• Mendelian Randomization •

Lifestyle behaviors, serum metabolites and high myopia: Mendelian randomization and mediation analysis

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Abstract

● **AIM:** To explore the causal relationship between several possible behavioral factors and high myopia (HM) using multivariable Mendelian randomization (MVMR) approach and to find the mediators among them with mediation analysis.

● **METHODS:** The causal effects of several behavioral factors, including screen time, education time, time spent outdoors, and physical activity, on the risk of HM using univariable Mendelian randomization (MR) and MVMR analyses were first assessed. Genome-wide association study summary statistics of serum metabolites were also used in mediation analysis to determine the extent to which serum metabolites mediate the effects of behavioral factors on HM.

● **RESULTS:** MR analyses indicated that both increased time spent outdoors and a higher frequency of moderate physical activity significantly reduced the risk of HM. Further MVMR analysis confirmed that moderate physical activity independently contributed to a lower risk of HM. Additionally, MR analyses identified 13 serum metabolites significantly associated with HM, of which 12 were lipids and one was an amino acid derivative. Mediation analysis revealed that six lipid metabolites mediated the protective effects of moderate physical activity on HM, with the highest mediation proportion observed for 1-(1-enyl-palmitoyl)-GPC (p-16:0; 30.83%).

● **CONCLUSION:** This study suggests that in addition to outdoor time, moderate physical activity habits may have an independent protective effect against HM and pointed to lipid metabolites as priority targets for the prevention due to low physical activity. These results emphasize the importance of physical activity and metabolic health in HM and underscore the need for further study of these complex associations.

● **KEYWORDS:** high myopia; physical activity; serum metabolites; multivariable Mendelian randomization; mediation analysis

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INTRODUCTION

Myopia is a refractive state in which parallel rays of light pass through the refractive system of the eye and focus before the retina, failing to make a clear image on the retina in a state of relaxed accommodation[1]. A myopic eye with a refractive error of -6 D or more is considered high myopia (HM)[1]. By 2050, it is projected that 50% of the global population will be affected by myopia, with 10% experiencing HM. This represents a doubling in the prevalence of myopia compared to 2000 (from 22% in 2000) but a fivefold increase in HM (from 2% in 2000)[2]. HM significantly elevates the risk of developing vision-threatening ocular conditions such as retinal detachment, glaucoma, and cataract[3-4]. Additionally, the progression of HM may cause pathological myopia, characterized by fundus abnormalities including posterior scleral staphyloma, optic neuropathy, and macular degeneration, significantly reducing patients' quality of life[5]. Therefore, it is important for studies to identify other potential risk factors for HM and to understand the possible

pathogenesis of HM in order to guide clinical practice in preventing its progression.

Behavioral factors associated with HM have been less well studied, but given that myopia can progress to HM, we speculate that HM may share myopia-related factors. The main environmental factors often considered to be associated with myopia are outdoor exposure, screen time, and education, *etc*[6]. It is now proven that participating in more outdoor activities reduces the risk of developing myopia and slows its progression[7]. Not only some Meta-analyses of the existing literature have found that increased outdoor activity significantly lowered the incidence of myopia, but in cross-sectional studies, each additional hour of outdoor activity per week was associated with a 2%-4% reduction in the odds of developing myopia[8-9]. Interventional studies have also demonstrated that increasing time spent outdoors reduces the prevalence of myopia in children[10-11]. Several studies have reported an association between increased physical activity and reduced myopia; however, this relationship is confounded by the fact that higher physical activity levels often occur outdoors[9,12-14]. A recent comprehensive study found no significant protective effect of increased physical activity against myopia[15]. Further research using more objective measures of physical activity and outdoor exposure is essential, yet few relevant studies have been done.

Besides these, educational attainment, measured in years of schooling, is a recognized risk factor for myopia[16-17]. Additionally, higher intelligence quotient and superior academic performance have been positively correlated with myopia and parental education level may also be a significant risk factor for myopia in children[18-19]. However, this relationship is likely modulated by factors such as parental myopia (genetic predisposition), socioeconomic status, occupation, and reduced time spent outdoors[20].

