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Association between Plasma Metabolite Levels and Myopia: A 2-Sample Mendelian Randomization Study

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Purpose: The role of plasma metabolites in myopia is still unclear, and previous studies are limited by various factors and were mostly observational. This study aims to investigate the causal relationship between plasma metabolites and myopia using 2-sample Mendelian randomization (MR).

Design: A 2-sample MR study.

Subjects and Participants: This study analyzed plasma metabolites consisting of 1091 metabolites and 309 metabolite ratios in 8299 individuals from the Canadian Longitudinal Study on Aging cohort. Summary statistics for myopia were obtained from the UK Biobank, encompassing 37 362 cases and 460 536 controls.

Methods: Causal effect estimates were primarily derived using the inverse variance weighting (IVW) method and the constrained maximum likelihood and model averaging-based MR method. Statistical significance for the MR effect estimate was defined as a false discovery rate (FDR) of <0.05. Additionally, we used the MR Steiger directionality test to examine whether exposure was directionally causal for the outcome. Furthermore, 4 supplementary methods were used for analysis: weighted median, MR-Egger, simple mode, and weighted mode.

Main Outcome Measures: Genetic causal association between plasma metabolites and myopia.

Results: The IVW analysis results indicated that elevated levels of 1-arachidonoyl-GPE (20:4n6) (P_FDR = 5.80E-06), linoleoyl-arachidonoyl glycerol (18:2/20:4)[1] (P_FDR = 2.24E-06), and linoleoyl-arachidonoyl-glycerol (18:2/20:4) [2](P_FDR = 0.0242) have a protective effect on myopia. Elevated levels of 4 plasma metabolite ratios, including the phosphate to linoleoyl-arachidonoyl-glycerol (18:2/20:4) [2] ratio (P_FDR = 0.0029), citrulline to dimethylarginine (SDMA + ADMA) ratio (P_FDR = 0.0207), oleoyl-linoleoyl-glycerol (18:1/18:2) [2] to linoleoyl-arachidonoyl-glycerol (18:2/20:4) [1] ratio (P_FDR = 0.0230), and retinol (vitamin A) to linoleoyl-arachidonoyl-glycerol (18:2/20:4) [2] ratio (P_FDR = 0.0230), were significantly associated with a higher risk of myopia.

Conclusions: This study provides evidence of a causal relationship between specific plasma metabolites and myopia, highlighting potential therapeutic targets and contributing to the understanding of myopia's etiology. Future research should include diverse populations to enhance the generalizability of these findings.

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Myopia affects approximately 23% of the world's population and has become a significant economic burden for individuals and society.[1] It increases the risk of sight-threatening complications such as myopic maculopathy, retinal detachment, glaucoma, and cataracts.[2] The prevalence of myopic maculopathy increases by 67% for every 1 diopter (D) increase in myopia.[1] The pathogenesis of myopia is complex and poorly understood. Metabolic scleral abnormalities seem to have an important role, but the underlying pathogenic mechanisms need to be further elucidated.[3]

Research has shown that myopic metabolites change not only in eye tissues but also in serum. Hou et al[4] found a significant association between myopia and carbohydrate metabolism (galactose metabolism; citric acid cycle), amino acid metabolism (arginine biosynthesis; alanine, aspartate, and glutamate metabolism), and translation processes (aminoacyl-tRNA biosynthesis).[5] Other studies, such as the study of Ke et al,[6] reported increased serum citrate levels, and Trier et al demonstrated how the 7-methylxanthine profile affected axial length growth and myopia progression.[7] Most previous clinical studies were designed as case-control studies, which makes it challenging to establish the timing of exposure and outcome. Additionally, in observational studies, the relationship between blood metabolites and myopia is susceptible to confounding factors such as age, environment, dietary pattern, and lifestyle. It is difficult to effectively control these factors in observational studies. These limitations hinder causal inferences between blood metabolites and myopia.

The purpose of this study was to investigate the causal relationship between plasma metabolite levels and myopia using a 2-sample Mendelian randomization (MR) approach. By analyzing data from the Canadian Longitudinal Study on

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Aging and UK Biobank, the study aimed to identify specific metabolites and metabolite ratios that could be causally associated with myopia. Our ultimate goal is to identify new, meaningful research directions and potential therapeutic targets for myopia from a comprehensive, whole-body perspective.

Mendelian randomization is a powerful method for exploring causal relationships by using genetic variants as instrumental variables (IVs).[8] This study employs 2-sample MR, which is particularly valuable for establishing causality rather than mere associations. By utilizing 2 independent datasets—one for genetic variant–exposure associations and another for genetic variant–outcome associations—this approach enhances the statistical power and reliability of causal inference.[9]

Methods

Study Design

This study utilized a 2-sample MR approach with publicly available datasets to examine the associations between 1400 plasma metabolites and myopia. An outline of the analytical plan is presented in Figure 1.

