccs and finn_Scoliosis (B) scatterplot between Dcs and finn_Scoliosis.)

Discussion

Mendelian randomization investigations are dependent on the availability of studies with linked genetic and epidemiological data. These have expanded in several directions in recent years: in size, in coverage, and in scope. Larger sample sizes enable more powerful analyses, as well as adequately powered analyses in population subgroups. This study explores the causal effect of strabismus and its subtypes on scoliosis using MR results. It suggests a genetic direction for further investigation, finding no evidence to support a causal effect of specific type of strabismus on scoliosis. These findings offer a fresh perspective on the mechanisms of visual abnormalities in scoliosis.

Scoliosis is a complex disease with genetic factors playing a significant role in its development. Despite extensive research, the exact genetic mechanisms are still not fully understood and show a lot of variation. Familial idiopathic scoliosis has been linked to various chromosomal regions, suggesting a polygenic inheritance pattern that requires further investigation to identify specific genetic factors [24]. For instance, genetic factors related to connective tissue structure, bone formation, melatonin signaling, puberty, and growth have all been associated with idiopathic scoliosis, indicating a complex genetic component influenced by ethnic and genetic diversity. Studies have demonstrated that idiopathic scoliosis may have a genetic basis with different inheritance patterns such as autosomal dominant, X-linked, polygenic, or multifactorial inheritance, leading to a complex genetic pattern due to

locus and allelic heterogeneity [25]. Dysregulation of Wnt signaling, as observed in Ptk7 mutant zebrafish, is linked to congenital and idiopathic scoliosis [26]. Polymorphisms in the chromodomain helicase DNA binding protein 7 Gene (CHD7) gene are associated with idiopathic scoliosis [27,28]. Gene-environment interactions, like the interplay between Notch signaling pathway gene haplo insufficiency and prenatal hypoxia, contribute to congenital scoliosis development, underscoring the intricate role of genetic and environmental factors [29]. A compound inheritance pattern involving rare null mutations and hypoalleles of the T-box transcription factor 6 (TBX6) gene was identified in a subset of congenital scoliosis cases, accounting for 11% of cases [30]. Overall, research indicates a significant genetic component in scoliosis, with multiple genes and pathways playing a role in its pathogenesis. Various inheritance patterns and gene-environment interactions further contribute to its complexity.

Many family members have a shared strabismus, indicating that strabismus may have a genetic component. Studies have found that nucleotide polymorphisms in certain genes are highly correlated with strabismus subtypes [31]. Studies have shown that gene mutations necessary for the normal development and connection of brainstem ocular motor neurons, such as PHOX2A, SALL4, KIF21A, ROBO3, and HOXA1, are associated with congenital strabismus syndrome. Meanwhile, strabismus in families is associated with chromosome 7p22.1. Genetic susceptibility exists at susceptibility loci, indicating genetic heterogeneity between strabismus and families [32]. The heritability of strabismus has a great impact on esotropia,

and the genetic effect is limited to esotropia and is not related to ametropia, suggesting that genetic factors may not play an important role in exotropia [33]. Genetic variants within the NPLOC4-TSPAN10-PDE6G gene cluster on chromosome 17q25 are associated with an increased risk of strabismus, with a population attributable risk of approximately 8.4% [34]. In summary, this suggests that certain types of strabismus have a strong genetic component. Genetic heterogeneity is evident, with different genes and loci associated with different forms of the disease. These findings highlight the complexity of strabismus genetics and point to specific biological pathways and brain regions that may be involved in its pathogenesis.