Previous studies have established associations between various behavioral factors and myopia[6]. However, it remains unclear whether these factors contribute to the development of HM. Mendelian randomization (MR) analysis offers a robust approach to address this question by utilizing genetic variations as instrumental variables (IVs) to infer potential causal relationships between exposures and outcomes. MR theoretically mitigates confounding and eliminates reverse causality[21]. The multivariable Mendelian randomization (MVMR), an extension of the univariable MR, further allows for the simultaneous assessment of independent effects of multiple exposures on an outcome, enhancing the exclusion of confounding factors[22]. Additionally, we aimed to identify plasma metabolites that may mediate the pathological processes of HM through mediation analysis, potentially serving as predictors or targets for intervention. To achieve this, we conducted two-sample MR analyses using publicly available genome-wide association study (GWAS) data to evaluate causal links between behavioral factors, plasma metabolites, and HM.

MATERIALS AND METHODS

Ethical Approval The original studies had obtained ethical approval and informed consent, and all data used in this study were de-identified. The study protocol for this secondary analysis was reviewed and approved by the Medical Ethics Committee of Beijing Hospital: 2024BJYYEC-KY086-01.

Study Design Figure 1 presented the flowchart of the study. Initially, several datasets related to behavioral traits, such as screen time, education duration, time spent outdoors, and physical activity, were obtained from the UK Biobank (UKB). Additionally, published GWAS summary datasets for serum metabolites and HM were acquired. Univariable two-sample MR analyses were first employed to investigate the causal relationships between behavioral traits mentioned above and serum metabolites and HM. Given the correlations among the selected behavioral traits, we conducted MVMR analyses for those behavioral traits showing significant associations with HM in the univariable MR. This allowed us to determine the independent effects of each behavioral trait on HM after accounting for mutual correction. Subsequently, we assessed the potential mediating role of serum metabolites between behavioral traits and HM using the two-step method, focusing on the behavioral traits that were significant in the MVMR. The survey used publicly available summary-level statistics from the IEU OpenGwas and UKB consortium.

Data Sources In this study, we selected 7 behavioral factors and 1400 serum metabolites as exposures. The GWAS summary statistics for serum metabolites were obtained from the GWAS catalog (https://www.ebi.ac.uk/gwas/, GCST90199621 to GCST90201020), encompassing data from 8299 individuals in the Canadian Longitudinal Study on Aging cohort, including 1091 metabolites and 309 metabolite ratios. Additionally, datasets for seven behaviors potentially associated with HM were sourced from the UKB (http://www.nealelab.is/uk-biobank). These behaviors included “Time spent using a computer” (n=498 731), “Time spent outdoors in summer” (n=498 733), “Time spent engaging in vigorous physical activity” (n=210 853), “Time spent engaging in moderate physical activity” (n=210 853), “Age at completion of full-time education” (n=337 224), “Number of days per week of vigorous physical activity lasting 10 or more minutes” (n=501 318), and “Number of days per week of moderate physical activity lasting 10 or more minutes” (n=501 318). Detailed information is provided in Table 1.

Instrumental Variable The following criteria were applied to select IVs: 1) single nucleotide polymorphisms (SNPs)

