

## ORIGINAL RESEARCH ARTICLE

# Educational attainment, screen time, body height, physical activity, sleep duration, and risk of astigmatism: A Mendelian randomization study

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**Citation:** Zhu C, Fan H, Zhang N, *et al.* Educational attainment, screen time, body height, physical activity, sleep duration, and risk of astigmatism: A Mendelian randomization study. *Gene Protein Dis.* 2026;5(2):025140030. doi: 10.36922/GPD025140030

**Received:** April 5, 2025

**Revised:** February 6, 2026

**Accepted:** February 9, 2026

**Published online:** April 29, 2026

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## Abstract

Astigmatism is a common refractive error with substantial visual and public health implications, yet its underlying causal determinants remain incompletely understood. To assess the independent causal effects of educational attainment, screen time, body height, sleep duration, and physical activity on astigmatism, we conducted a Mendelian randomization (MR) study. This analysis was based on a two-sample MR design using publicly available genome-wide association study summary data from individuals of European descent. Genetic variants significantly associated with each exposure at the genome-wide level were chosen as instrumental variables. Causal associations were primarily estimated using the inverse variance-weighted (IVW) method, while weighted median and MR-Egger approaches were applied to evaluate the robustness of the results. Heterogeneity and pleiotropy were assessed with Cochran's Q, MR-Egger intercept, MR-PRESSO, and leave-one-out analyses. The findings from IVW indicated that higher educational attainment (odds ratio [OR] = 1.058; 95% confidence interval [CI] = 1.048–1.067;  $p = 1.91 \times 10^{-32}$ ), longer screen time (OR = 1.028; 95% CI = 1.016–1.041;  $p = 3.19 \times 10^{-6}$ ), and greater body height (OR = 1.004; 95% CI = 1.002–1.006;  $p = 4.00 \times 10^{-4}$ ) were causally associated with increased astigmatism risk. No evidence supported causal effects for physical activity or sleep duration. Sensitivity analyses (weighted median, MR-Egger, MR-PRESSO, leave-one-out) yielded consistent results and did not indicate directional pleiotropy. Our MR study supports causal roles for educational attainment, screen time, and body height in astigmatism development among individuals of European ancestry. These findings highlight potential targets for early screening and motivate mechanistic studies to clarify biological pathways.

**Keywords:** Mendelian randomization; Astigmatism; Educational attainment; Screen time; Body height

## 1. Introduction

Astigmatism is a common refractive error characterized by unequal refractive power across ocular meridians, causing light to focus at different planes rather than at a single point on the retina; it remains uncorrectable through changes in viewing distance or standard optical prescriptions.<sup>1</sup> Affecting more than 40% of cataract patients, astigmatism is a growing public health problem.<sup>2</sup> The challenges of correcting astigmatism often result in under-correction, which can impair visual acuity.<sup>3,4</sup> Therefore, identifying risk factors for astigmatism is clinically important.

Several large population-based observational studies have reported correlations between education, near-work, digital device exposure, body size, and refractive errors (including astigmatism), but with inconsistent magnitudes and directions across age groups and geographic settings. These discrepancies likely arise from heterogeneity in phenotype definitions (e.g., corneal astigmatism vs. refractive astigmatism), age at measurement, environmental context (urban vs. rural), and measurement methods (cycloplegic vs non-cycloplegic refraction).<sup>5</sup>

Mechanistically, prolonged near-work and extended periods of screen exposure during critical ocular development windows could influence anterior segment morphology through accommodative stress, eyelid position changes, tear film alterations, and changes in corneal biomechanics.<sup>6</sup> Growth-related factors such as stature may be markers of systemic growth hormone exposure and skeletal development patterns that also influence ocular axial length and corneal curvature.<sup>7</sup> Importantly, educational attainment and screen time are socially patterned exposures tied to socioeconomic status, learning environment, and behaviors that may confound observational associations; Mendelian randomization (MR) offers an approach to partially separate lifelong genetic propensity to these exposures from short-term environmental confounding.<sup>8</sup> Finally, because astigmatism affects visual function, educational performance, and quality of life—and because correction often remains suboptimal—identifying modifiable upstream causes is clinically relevant. This provides a rationale for applying genetic epidemiology tools to refine etiologic inference and prioritize interventions.

Although several factors have been associated with astigmatism, the exact causes of astigmatism remain unclear. Studies have suggested that modifiable risk factors, such as educational attainment, may play a role.<sup>9–11</sup> Screen time<sup>12–14</sup>, body height<sup>15,16</sup>, sleep duration<sup>17,18</sup>, and physical activity<sup>19</sup> may influence the development of astigmatism, but the evidence remains weak and inconsistent. Current findings remain inconclusive regarding the direct

contribution of these exposures to astigmatism risk, largely due to inadequate sample sizes and residual confounding. Further well-designed studies are needed to clarify these associations. However, conducting randomized controlled trials is challenging due to human, financial, and ethical constraints.