Previous research has indicated that the CHD7 gene is associated with susceptibility to adolescent idiopathic scoliosis and shares commonalities with the rare CHARGE syndrome. Mutations, such as missense and splicing mutations, in the coding exon of the CHD7 gene have been linked to CHARGE syndrome, with approximately 60% of patients exhibiting symptoms like eye diseases and heart defects. However, the mortality rate among infants with CHARGE syndrome is notably high, and there is a scarcity of research data on this condition. Studies on ROBO3 gene polymorphisms have revealed a connection to the development of horizontal gaze palsy. Notably, a specific ROBO3 gene variation (rs74787566) has been significantly associated with adolescent idiopathic scoliosis [35]. The correlation between certain ROBO3 gene polymorphisms and strabismus disorder aligns with previous findings that individuals with strabismus have a higher prevalence of idiopathic scoliosis, particularly those with exotropia [36,37]. Visual impairments associated with idiopathic scoliosis can range from severe visual impairment to myopia and heterosopia (refractive errors in both eyes). Animal studies have shown that early-onset strabismus can disrupt the astigmatism process, leading to heteropia. Early hyperopic strabismus is a significant risk factor for amblyopia, while early esotropia can result in both strabismus and amblyopia [38]. Research has suggested that thinning of the choroidal layer of the eye may underlie the development of anisotropy, with amblyopia, refractive error, and strabismus potentially coexisting. Therefore needs to be confirmed by further studies [39].

There is currently insufficient evidence to support a genetic risk for both strabismus and scoliosis. Previous research has indicated that various visual impairments, including blind-

ness, refractive errors, and strabismus, may increase the likelihood of developing scoliosis [15]. However, further studies are required to comprehensively understand the genetic link between these conditions. Our study utilized data from large cohorts in the UK Biobank and Finnish databases to explore the genetic relationship between strabismus and scoliosis in terms of single nucleotide polymorphisms. Our findings suggest that there is no direct causal connection between strabismus and scoliosis. This conclusion is supported by the limitations of existing studies, which often rely on cross-sectional methods and lack consistency in evaluating scoliosis cases. Additionally, our study is limited by its focus on European populations, which may not be generalizable to other groups. Furthermore, subgroup analyses based on age, health status, and gender were not feasible due to data constraints [40].

This study offers several advantages. While randomized controlled trials are considered a robust clinical research method, they can be costly, challenging to track over time, and complex to execute in practice. In this study, the two-sample Mendelian randomization research design was utilized to minimize the impact of confounding variables and reverse causality, effectively emulating a randomized controlled trial. Additionally, the study carefully selected single nucleotide polymorphisms highly correlated with the exposure of interest as instrumental variables, and employed sensitivity analysis techniques to validate the research findings.

Conclusion

Ultimately, the study concludes that there is no current evidence supporting a causal relationship between strabismus and its associated subtypes with scoliosis. The findings of this study offer a fresh perspective for further investigating the underlying mechanisms of scoliosis in individuals with visual impairments.

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Conflicts of Interest

The authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

Availability of Data and Material

All data used to support the findings of this study are included within the article.

Code Availability

Not applicable.

Authors' Contributions

Dr Liguozhu conceptualized, conceived and designed the re-

view. Dr Changsui Yu, Dr Zifeng Xu and Dr Xiaofeng Zhang wrote the first draft of the manuscript and critically revised the final manuscript. Dr Zhongbao Yu, Shuren Wang and Kejian Lu wrote sections and guided part of the manuscript. Dr Fengyuan Zhan and Kun Zhang conceived and drafted the figures. All of the authors contributed to the article and approved the submitted version.

Ethics Approval

Not applicable.

Consent to Participate

Not applicable.

Consent for Publication

Not applicable.