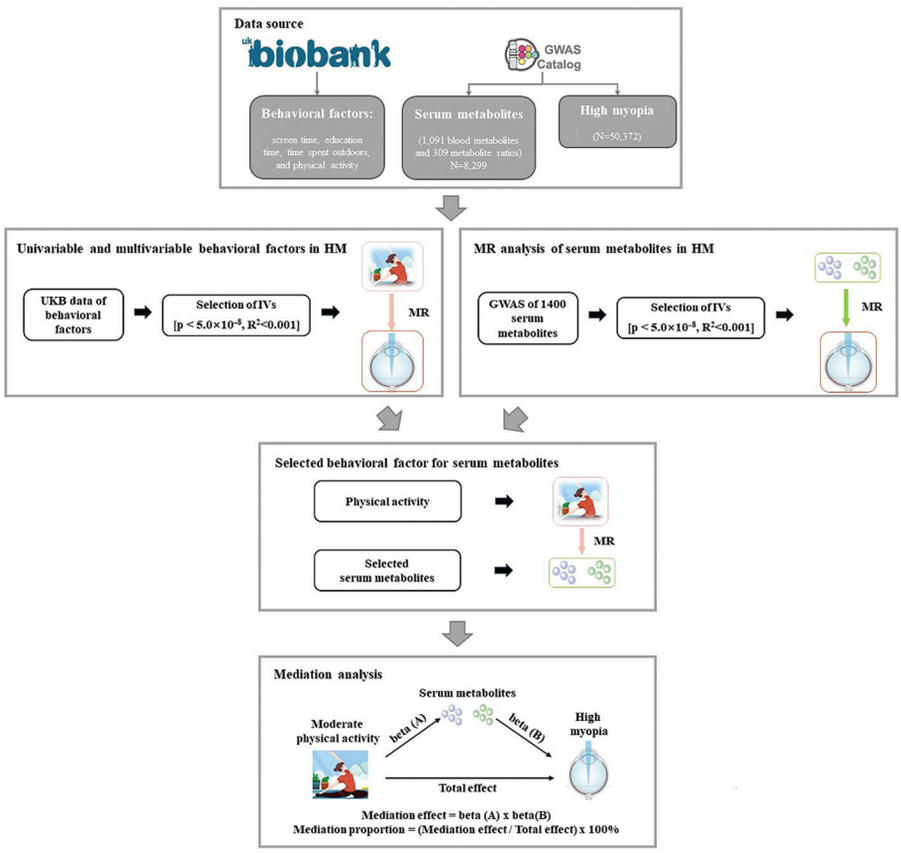

Figure 1 Flow chart of the study GWAS: genome-wide association study; HM: High myopia; MR: Mendelian randomization; IV: Instrumental variable; UKB: UK Biobank.

Table 1 Summary information of the GWAS database in the MR study

Phenotype	Sample size	Population ethnicity	Web source
Exposure			
Time spent using computer	498731	European	https://www.ukbiobank.ac.uk/
Time spent outdoors in summer	498733	European	https://www.ukbiobank.ac.uk/
Time spent doing vigorous physical activity	210853	European	https://www.ukbiobank.ac.uk/
Time spent doing moderate physical activity	210853	European	https://www.ukbiobank.ac.uk/
Age completed full time education	337224	European	https://www.ukbiobank.ac.uk/
Number of days/week of vigorous physical activity 10+ minutes	501318	European	https://www.ukbiobank.ac.uk/
Number of days/week of moderate physical activity 10+ minutes	501318	European	https://www.ukbiobank.ac.uk/
Serum metabolites	8299	European	https://www.ebi.ac.uk/gwas/
Outcome			
HM	2737 cases, 47635 controls	European	https://www.ebi.ac.uk/gwas/

HM was used as the outcome, with GWAS summary statistics also extracted from the GWAS Catalog. Data for HM were derived from the GWAS involving 50 372 individuals (2737 cases and 47 635 controls). GWAS: Genome-wide association study; HM: High myopia.

associated with each gene that surpassed the genome-wide significance threshold (P<5.0×10^{-8}) were considered as potential IVs; 2) To ensure the independence of SNPs, linkage disequilibrium was assessed using a reference panel, applying a threshold of R^2<0.001 and a window size of 10 000 kb; 3) The effect alleles of outcome-associated SNPs were compared with those of exposure-associated SNPs, excluding palindromic SNP alleles.