Over the past few years, genome-wide association studies (GWAS) have experienced rapid development and have effectively uncovered associations for a wide range of common genetic variants.<sup>20,21</sup> These advances enable a more robust exploration of independent causal relationships between suspected risk factors and astigmatism. Within genetic epidemiology, MR capitalizes on the random assortment of genetic variants at conception, applying genotype-based instrumental variables to assess causal associations between exposures and disease outcomes.<sup>22,23</sup> From a theoretical perspective, MR is able to mitigate confounding, minimize the risk of reverse causation, and yield statistically reliable causal inferences.<sup>24,25</sup> MR has been widely used to study the causality of risk factors for various diseases<sup>26</sup>, leveraging valuable data from GWAS.<sup>27</sup> However, MR has not been used to investigate the causal relationship between specific potential risk factors and astigmatism.

Using an MR approach, this study systematically evaluated the potential causal roles of educational attainment, screen time, body height, physical activity, and sleep duration in astigmatism. The analyses revealed that educational attainment, screen time, and body height are important contributors to the risk of developing astigmatism.

## 2. Data sources and methods

### 2.1. Mendelian randomization

Mendelian randomization serves as a tool for investigating causal relationships between modifiable risk factors and clinically relevant endpoints. It is particularly advantageous when randomized controlled trials cannot be conducted, and observational evidence is limited by confounding bias or reverse causality. MR uses genetic variants as instrumental variables to detect exposure and overcomes these problems because alleles of genetic variants associated with exposure are randomly assigned and not subject to reverse causation. This method, together with the abundance of published genetic association data available for screening appropriate genetic instrumental variables, makes MR a time-saving and cost-effective approach that is becoming increasingly popular for assessing and screening potential causal associations. Observed relationships between the genetic instrumental variables and the outcome are consistent with a causal

association between the exposure under investigation and the clinical outcome.

## 2.2. Data sources

Body height data were derived from the 2021 dataset EBI-A-GCST90018959, which contains 19,028,518 single-nucleotide polymorphisms (SNPs) and 360,388 samples from European populations, both male and female. Data on screen time were sourced from the 2017 UKB-A-6 dataset, which includes 10,894,596 SNPs from a sample of 261,987 European individuals, both male and female. Physical activity data were derived from the 2018 dataset UKB-B-13184, which contains 9,851,867 SNPs from a sample of 460,376 European individuals, both male and female. Sleep duration data were obtained from the 2018 dataset UKB-B-4424, which includes 9,851,867 SNPs from 460,099 European samples, both male and female. Educational attainment data were from the 2018 dataset EBI-A-GCST90029012, comprising 11,972,619 SNPs from 470,941 European samples, both male and female. The outcome variable, astigmatism, was derived from the 2017 dataset UKB-A-422, which contains 10,894,596 SNPs from 326,836 European samples, both male and female. Because the analyses were based on previously published datasets from populations of European descent, no new ethical approval was needed for this study.

Regarding phenotype definitions and harmonization, for each exposure and the astigmatism outcome, we carefully harmonized effect alleles and aligned SNPs to the reference strand. Exposures were defined according to the original GWAS publications: educational attainment was coded as years of schooling; screen time represented self-reported average daily leisure screen use; body height was measured in centimeters; physical activity and sleep duration were self-reported as standard UK Biobank phenotypes. The astigmatism outcome was defined using International Classification of Diseases-coded diagnoses and self-report items as in the source GWAS; where multiple phenotype definitions existed, we used the primary summary statistics provided by the GWAS consortium. Palindromic SNPs with ambiguous allele frequency were excluded to avoid strand misalignment.

For instrument selection and strength, genome-wide significant SNPs ( $p < 5 \times 10^{-8}$ ) were clumped at  $r^2 < 0.001$  within 10,000 kb windows. We computed the  $F$ -statistic for each instrument and excluded SNPs with  $F \leq 10$  to reduce weak-instrument bias. For multi-allelic exposures, we used many-SNP instruments and evaluated their collective strength using the mean  $F$ -statistic and variance explained ( $R^2$ ).

## 2.3. Detailed methods

To guarantee the reliability and validity of the findings, instrumental variable SNPs were selected in accordance with the three fundamental assumptions of MR: correlation, exclusion restriction, and independence. The European reference panel from the 1000 Genomes Project was used for linkage disequilibrium clumping. For each exposure, SNPs associated at genome-wide significance ( $p < 5 \times 10^{-8}$ ) were selected as instrumental variables. The linkage disequilibrium threshold ( $r^2$ ) was set at 0.001, and the distance parameter ( $k$ ) was set at 10,000 kb. SNPs with the smallest  $p$ -values were selected to ensure independence between instrumental variables and to exclude the effects of linkage disequilibrium. An  $F$ -test value  $> 10$  was used to indicate no bias from weak instrumental variables. To avoid the influence of weak instruments, only SNPs with  $F$ -test values  $> 10$  were included, and SNPs with palindromic structures were excluded.

We conducted MR analyses of the causal relationships between educational attainment, screen time, body height, physical activity, sleep duration, and astigmatism using the TwoSampleMR and MR-PRESSO packages in R v.4.4.0 software (<https://www.r-project.org>). The primary MR analysis method was the random effects inverse variance-weighted (IVW) approach, supplemented by the weighted median (WM) approach. Statistical significance was set at  $p < 0.05$ .