This study utilized data obtained from publicly available databases, ensuring compliance with the ethical principles outlined in the Declaration of Helsinki. All studies contributing data to these analyses received relevant institutional review board approvals from each participating organization's ethics committee. Specifically, the Canadian Longitudinal Study on Aging received approvals from committees including the Hamilton Health Sciences Research Ethics Board and others where applicable. The UK Biobank's ethical approval was obtained from the North West Multi-center Research Ethics Committee. All participants provided informed consent. Because the data were anonymized and collected by the original data providers with appropriate ethical approvals, individual informed consent was not required for this secondary analysis.

Mendelian randomization analysis generates robust causal inferences, which overcome measurement limitations, errors, and confounding, frequently encountered in observational studies, if the following assumptions are satisfied: (I) the IV is associated with the exposure, (II) the IV is not associated with the outcome via a confounding pathway, and (III) the IV does not affect the outcome directly but only through the exposure.[10]

Data Sources

The genome-wide association study (GWAS) summary data for plasma metabolites were obtained from the Canadian Longitudinal Study on Aging cohort.[11] Firstly, the levels of 1458 metabolites were quantified in plasma samples by Metabolon, Inc. using the ultrahigh performance liquid chromatography–tandem mass spectroscopy platform. Secondly, normalized levels of metabolites provided by the Metabolon were used, and only metabolites with missing measurements in fewer than 50% of samples (N = 1091) were retained. In total, the database contained 1091 metabolites and 309 metabolite ratios for 8299 individuals of European descent. Additionally, the inverse rank normal transformation was applied to the metabolite ratios but not to the metabolite levels. And the metabolite ratios were trimmed, keeping those that fall within 3 standard deviations. The genetic data related to myopia were sourced from the largest genome-wide meta-analysis for myopia, using data from the UK Biobank.[12] The UK Biobank is a substantial long-term medical research project that has compiled genetic and medical data from nearly half a million adults aged 40 to 69 within the UK. In this study, myopia was ascertained based on self-reported definitions. It included a total of 460 536 European subjects, with 37 362 cases and 423 174 controls.

Instrumental Variable Selection

In this study, plasma metabolites were treated as the exposure and myopia as the outcome. The selection of genetic IVs was carried out as follows: (1) selected single-nucleotide polymorphisms (SNPs), on which exposure effects were significant ($P < 1 \times 10^{-5}$); (2) SNPs were independently obtained through clumping procedures based on linkage disequilibrium with $r^2 < 0.1$ and a physical distance of more than 500 kb; (3) SNPs matched with the outcome dataset, and during harmonization, palindromic SNPs (e.g., A/T or G/C alleles) were excluded; (4) SNPs were excluded when its F-statistics $\leq$10, as an F-statistic greater than 10 is robust against weak instrument bias.

Statistical Analysis

The 2-sample MR study sought to assess the causal links between plasma metabolites and myopia. The main method, inverse variance weighted (IVW)[13] random-effects models, was used to estimate causal effects when traits were instrumented by 2 or more SNPs.[14] To reduce the risk of false-positive findings, a method based on constrained maximum likelihood and model averaging[15] was also conducted. Four additional methodologies—weighted median method, MR-Egger regression, simple mode, and weighted mode—were employed as complementary analyses. The association was considered causal if at least 2 methods provided consistent results. Additionally, we used the MR Steiger directionality test to examine whether exposure was directionally causal for the outcome.[16]

Sensitivity Analysis

The Cochran Q test within the IVW method was used to identify heterogeneity among SNPs, with $P < 0.05$ indicating heterogeneity.[17] The MR Egger method's intercept assessed the Instrument Strength Independent of Direct Effect (InSIDE) assumption, with $P_{intercept} < 0.05$ suggesting horizontal pleiotropy. A leave-one-out analysis was also conducted to enhance robustness, checking whether results depended heavily on any SNP by excluding each SNP in turn. Statistical significance for the MR effect estimate was defined as a false discovery rate (FDR) of <0.05, with the Benjamini–Hochberg procedure used for correction, addressing multiple comparisons.

Mendelian randomization analyses were performed using the "TwoSampleMR" (version 0.5.6) and "MRcML" (version 0.0.0.9)[15] packages in R (version 4.3.0, R Foundation for Statistical Computing).