Statistical Analysis

Two-sample Mendelian randomization and MVMR analyses In this study, we conducted both univariable and multivariable MR analyses to investigate the causal relationships between behavioral traits (exposures) and HM (outcome). The MR study relies on three fundamental assumptions: 1) The selection of IVs must exhibit a significant and robust association with the exposure; 2) The selected IVs

Table 2 Univariable MR estimates of the associations between behavioral factors and risk of HM from the IVW method

Exposure	nSNP	Beta	SE	OR (95%CI)	*P*
Screen time	35	0.06	0.02	1.06 (1.04-1.08)	0.03
Time spent outdoors	27	-0.11	0.02	0.90 (0.88-0.92)	2.15×10^{-6}
Education time	29	0.04	0.02	1.04 (1.02-1.06)	0.08
Number of days/week of vigorous physical activity 10+ minutes	8	-0.01	0.02	0.99 (0.97-1.01)	0.65
Number of days/week of moderate physical activity 10+ minutes	8	-0.04	0.02	0.96 (0.95-0.98)	0.03
Time spent doing vigorous physical activity	1				
Time spent doing moderate physical activity	1				

MR: Mendelian randomization; HM: High myopia; IVW: Inverse-variance weighted; SNP: Single nucleotide polymorphisms; SE: Standard error; OR: Odds ratio; CI: Confidence interval.

should be independent of any potential confounding factors that may influence the outcome; 3) The elected IVs exert a direct effect on the outcome through the exposure variable, without involvement of alternative pathways. Univariable MR analyses were first used to evaluate the direct effects of behavioral traits and serum metabolites on HM, independent of potential mediators or confounders. Five MR methods were employed to estimate causal effects: inverse variance weighted (IVW), MR Egger, Weighted Median, Simple Mode, and Weighted Mode, with IVW serving as the primary method for causal inference. Considering the potential associations between various behavioral traits, we further performed MVMR analysis using traits that showed significant IVW results in the univariable MR. MVMR allowed us to estimate the independent effects of multiple exposures on the outcome by leveraging genetic variants associated with these exposures. MR-Egger regression was applied to detect potential directional pleiotropy, with a significant intercept indicating the presence of horizontal pleiotropy. The MR-PRESSO method was utilized to identify and correct for potential outliers, and its global test assessed horizontal pleiotropy through heterogeneity in SNP estimates.

Sensitivity analyses were conducted using the MR-Egger and IVW methods, with Cochran's Q statistics evaluating the heterogeneity among IVs. To identify potential heterogeneous SNPs, a "leave-one-out" analysis was performed, excluding each instrumental SNP sequentially to assess its impact on the overall results. Additionally, the F statistic was calculated for each SNP to assess the strength of the IVs, with values exceeding 10 indicating a minimal risk of weak instrument bias. All analyses were conducted using the R packages "TwoSampleMR," "meta," and "MRPRESSO" in R version 4.3.2.

Mediation analysis We conducted mediation analyses to investigate the potential mechanisms through which exposures influence outcomes, particularly focusing on the role of serum metabolites in mediating the effects of behavioral factors on HM. First, two-sample MR analyses were used to assess the causal relationships between behavioral traits and serum metabolites, yielding the effect estimate β(A). Next, the impact of selected serum metabolites on HM was evaluated using two-sample MR to obtain the effect estimate β(B). The mediation effect was calculated using the two-step method: mediation effect=β(A)×β(B). The total effect of the behaviors on HM was directly calculated, with the direct effect then being (total effect-mediation effect). Mediation proportion=(mediation effect/total effect) ×100%. The Delta method was employed to estimate 95% confidence intervals (CI) for both the mediating effect and the mediation proportion[23]. Serum metabolites were identified as potential mediators in the pathway from behavioral traits to HM if causal relationships were observed between the exposure and outcome, mediator and outcome, and exposure and mediator.

RESULTS

Causal Effects of Lifestyle Behaviors on High Myopia

In this study, we investigated the genetically predicted causal relationship between seven behavioral habits and HM using univariable MR. And our findings suggested that both time spent outdoors and more days/week of moderate physical activity were protective factors for HM (Table 2). In addition, although the results of the univariable analyses showed that screen time was a significant risk factor for HM, it was excluded because the results of its MRPRESSO analysis suggested the presence of horizontal pleiotropy. Also, time spent doing moderate/vigorous physical activity were also excluded because both datasets had only 1 SNP left after merging with the dataset of HM, which did not allow subsequent analyses to be performed and reliable results to be obtained (Table 2).