## 2.4. Statistical analysis

MR-Egger regression was used to assess directional pleiotropy and to generate an additional causal estimate (Figure 1). The MR-Egger intercept test estimates potential horizontal pleiotropy if the intercept term is significant. The MR-PRESSO method was also used to identify and exclude potential horizontal pleiotropy outliers that may seriously affect the estimation results. Cochran's  $Q$  test for heterogeneity and the MR-Egger intercept test were used to estimate potential horizontal pleiotropy and to assess the robustness of causality. The MR-PRESSO method excluded possible horizontal pleiotropy outliers, and the MR analysis was repeated after removing these outliers (Figure 2). The leave-one-out method sequentially excluded SNPs to test whether their removal led to biased causal estimates. Funnel plots assessed the symmetry of the selected SNPs, forest plots assessed the confidence and heterogeneity of the estimates, and scatter plots analyzed the exposure-outcome relationship. All results were expressed as odds ratios (OR) with 95% confidence intervals (95% CI). Statistical significance was defined as  $p < 0.05$  for all methods, and all analyses were performed using R software.

### 3. Results

We investigated whether educational attainment, screen time, body height, sleep duration, and physical activity have independent causal effects on astigmatism using MR. The IVW method showed that higher educational attainment (OR = 1.058, 95% CI = 1.048–1.067;  $p = 1.91 \times 10^{-32}$ ), longer screen time (OR = 1.028, 95% CI = 1.016–1.041;  $p = 3.19 \times 10^{-6}$ ), and greater body height (OR = 1.004, 95% CI = 1.002–1.006;  $p = 4 \times 10^{-4}$ ) were associated with an increased risk of astigmatism. Conversely, there was no significant causal relationship between physical activity, sleep duration, and astigmatism. More detailed data are presented in Table 1. For educational attainment and screen time, the WM and MR-Egger methods were in agreement with the IVW method, indicating directionally consistent estimates across methods. For body height, the WM and IVW methods also showed consistent results.

Based on the IVW method analysis, we used the MR-PRESSO test to exclude outliers, Cochran's Q test for heterogeneity, and MR-Egger regression to assess horizontal pleiotropy among the SNPs. Although Cochran's Q tests for educational attainment, screen time, body height, and sleep duration indicated heterogeneity ( $p < 0.05$ ), the use of a random effects model minimized the impact of this heterogeneity on our analysis. Thus, our conclusions are primarily based on the IVW method.<sup>28</sup>

No outliers were found for educational attainment and screen time. The causal relationship between body height and astigmatism remained significant after excluding three outliers. To address potential horizontal pleiotropy, we applied the MR-Egger intercept test, which yielded p-values greater than 0.05 for all intercepts, indicating no pleiotropy affecting the causal relationship (Figures 3–5).

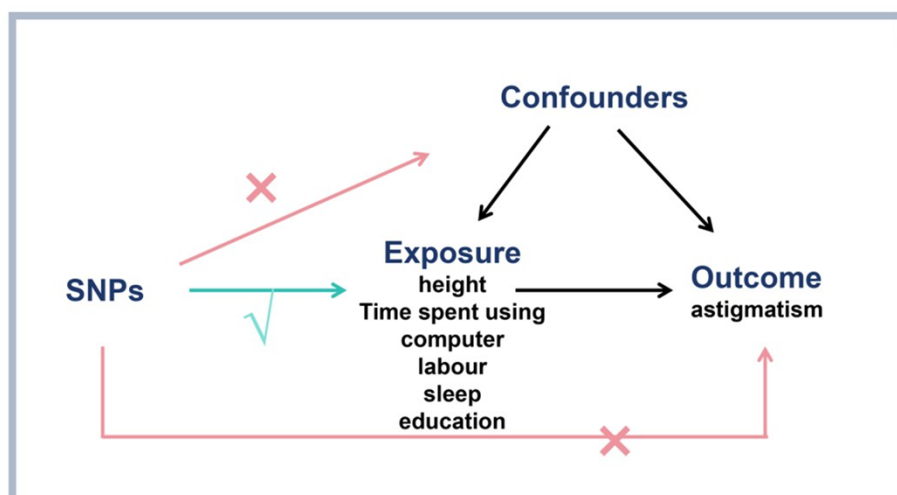
A leave-one-out analysis confirmed that the causality was not driven by a single SNP (Figures S1–S3). The sensitivity analyses did not indicate that the observed associations were driven by any single SNP. The forest plot highlighted the role of individual SNPs, with all SNPs for educational attainment, screen time, and body height contributing positively to the outcome (Figures S4–S6). In addition, the funnel plot showed a symmetric scatter, indicating the absence of bias (Figures S7–S9).