References

- Lai B, Jiang H, Gao Y, Zhou X (2023) Causal effects of gut microbiota on scoliosis: a bidirectional two-sample mendelian randomization study. *Heliyon*, 9: e21654.
- Negrini S, Donzelli S, Aulisa AG, Czaprowski D, Schreiber S, et al. (2018) Consort guidelines: orthopaedic and rehabilitation treatment of idiopathic scoliosis during growth. *Scoliosis Spinal Disord*, 13: 3.
- Yetiş M, Yildiz NT, Canli M, Kocaman H, Yildirim H, et al. (2024) Determination of predictors associated with pain in non surgically treated adults with idiopathic scoliosis. *J Orthop Surg Res*. 19: 406.
- Xu S, Su Y, Wang Z, Liu C, Jin L, Liu H (2021) The prevalence and characteristics of primary and middle-school students in China: a Meta-analysis based on 72 epidemiological research. *Chin. J. Spine Spinal Cord*, 31: 901-10.
- Kemta Lekpa F, Eloundou P, Moulion Tapouh JR, Simeni Njonnou SR, Fojo Talongong B, et al. (2024) Clinical presentation and imaging findings in juvenile-onset back pain: a ten-year hospital-based retrospective analysis in Douala (Cameroon). *Front Pediatr*. 12: 1424391.
- Peng Y, Wang SR, Qiu GX, Zhang JG, Zhuang QY (2020) Research progress on the etiology and pathogenesis of adolescent idiopathic scoliosis. *Chin. Med. J.* 133: 483-93.
- Zhu Z, Tang NL, Xu L, Qin X, Mao S, et al. (2015) Genome-wide association study identifies new susceptibility loci for adolescent idiopathic scoliosis in chinese girls. *Nat. Commun*, 6: 8355.
- Konieczny MR, Senyurt H, Krauspe R (2013) Epidemiology of adolescent idiopathic scoliosis. *J. Child. Orthop*. 7: 3-9.
- Wang A, Ji Z, Chen H, Yang Q, Yang Q (2023) Research progress on influencing factors and clinical treatment of adolescent scoliosis. *IMHGN*, 29: 3176-80.
- Zhao C, Yao J (2020) Standardizing the diagnosis and treatment of strabismus: interpreting the 2017 clinical guidelines for esotropia and exotropia of the American Academy of Ophthalmology. *Chin J Ophthalmol*, 56: 176-82.
- Hao J, Wang M, Liu J, Yusufu M, Cao K, Fu J (2024) Alteration of neurotrophic factors and innervation in extraocular muscles of individuals with concomitant esotropia. *Invest. Ophthalmol. Vis. Sci.* 65: 1.
- Hashemi H, Pakzad R, Heydarian S, Yekta A, Aghamirsalim M, et al. (2019) Global and regional prevalence of strabismus: a comprehensive systematic review and meta-analysis. *Strabismus*, 27: 54-65.
- Jones-Jordan L, Wang X, Scherer RW, Mutti DO (2014) Spectacle correction versus no spectacles for prevention of strabismus in hyperopic children. *Cochrane Database Syst Rev*. 8: CD7738.
- Wallnöfer A, Burgstaller JM, Weiss K, Rosemann T, Senn O, Markun S (2024) Developing and testing a framework for coding general practitioners' free-text diagnoses in electronic medical records - a reliability study for generating training data in natural language processing. *BMC Prim Care*. 25: 257.
- Gallego-Siles JR, Siles-Fuentes MJ, Ibanez-Vera AJ, Cortes-Perez I, Obrero-Gaitan E, Lomas-Vega R (2024) Idiopathic scoliosis in subjects with eye diseases: a systematic review with meta-analysis. *Ann. N.Y. Acad. Sci.*
- Birney E (2022) Mendelian randomization. *Cold Spring Harb. Perspect. Med*. 12.
- Kim DJ, Dermott JA, Mitani AA, Doria AS, Howard AW, Lebel DE (2024) The diagnostic accuracy of community spine radiology for adolescent idiopathic scoliosis brace candidates. *Eur Spine J*.
- Ni JJ, Li XS, Zhang H, Xu Q, Wei XT, et al. (2022) Feng, G. J.; Zhao, M.; Zhang, Z. J.; Zhang, L.; Shen, G. H.; et al. Mendelian randomization study of causal link from gut microbiota to colorectal cancer. *Bmc Cancer*, 22: 1371.
- Wang C, Wu W, Yang H, Ye Z, Zhao Y, et al. (2022) Mendelian randomization analyses for pcos: evidence, opportunities, and challenges. *Trends Genet*. 38: 468-82.
- Carrasquilla GD, Garcia-Urena M, Fall T, Sorensen T, Kilpelainen TO (2022) Mendelian randomization suggests a bidirectional, causal relationship between physical inactivity and adiposity. *Elife*, 11.