As MVMR allows for the simultaneous assessment of the causality of multiple influences on an outcome, which helps to address the issue of collinearity among multiple influences while providing a more comprehensive causal estimation controlling the effects of other potential confounders, we further conducted MVMR analysis on these seven behavioral traits after the univariable MR analysis, which, showed the presence of horizontal pleiotropy.

Table 3 MVMR analysis of the association between time spent outdoors/moderate physical activity and HM

Exposure	MV-IVW		MV-LASSO		MV-Egger	
	OR (95%CI)	*P*	OR (95%CI)	*P*	OR (95%CI)	*P*
Time spent outdoors	0.97 (0.93-1.01)	0.12	0.96 (0.92-0.99)	0.02	0.97 (0.91-1.03)	0.29
Number of days/week of moderate physical activity 10+ minutes	0.93 (0.88-0.99)	0.02	0.92 (0.88-0.97)	2.63×10^{-3}	0.92 (0.76-1.11)	0.38

MVMR: Multivariable Mendelian randomization; IVW: Inverse-variance weighted; LASSO: Least absolute shrinkage and selection operator; OR: Odds ratio; CI: Confidence interval.

Table 4 Mendelian randomization estimates of the associations between serum metabolites and risk of HM from the IVW method

Exposure	nSNP	OR (95%CI)	*P*
Linoleoyl-arachidonoyl-glycerol (18:2/20:4)[2] levels	4	0.98 (0.98, 0.99)	4.82×10^{-4}
1-arachidonoyl-GPC (20:4n6) levels	5	0.99 (0.98, 0.99)	5.68×10^{-4}
1-(1-enyl-stearoyl)-2-arachidonoyl-GPE (p-18:0/20:4) levels	3	0.98 (0.97, 0.99)	9.06×10^{-4}
1-linoleoyl-2-arachidonoyl-GPC (18:2/20:4n6) levels	5	0.98 (0.98, 0.99)	9.06×10^{-4}
1-(1-enyl-palmitoyl)-2-arachidonoyl-GPC (p-16:0/20:4) levels	3	0.99 (0.98, 0.99)	1.26×10^{-3}
1-(1-enyl-palmitoyl)-GPC (p-16:0) levels	3	0.97 (0.96, 0.99)	1.33×10^{-3}
1,2-dilinoleoyl-GPE (18:2/18:2) levels	3	1.02 (1.01, 1.03)	1.33×10^{-3}
1-stearoyl-2-linoleoyl-GPC (18:0/18:2) levels	3	1.02 (1.01, 1.04)	1.54×10^{-3}
Linoleoyl-arachidonoyl-glycerol (18:2/20:4)[1] levels	3	0.98 (0.98, 0.99)	2.35×10^{-3}
1-palmitoyl-2-linoleoyl-GPC (16:0/18:2) levels	4	1.02 (1.01, 1.03)	3.32×10^{-3}
1-palmitoyl-2-linoleoyl-GPE (16:0/18:2) levels	5	1.01 (1.00, 1.01)	5.86×10^{-3}
1-oleoyl-2-linoleoyl-GPE (18:1/18:2) levels	5	1.01 (1.00, 1.02)	0.01
Gamma-glutamyltyrosine levels	3	0.98 (0.96, 0.99)	0.03

IVW: Inverse-variance weighted; SNP: Single nucleotide polymorphisms; OR: Odds ratio; CI: Confidence interval; GPC: Glycerophosphocholine; GPE: Glycerophosphoethanolamine.

In addition, as mentioned above, realizing that there might be a potential association between time spent outdoors and number of days/week of moderate physical activity 10+ minutes (later briefly referred to as physical activity), which were significantly and causally associated with HM in the results of the univariable MR analyses, we further assessed both the independent effects of time spent outdoors and physical activity in the presence of each other on HM.