### 4. Discussion

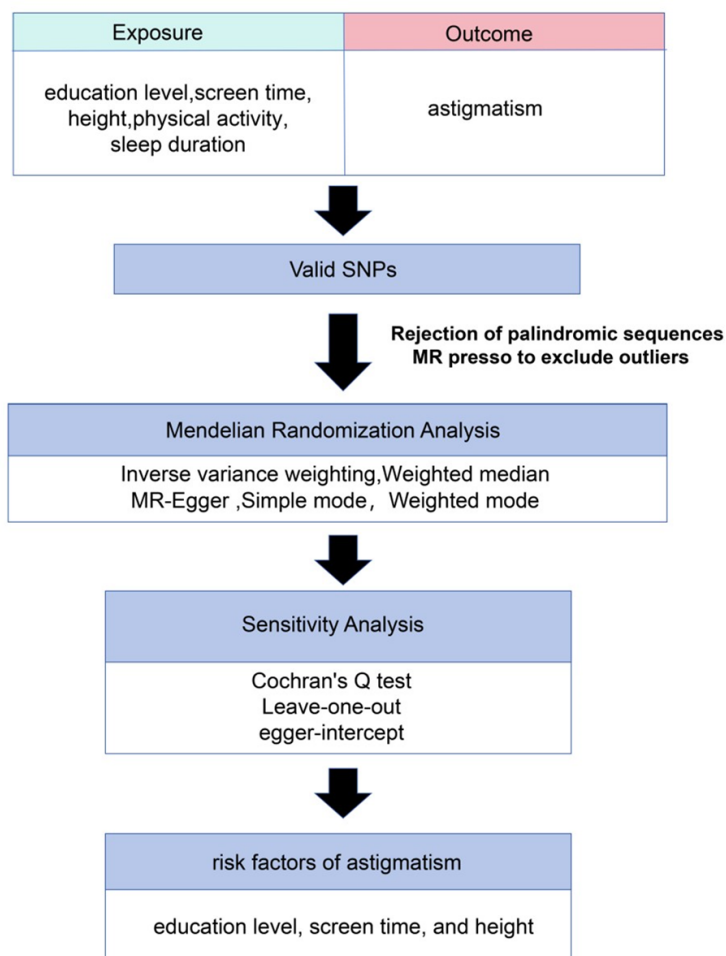
Observational evidence has implicated body height, screen time, educational attainment, physical activity, and sleep duration as potential risk factors for astigmatism; nevertheless, findings regarding their causal relationships have been inconsistent. Grounded in the random segregation of genetic variants, MR provides a framework

for evaluating causal associations between exposures and outcomes, resembling the design of randomized controlled trials. Relative to traditional observational designs, MR offers advantages in limiting confounding influences and avoiding reverse causal bias. By applying MR, this study provides novel and more robust genetic evidence linking these exposures to astigmatism. Based on the findings of this MR study, greater levels of educational attainment, extended screen time, and taller body height are linked to an elevated risk of developing astigmatism. Astigmatism is a vision disorder that causes light rays to not focus on the retina at the same time, resulting in blurred or distorted images.<sup>29</sup> The primary symptoms of astigmatism are blurred or reduced vision, eye fatigue, and, in severe cases, neck tilting and headaches. Accompanying symptoms include distorted vision (especially hyperopic astigmatism) and head tilting due to difficulty in seeing.<sup>30</sup> The underlying factors of the disease are primarily genetic, with children having an increased likelihood of developing the disease if one parent has it.<sup>31</sup> Although astigmatism can be corrected using spectacles, contact lenses, toric intraocular lenses, or refractive procedures, its underlying pathophysiological mechanisms remain incompletely understood.<sup>32</sup> Identification of modifiable risk factors is essential for early diagnosis and prevention of astigmatism. Ayed *et al.*<sup>10</sup> found a significant association between all types of refractive error and educational attainment. In another study, it was reported that the prevalence of astigmatism increased with age and that educational attainment was associated with all refractive errors.<sup>11</sup> Nangia *et al.*<sup>9</sup> found that astigmatism was significantly associated with older age ( $p < 0.001$ ), educational attainment ( $p = 0.01$ ), and higher keratoconic changes ( $p < 0.001$ ). Previous studies have suggested that greater height is associated with refractive traits such as myopia, supporting the possibility that growth-related biological mechanisms may also be relevant to astigmatism.