21. Weith M, Beyer A (2023) The next step in mendelian randomization. *Elife*, 12,
22. Yuan S, Mason AM, Titova OE, Vithayathil M, Kar S, et al. (2023) Morning chronotype and digestive tract cancers: mendelian randomization study. *Int. J. Cancer*, 152: 697-704.
23. Sanderson E (2021) Multivariable mendelian randomization and mediation. *Cold Spring Harb. Perspect. Med.* 11.
24. Larsson SC, Butterworth AS, Burgess S (2023) Mendelian randomization for cardiovascular diseases: principles and applications. *Eur Heart J.* 44: 4913-24.
25. Zhou L, Cui X, Mo G, Wei J, Mo M, Zhong Y (2024) Immediate fever during anaesthesia recovery after surgical procedure with scoliosis: A case report and literature review. *Int J Surg Case Rep.* 121: 110027.
26. Hayes M, Gao X, Yu LX, Paria N, Henkelman RM, et al. (2014) B. Ptk7 mutant zebrafish models of congenital and idiopathic scoliosis implicate dysregulated wnt signalling in disease. *Nat. Commun.* 5: 4777.
27. Borysiak K, Janusz P, Andrusiewicz M, Chmielewska M, Kozinoga M, et al. (2020) Chd7 gene polymorphisms in female patients with idiopathic scoliosis. *Bmc Musculoskelet. Disord*, 21: 18.
28. Wang W, Chen T, Liu Y, Wang S, Yang N, Luo M (2022) Predictive value of single-nucleotide polymorphisms in curve progression of adolescent idiopathic scoliosis. *Eur. Spine J.* 31: 2311-25.
29. Sparrow DB, Chapman G, Smith AJ, Mattar MZ, Major JA, et al. (2012) A mechanism for gene-environment interaction in the etiology of congenital scoliosis. *Cell.* 149: 295-306.
30. Wu N, Ming X, Xiao J, Wu Z, Chen X, et al. (2015) Tbx6 null variants and a common hypomorphic allele in congenital scoliosis. *N. Engl. J. Med.* 372: 341-50.
31. Bowden J, Holmes MV (2019) Meta-analysis and Mendelian randomization: A review. *Res Synth Methods.* 10: 486-96.
32. Yeung CHC, Schooling CM (2021) Systemic inflammatory regulators and risk of Alzheimer's disease: a bidirectional Mendelian-randomization study. *Int J Epidemiol.* 50: 829-40.
33. Sanfilippo PG, Hammond CJ, Staffieri SE, Kearns LS, Melissa LS, et al. (2012) Heritability of strabismus: genetic influence is specific to eso-deviation and independent of refractive error. *Twin Res. Hum. Genet.* 15: 624-30.
34. Plotnikov D, Shah RL, Rodrigues JN, Cumberland PM, Rahi JS, et al. (2019) A commonly occurring genetic variant within the nploc4-tspan10-pde6g gene cluster is associated with the risk of strabismus. *Hum. Genet.* 138: 723-37.
35. Zhang Z, Zhang Z, Shu L, Meng Y, Ma J, Gao R, Zhou X (2023) A genetic variant of the robo3 gene is associated with adolescent idiopathic scoliosis in the chinese population. *Spine*, 48: E20-4,
36. Pan XX, Huang CA, Lin JL, Zhang ZJ, Shi YF, et al. (2020) Prevalence of the thoracic scoliosis in children and adolescents candidates for strabismus surgery: results from a 1935--patient cross-sectional study in china. *Eur. Spine J.* 29: 786-93.
37. Zhu B, Wang X, Fu L, Yan J (2022) Pattern strabismus in a tertiary hospital in southern china: a retrospective review. *Med. Lith.* 58.
38. Smith ER, Hung LF, Arumugam B, Wensveen JM, Chino YM, et al. (2017) Observations on the relationship between anisometropia, amblyopia and strabismus. *Vision Res.* 134: 26-42.
39. Karaca EE, Cubuk MO, Akcam HT, Uzun F, Yuksel E (2017) Choroidal thickness in turkish children with anisometric amblyopia. *Semin. Ophthalmol.* 32: 291-6.
40. Damask A, Paulding C, Baras A, Carey D, Abecasis GR (2020) Mendelian randomization study of acly and cardiovascular disease. *N. Engl. J. Med.* 383: e50.