Unexpectedly, MVMR results suggested that physical activity was a significant protective factor for HM independently of time spent outdoors after mutual correction (Table 3).

Causal Effects of Serum Metabolites on High Myopia To investigate the causal effect of serum metabolites on HM, we used the same method as previously described. Our analyses identified 13 significantly different metabolites, of which 8 were protective factors and 5 were risk factors (Table 4[1-2]).

In addition, we found that 12 of these 13 metabolites were lipids and gamma-glutamyltyrosine [IVW odds ratio (OR)=0.98, 95%CI=(0.96-0.99), *P*=0.03] was amino acid derivative. Further breakdown revealed that of the 12 lipid metabolites, only 1-(1-enyl-palmitoyl)-GPC (p-16:0) [IVW OR=0.97, 95%CI=(0.96-0.99), $P=1.33\times10^{-3}$] belonged to saturated fatty acids, whereas the remaining 11 metabolites were unsaturated fatty acids, with all five of the above risk factors belonging to them (Table 4).

Mediating Role of Serum Metabolites in the Effect of Physical Activity on High Myopia To identify mediating serum metabolites that were causally associated with both physical activity and HM, we performed two successive two-sample MR analyses using the two-step method. First, physical activity was used as the exposure for MR analysis with 1400 serum metabolites, of which we identified 131 significant serum metabolites Subsequently these 131 metabolites were again used as exposures for MR analysis with HM, and positive results in both steps were extracted for mediation analysis. The results were shown in Table 5[1-2].

As mentioned above, physical activity (number of days/week of moderate physical activity 10+ minutes) had a protective effect on HM (beta=-0.04, *P*=0.03, Table 2). And we identified six mediators between physical activity and HM (Table 5). Among them, physical activity inhibited the development of HM by decreasing the Oleoyl-linoleoyl-glycerol (18:1 to 18:2)[2] to linoleoyl-arachidonoyl-glycerol (18:2 to 20:4)[1] ratio, whereas it prevented the development of HM by increasing the 1-stearoyl-2-arachidonoyl-gpc (18:0/20:4) levels, 1-arachidonoyl-gpc (20:4n6) levels, 1-palmitoyl-2-arachidonoyl-gpc (16:0/20:4n6)

Table 5 Mediation effect of physical activity on HM *via* serum metabolites

Mediators	Effect[a]	Effect[b]	Mediation effect	Mediated proportion
Oleoyl-linoleoyl-glycerol (18:1 to 18:2)[2] to linoleoyl-arachidonoyl-glycerol (18:2 to 20:4)[1] ratio	-0.49	0.01	-0.01	18.81%
1-stearoyl-2-arachidonoyl-GPC (18:0/20:4) levels	0.52	-0.01	-0.01	15.31%
1-arachidonoyl-gpc (20:4n6) levels	0.72	-0.01	-0.01	24.62%
1-palmitoyl-2-arachidonoyl-GPC (16:0/20:4n6) levels	0.45	-0.01	-0.01	14.20%
1-linoleoyl-2-arachidonoyl-GPC (18:2/20:4n6) levels	0.56	-0.02	-0.01	26.22%
1-(1-enyl-palmitoyl)-gpc (p-16:0) levels	0.42	-0.03	-0.01	30.83%

Effect[a]: The effect of exposure on mediators; Effect[b]: The effect of mediators on outcome; Mediation effect: The indirect effect of exposure on outcome *via* mediators. GPC: Glycerophosphocholin.

levels, 1-linoleoyl-2-arachidonoyl-GPC (18:2/20:4n6) levels and 1-(1-enyl-palmitoyl)-GPC (p-16:0) levels. All of these mediators played mediating roles of more than 10%, with the highest percentages being 1-(1-enyl-palmitoyl)-GPC (p-16:0), 1-linoleoyl-2-arachidonoyl-GPC (18:2/20:4n6) and 1-arachidonoyl-gpc (20:4n6) which accounted for 30.83%, 26.22% and 24.62% of the total effect.