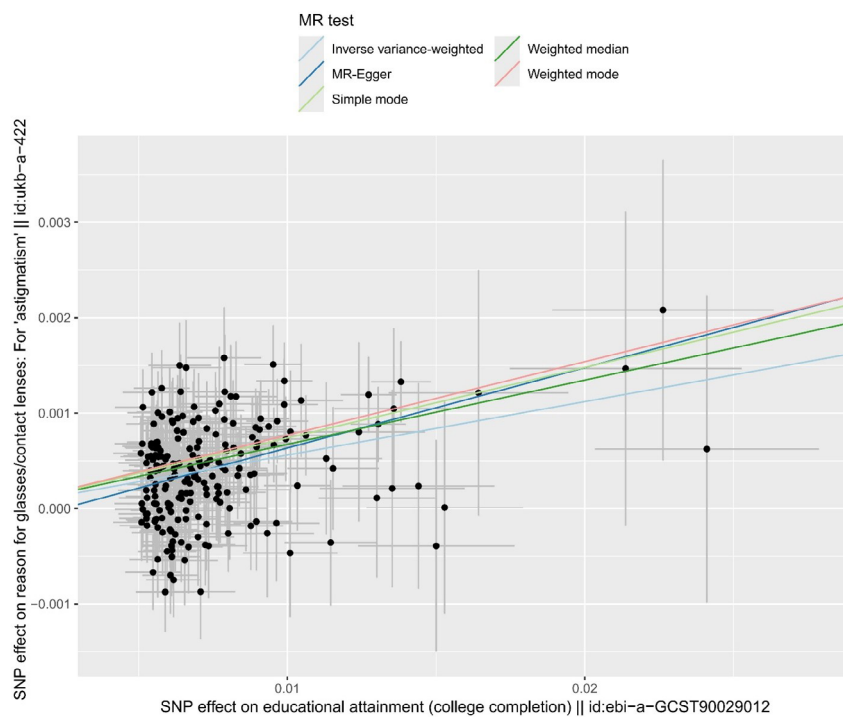
In addition to height, screen time has also been implicated as a potential risk factor for refractive abnormalities. A previous study demonstrated that longer screen time in early childhood was linked to a higher likelihood of developing myopia and astigmatism.<sup>12</sup> A separate study reported an elevated risk of astigmatism among preschoolers with daily electronic screen time exceeding two hours, relative to those exposed for shorter durations.<sup>13</sup> Siofra Harrington *et al.* applied multiple linear regression and found that longer screen time was linked to increased myopic refractive error, a higher axial length/corneal radius ratio, and more severe astigmatism.<sup>14</sup> The MR findings further support that increased screen time contributes to the risk of astigmatism.



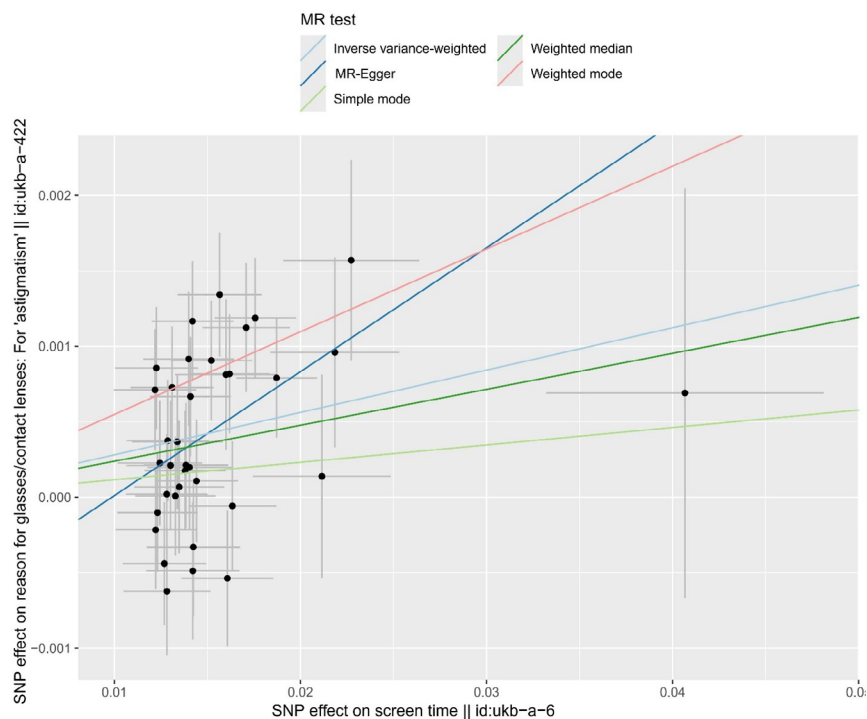
**Figure 1.** Schematic diagram illustrating the three core assumptions of Mendelian randomization in the current study



**Figure 2.** Flow chart of the Mendelian randomization (MR) analysis. The exposure and outcome dataset were selected, valid single-nucleotide polymorphism (SNP) instruments were identified, outliers and palindromic SNPs were removed where appropriate, and MR and sensitivity analyses were performed to evaluate potential causal risk factors for astigmatism.