DISCUSSION

While recent studies have advanced our understanding of behavioral risk factors for myopia progression[24], our work provides three fundamental methodological and mechanistic breakthroughs: 1) First application of integrated MVMR-mediation analysis framework to dissect complex pathways in HM. Unlike conventional bidirectional MR studies, our approach simultaneously quantified independent exposure effects (MVMR) and downstream metabolite mediators- a design not previously applied to HM; 2) Clinical specificity: Using univariable MR and MVMR methods, we identified the behavioral trait, *i.e.* physical activity, that had a significant causal effect on the risk of HM, which significantly reduced the risk of HM (univariable effect=0.96, P=0.03; multivariable effect=0.93, P=0.02), resolving long-standing confounding by outdoor exposure and providing actionable intervention targets; 3) Discovery of lipid-centric mediation pathway: Our study illustrated important insights into the relationship between physical activity habits and the risk of HM mediated through plasma lipid metabolites. Our mediation analyses highlighted the key role of six plasma lipid metabolites [*e.g.*, 1-(1-enyl-palmitoyl)-GPC with 30.83% mediation], which played rather substantial roles in mediating the protective effects of physical activity against HM (Table 5). This represents the first evidence of serum lipids as causal mediators in the HM pathogenesis cascade. And this mediating effect highlighted the complex role of lipid metabolic pathways in the pathogenesis of HM.

HM is a condition resulting from the interaction of genetic and environmental factors[25]. Numerous factors have been identified as influencing the onset and progression of HM, such as higher education, occupational status, close work, and screen time[26]. Therefore, we selected several popular factors to investigate their impact on HM. Notably, screen time and education duration may serve as risk factors for myopia. Previous studies have explored the relationship between educational duration and myopia, finding that individuals who graduated after 13y of schooling exhibited greater myopia (median: -0.5 D) compared to those who completed 10y (-0.2 D), 9y (+0.3 D), or those who never finished secondary school (+0.2 D)[27]. Additionally, the prevalence of myopia was found to be higher among individuals with tertiary education (36.6%) compared to those who completed secondary (29.1%) or primary (25.4%) education[28]. Myopia may continue to develop after university attendance; a three-year observational study indicated that college students experienced a refractive error shift of -0.5 D, primarily attributed to vitreous chamber elongation[29]. Furthermore, Enthoven *et al*[30] utilized a mobile application to examine the relationship between smartphone use and refractive error, discovering that increased consecutive smartphone usage correlated with a higher degree of myopia. However, this association was not evident in adolescents who engaged in more outdoor activities, suggesting that outdoor activity may mitigate the effects of smartphone use on myopia development[30]. Similarly, a study involving 9-year-old Irish schoolchildren revealed that those with over three hours of daily screen exposure had a higher incidence of myopia[31].

Conversely, outdoor time and physical activity are considered protective factors against myopia. Both clinical trials and longitudinal cohort studies have shown that increased outdoor activity significantly reduces the incidence of myopia, with risk ratios ranging from 0.54 to 0.57 for those spending more time outdoors and 0.96 for each additional hour in cross-sectional studies[32]. However, our MR analysis revealed that the effects of these influences on HM did not exactly align with those in myopia. In univariable MR analyses, we found that outdoor time and the number of days per week of moderate physical activity (≥10min) remained protective factors against HM, while education duration and screen time showed no causal relationship with HM. This appears to be similar to the findings

of a previous cross-sectional study that reported mobile device use in adolescents was only associated with myopia and not HM[33]. Additionally, Yurova *et al*[34] found that among 600 adolescents, those who were physically active had a lower incidence of myopia, and moderate physical activity effectively maintained existing vision and slowed myopia progression. Jacobsen *et al*[35] conducted a two-year follow-up study with 156 students at the University of Copenhagen, which revealed a negative correlation between physical activity and myopia, contributing to its improvement.