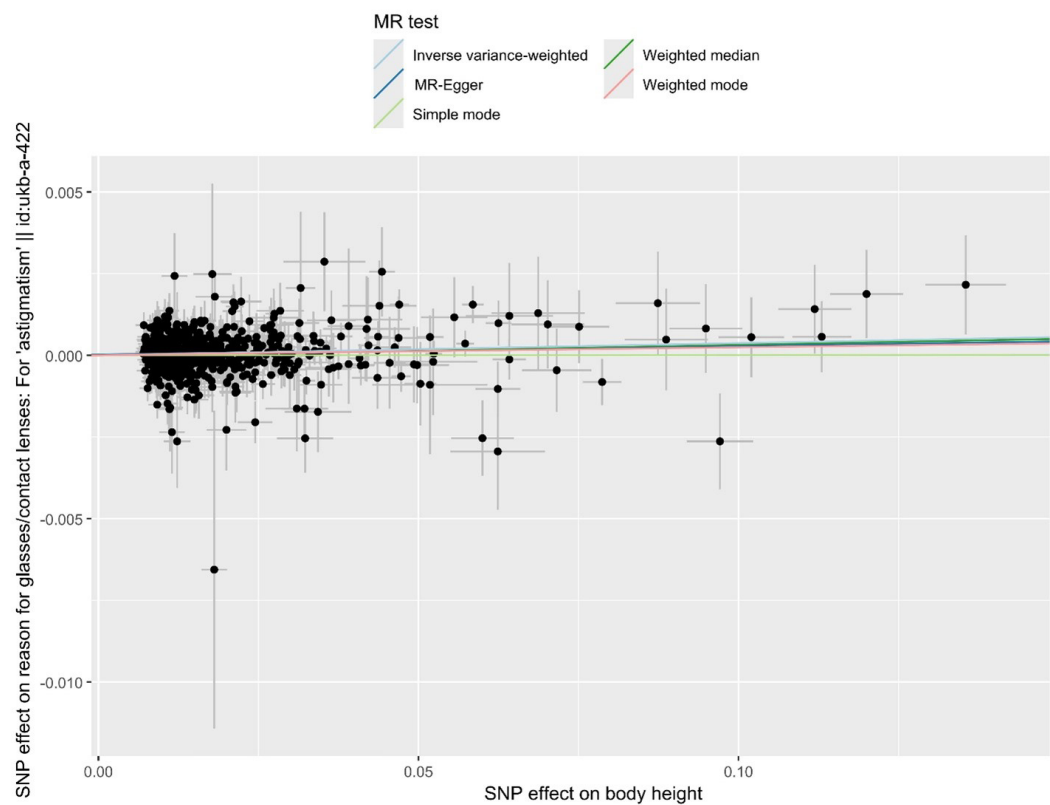


**Figure 3.** Scatter plot for educational attainment and astigmatism. The plot shows the effect sizes of the single-nucleotide polymorphism (SNP) effects on astigmatism (y-axis) and the SNP effects on educational attainment (x-axis) with 95% confidence intervals. Each dot represents one of the SNPs used in the Mendelian randomization (MR) analysis. The slopes indicate the estimate for each of the five different MR tests.



**Figure 4.** Scatter plot for screen time and astigmatism. The plot shows the effect sizes of the single-nucleotide polymorphism (SNP) effects on astigmatism (y-axis) and the SNP effects on screen time (x-axis) with 95% confidence intervals. Each dot represents one of the SNPs used in the Mendelian randomization (MR) analysis. The slopes indicate the estimate for each of the five different MR tests.





**Figure 5.** Scatter plot for body height and astigmatism. The plot shows the effect sizes of the single-nucleotide polymorphism (SNP) effects on astigmatism (y-axis) and the SNP effects on body height (x-axis) with 95% confidence intervals. Each dot represents one of the SNPs used in the Mendelian randomization (MR) analysis. The slopes indicate the estimate for each of the five different MR tests.

**Table 1.** Mendelian randomization estimated the effects of exposures on astigmatism

Exposures	Number of SNPs	Methods	<i>p</i> -value	OR (95% CI)	Pleiotropy
Educational attainment	216	IVW	$1.91 \times 10^{-32}$	1.058 (1.048–1.067)	0.127
		MR-Egger	$1.45 \times 10^{-5}$	1.088 (1.048–1.129)	
		WM	$1.01 \times 10^{-24}$	1.070 (1.056–1.083)	
Screen time	38	IVW	$3.19 \times 10^{-6}$	1.028 (1.016–1.041)	0.109
		MR-Egger	$1.91 \times 10^{-2}$	1.086 (1.017–1.159)	
		WM	$1.32 \times 10^{-3}$	1.024 (1.009–1.039)	

(Cont'd...)

Table 1. Continued

Exposures	Number of SNPs	Methods	p-value	OR (95% CI)	Pleiotropy
Body height	623	IVW	$4.00 \times 10^{-4}$	1.004 (1.002–1.006)	0.563
		MR-Egger	$2.04 \times 10^{-1}$	1.003 (0.999–1.007)	
		WM	$4.24 \times 10^{-2}$	1.003 (1.000–1.007)	
Physical activity	18	IVW	$6.06 \times 10^{-1}$	0.991 (0.957–1.026)	0.504
		MR-Egger	$4.64 \times 10^{-1}$	0.912 (0.717–1.160)	
		WM	$1.97 \times 10^{-1}$	0.972 (0.930–1.015)	
Sleep duration	71	IVW	$8.40 \times 10^{-1}$	1.001 (0.991–1.011)	0.912
		MR-Egger	$8.74 \times 10^{-1}$	1.003 (0.966–1.042)	
		WM	$6.94 \times 10^{-1}$	0.997 (0.983–1.012)	

Note: Estimated causal effects of educational attainment, screen time, body height, physical activity, and sleep duration on astigmatism are shown. Only the three principal methods are presented in the main table, and the others were used as supplementary/sensitivity analyses.

Abbreviations: CI: Confidence interval; IVW: Inverse variance-weighted; MR-Egger: Mendelian randomization Egger regression; OR: Odds ratio; SNP: Single-nucleotide polymorphism; WM: Weighted median.

The potential link between body height and astigmatism has been increasingly investigated in recent studies. Significant associations between stature and refractive error were observed in girls in a study of Chinese children conducted in Singapore.<sup>16</sup> Significant associations between corneal astigmatism and anthropometric measures, including weight and body height, were reported by ElkitKat *et al.*<sup>15</sup> Jonuscheit *et al.*<sup>33</sup> observed a weak correlation between body height and central and peripheral corneal thickness, and a moderate correlation with corneal radius. In a study by Tang *et al.*<sup>34</sup>, temporal patterns in refractive error prevalence were analyzed in a pediatric population. Because observational associations between body height and astigmatism may be influenced by growth-related and environmental confounding, MR analysis provides a more robust framework for causal inference, and our findings suggest that greater body height is associated with an increased risk of astigmatism.

Current research on the relationship between sleep

duration, physical activity, and astigmatism remains weak and inconsistent. One study found no significant association between a sedentary lifestyle and vision problems (nearsightedness, farsightedness, astigmatism, strabismus) or spinal deformities.<sup>35</sup> Another study found that while sleep duration was associated with several health indicators, the association with vision, specifically astigmatism, was not significant.<sup>36</sup> Our MR analysis also suggests that physical activity and sleep duration are not significantly associated with astigmatism.

For biological plausibility and potential pathways, several biologically plausible mechanisms may link the identified exposures to astigmatism. Educational attainment and prolonged near-work/screen time can increase accommodative demand, alter blink dynamics and eyelid pressure, and modify corneal shape over developmental windows.<sup>37</sup> Body height may proxy for systemic growth processes (e.g., growth hormone/insulin-like growth factor 1 [IGF-1] signaling) that influence



ocular axial length and corneal curvature; shared genetic determinants between body height and ocular biometry are plausible given pleiotropic loci identified in GWAS of body size and ocular traits.<sup>38</sup> These mechanisms are not mutually exclusive and may act synergistically during childhood and adolescence, critical periods for ocular development. Critically, translating these genetic associations into a mechanistic understanding requires targeted functional studies (for example, gene expression profiling in ocular tissues, in vitro assays of corneal stromal cell behavior, and animal models manipulating candidate genes/pathways). Functional characterization of implicated genes and proteins is essential to move from statistical association to biological causation and to identify molecular entry points for prevention or therapy.<sup>39</sup>

Compared with prior studies, our MR findings are broadly consistent with observational evidence linking higher educational attainment and greater near-work to refractive errors but offer stronger causal inference by minimizing confounding and reverse causation. The association of body height with refractive outcomes has been reported previously; MR provides complementary evidence suggesting a causal component rather than simple correlation via shared environment. Null findings for sleep duration and physical activity align with several observational studies finding weak or inconsistent associations, though measurement heterogeneity and instrument strength may limit power to detect modest causal effects.

Regarding public health and clinical implications, if confirmed in diverse populations, our results support targeted vision screening for children and adolescents with high educational attainment and substantial screen time, and suggest that growth-related biomarkers might be considered when modeling refractive development. Interventions to limit excessive screen time during early life, optimize lighting and ergonomics, and enforce regular breaks may reduce risk; however, MR itself does not prescribe specific behavioral interventions, so intervention studies remain necessary. Framed within the genes, proteins, and diseases, these findings also speak to prevention across the continuum from “suboptimal health” to manifest disease: genetic and exposure-based risk stratification could help identify individuals in a suboptimal health state (early alterations in ocular biometry or visual function) for timely, non-invasive interventions that prevent progression to clinically significant astigmatism. Although astigmatism is a non-communicable condition and not subject to person-to-person transmission, the translational pipeline we describe—linking genetic loci to protein function to pathophysiology—can similarly inform susceptibility and

transmission dynamics for infectious diseases where host genetic variation affects infection risk, pathogen load, or transmissibility.<sup>40</sup> In short, integrating genetic insights with functional protein studies and population-level screening enables prevention strategies that span early subclinical changes through to established disease, and the same framework can be adapted to contexts involving disease transmission where host genetics modulates susceptibility or spread.

The current study has several policy and research implications. We recommend that future work combine genetic risk scores with objective measures of near-work and device exposure, longitudinal ocular imaging, and biochemical markers to decipher causal pathways. Randomized or quasi-experimental interventions that reduce screen time during critical developmental windows and evaluate subsequent refractive outcomes would provide complementary evidence to our genetic analyses.

Beyond genetic predisposition and behavioral exposures, astigmatism—like many complex traits—is likely shaped by a web of metabolic, endocrine, nutritional, and environmental influences that interact with developmental timing and genetic background. Emerging evidence suggests that systemic metabolic states (for example, dysglycemia or altered lipid metabolism), endocrine signals (notably growth hormone/IGF-1 pathways), and the availability of micronutrients and trace elements can influence extracellular matrix composition, collagen cross-linking, and tissue remodeling in growing ocular structures, thereby plausibly altering corneal curvature and lens biomechanics. Oxidative stress and subclinical inflammation may further modulate corneal stromal homeostasis and wound-healing responses, while environmental factors such as ultraviolet exposure, air pollution, and early-life nutritional status could exert additional effects on ocular surface health and biomechanical properties. Even the ocular surface microbiome and local immune milieu, by shaping inflammatory tone and protease activity, represent potential modifiers of corneal structure during sensitive developmental windows. Recent work has highlighted how blood levels of trace elements (e.g., molybdenum) are associated with disease risk and can modulate oxidative stress and enzymatic activities involved in tissue development.<sup>41</sup> Although that particular study focuses on cancer risk in *BRCA1* carriers, it illustrates a broader conceptual framework: trace elements and micronutrients can have measurable effects on biological processes that, in principle, could influence ocular development. Consequently, while our MR results identify educational attainment, screen time, and body height as causal factors