To further investigate the impact of physical activity on HM, we utilized different databases considering the intensity of physical activity, categorizing it into moderate and vigorous activity. Furthermore, we accounted for the frequency and duration of physical activity as potential influencing factors, using the number of days per week of physical activity (≥10min) as a habitual indicator and time spent on physical activity as a characteristic. The results indicated that moderate-intensity rather than vigorous-intensity physical activity and the establishment of habitual physical activity had a significant protective effect against HM.

Moreover, MVMR analysis revealed surprising independent effects of outdoor time and physical activity on HM. Our findings suggested that physical activity had a protective effect against HM independent of outdoor time. This does not undermine the role of outdoor time in myopia or HM; rather, it offers a new perspective on preventing or intervening in the progression of HM through the establishment of outdoor physical activity habits. We hypothesize that moderate-intensity activities are more likely to involve aerobic exercise, while vigorous activities are more anaerobic. Cultivating a routine of aerobic exercise is more beneficial for vascular health, particularly that of the choroidal vessels[36]. Choroidal vessel dilation and increased blood flow had been shown to slow the progression of myopia[37-38]. Additionally, certain metabolites produced during aerobic exercise may play a role in inhibiting HM.

To explore which metabolites were influenced by physical activity in relation to HM, we conducted a two-step mediation analysis. We identified six candidate serum mediators, notably all belonging to lipid categories. Physical activity was found to inhibit the development of HM by increasing five lipid metabolites and decreasing one, with the mediating effects of these metabolites comprising a substantial proportion of the total effect, each exceeding 10%, and the highest reaching over 30%. These findings indicated that lipid metabolites may serve as crucial targets for HM intervention.

And lipids are essential nutrients for the human body, playing a critical role in energy supply and cellular composition, including that of the retina, which significantly depends on lipid components[39]. Epidemiological studies and animal experiments have shown that dietary intake influences the lipid composition of the retina[40]. In particular, the proportion of lipids in the structure of photoreceptor membrane discs and retinal pigment epithelium is substantial[41-42], as these structures are primarily responsible for receiving and processing visual signals[43-44], greatly affecting the progression of HM. Furthermore, these lipids may influence the homeostasis of choroidal vessels[45-46]. Consequently, these lipids could inhibit the development of HM by impacting two critical components within the retina-choroid-sclera cascade.

However, there are several limitations that need to be considered. When performing MVMR analysis, although we did not analyze all seven behavioral traits as exposures at the same time because of horizontal pleiotropy, considering that outlier SNPs were not identified during MRPRESSO analysis, we speculated that it may be because the effects of IVs were relatively uniform and did not reach statistical significance: even if pleiotropy exists, the pleiotropic effects of all IVs were relatively consistent, which may suggest that the pleiotropic effects were global, rather than dominated by certain specific SNPs. In any case, we finally used two exposures in univariate MR analysis that had significant impacts on HM for MVMR analysis. In addition, our study mainly involved people of European ancestry, which may limit the generalizability of the results to other ethnic groups. Thirdly, residual confounders may also be present due to unmeasured variables that may influence plasma metabolite levels and HM risk.

Future research should also focus on several key areas. Longitudinal studies are needed to track changes in physical activity and plasma markers over time and whether these changes are related to the development of HM. And experimental studies should investigate the predictive or therapeutic potential of modulating specific lipid species. For example, exploring the impact of lipid-based interventions on HM models can provide valuable clinical evidence for new therapeutic approaches. Finally, combining plasma and intraocular lipidomic and genomic data with advanced bioinformatics tools can discover new biomarkers and therapeutic targets, providing new perspectives for precision medicine approaches to HM management.

In conclusion, our study revealed a protective effect of physical activity independent of outdoor time on HM and identified 13 serum metabolites involved in HM, most of which were lipid metabolites. In addition, we identified six lipid metabolic mediators in the inhibition of HM by physical activity through mediator analysis, which deepened our understanding of the underlying mechanisms of HM and provided new therapeutic targets to reduce the risk of HM by modulating specific lipid metabolites. Future studies could focus on validating these

mechanisms and exploring targeted interventions against these lipid metabolites.

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