for astigmatism, future studies should also evaluate systemic biochemical and nutritional exposures (including trace elements), endocrine regulation, and growth-related metabolic pathways as potential contributors or modifiers of astigmatism risk.

Although MR reduces confounding and reverse causation relative to observational designs, several limitations should be noted. First, our analyses are restricted to individuals of European ancestry, which limits the generalizability of the findings to other populations and ethnicities. Second, despite multiple sensitivity analyses (MR-Egger, MR-PRESSO, Cochran's *Q*, and leave-one-out), horizontal pleiotropy cannot be entirely excluded and may bias causal estimates. Third, some exposure GWAS (e.g., screen time, educational attainment) rely on self-reported measures or heterogeneous phenotyping across cohorts, which may introduce measurement error and attenuate effect estimates. Fourth, potential sample overlap between some exposure and outcome GWAS could bias estimates toward observational associations; although we used two-sample MR methods, we cannot fully exclude the possibility of partial overlap for some datasets. Fifth, MR assumes linear and time-invariant effects of genetic proxies on exposures and outcomes; complex, nonlinear, or developmental-stage-specific effects may not be captured. Finally, the observed effect sizes are modest and do not by themselves clarify biological mechanisms; experimental and longitudinal studies are required to translate these genetic findings into mechanistic understanding and actionable interventions. In particular, functional genomics and protein-level investigations (e.g., CRISPR perturbations in corneal cell types, proteomic profiling, and *in vivo* modeling) are critical next steps to validate the causal variants identified here and to define the molecular pathways that mediate susceptibility.<sup>42</sup> Without such functional validation, translation from genetic association to prevention or therapeutic targeting remains speculative. These limitations highlight the need for replication in non-European cohorts, integration with biochemical and imaging data, and mechanistic studies to elucidate pathways linking the identified exposures and astigmatism.

This study analyzed the associations of educational attainment, screen time, body height, sleep duration, and physical activity with astigmatism using MR. The results showed a positive association between educational attainment, screen time, and body height with astigmatism, which may help to better characterize the developmental mechanisms of astigmatism. These associations may suggest common biological pathways or genetic factors related to growth hormone secretion, rate of skeletal

development, or changes in lens curvature. Further study of these biological pathways may reveal new therapeutic targets or prevention strategies. These findings may help clinicians consider patients' exposures when diagnosing and treating astigmatism. In public health screening, children and adolescents with higher educational attainment and prolonged screen time may warrant closer vision screening for effective prevention and treatment of astigmatism. In areas with limited medical resources, focusing on these children or adolescents through regular eye examinations can ensure early detection and treatment of astigmatism and improve overall eye health. In the future, big data and artificial intelligence technologies could be used to develop predictive models based on these exposures and genetic information to identify high-risk groups for astigmatism early and provide personalized health management services.

## 5. Conclusion

In conclusion, this study provides important clues for further research into the biological mechanisms underlying the association of educational attainment, screen time, and body height with astigmatism. It offers new perspectives on the etiology of astigmatism and may inform future clinical practice and public health strategies. However, further studies are needed to clarify the biological mechanisms underlying these associations and to validate the findings in diverse populations.

## Acknowledgments

The authors thank participants and researchers in the UK Biobank study and GWAS studies from which we used summary statistics data. We express our highest gratitude to all the scholars who participated in this research.

## Funding

This work was financed by the National Natural Science Foundation of China (No. 81870591), Key R&D and Promotion Projects in Henan Province (No. 242102310407), the Key Scientific Research Projects of Colleges and Universities in Henan Province (No. 23A310011), and the Henan Province Medical Science and Technology Research Program Project (No. LHGJ20230428).

## Conflict of interest

Lei Zhang and Xinying Ji serve as an Editorial Board Member and an Associate Editor of this journal, respectively, but they were not in any way involved in the editorial and peer-review process conducted for this paper, directly or indirectly. Separately, other authors declared that they have no known competing financial interests or

personal relationships that could have influenced the work reported in this paper.

### Author contributions

**Conceptualization:** Xinying Ji, Yalong Dang

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### Ethics approval and consent to participate

Not applicable.

### Consent for publication

Not applicable.

### Availability of data

The GWAS summary statistics analyzed in this study were obtained from publicly available datasets, including EBI-A-GCST90018959, UKB-A-6, UKB-B-13184, UKB-B-4424, EBI-A-GCST90029012, and UKB-A-422. The processed results generated in this study are included in the article and/or Supplementary File. Further inquiries can be directed to the corresponding authors.

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