Results

As shown in Table 1 and Figure 2, 9 plasma metabolites and metabolite ratios were found to be significantly associated with myopia after FDR correction. Notably, genetically predicted elevated levels of certain metabolites, including 1-arachidonoyl-GPE (20:4n6), were associated with a lower risk of myopia. Consistent results were obtained across multiple methods, including MR Egger, weighted median, simple mode, and weighted mode, with no evidence

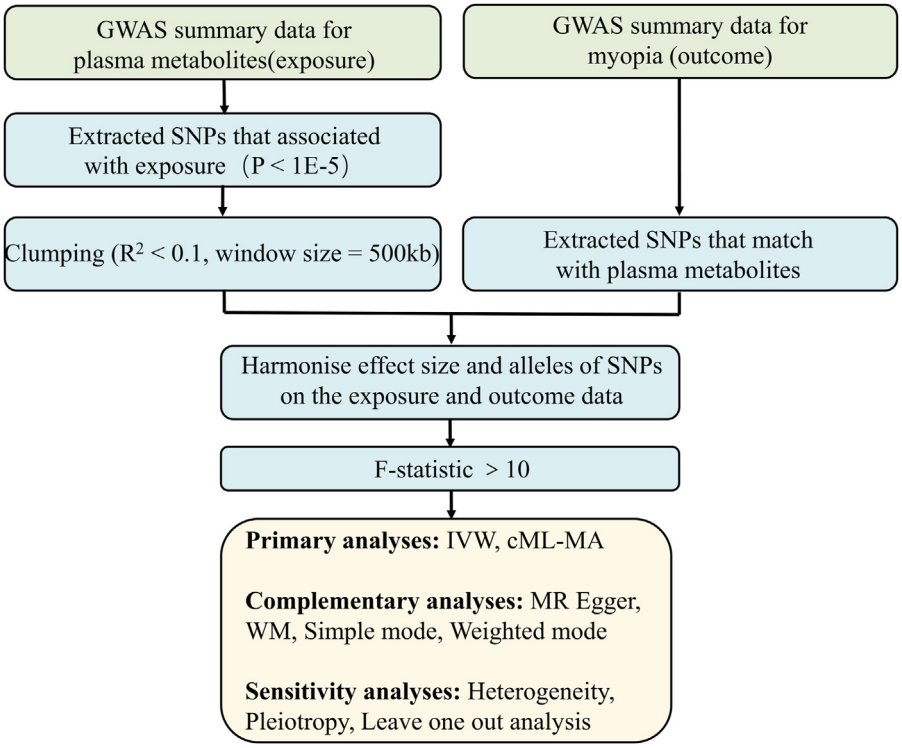

Figure 1. Overview of this Mendelian randomization (MR) analysis. cML-MA = constrained maximum likelihood and model averaging; GWAS = genome-wide association study; IVW = inverse variance weighted; SNPs = single-nucleotide polymorphisms; WM = weighted median.

of heterogeneity or pleiotropy as per the Cochran Q test and MR Egger method.

Two metabolites, linoleoyl-arachidonoyl glycerol (18:2/20:4) [1] and linoleoyl-arachidonoyl-glycerol (18:2/20:4) [2], also exhibited strong protective effects against myopia risk. Complementary analyses using 4 methods yielded consistent outcomes, reinforcing the robustness of these findings without indicating any heterogeneity or pleiotropy.

Conversely, elevated levels of 4 plasma metabolite ratios, including phosphate to linoleoyl-arachidonoyl-glycerol (18:2/20:4) [2] ratio, citrulline to dimethylarginine (SDMA + ADMA) ratio, oleoyl-linoleoyl-glycerol (18:1/18:2) [2] to linoleoyl-arachidonoyl-glycerol (18:2/20:4) [1] ratio, and retinol (vitamin A) to linoleoyl-arachidonoyl-glycerol (18:2/20:4) [2] ratio were significantly associated with an increased risk of myopia. These results were consistent across all complementary methods, and neither heterogeneity nor pleiotropy was detected.

Additionally, estimates from both IVW and constrained maximum likelihood and model averaging methods suggested that hexanoylglutamine and X-07765 had an unprotective effect on myopia. While heterogeneity was found using the Cochran Q test, no pleiotropy was detected, maintaining the validity of the causal relationships.

Leave-one-out analysis (Fig 3) demonstrated that excluding individual SNPs did not substantially alter the overall findings for the 9 plasma metabolites and metabolite ratios, as indicated by consistent error bar positioning. All positive causal associations in this study were TRUE on the MR Steiger directionality test (Table 1). This supports the reliability of the causal associations identified between these plasma metabolites and myopia.

Discussion

In this study, we conducted a 2-sample MR analysis using data from 1091 blood metabolites and 309 metabolite ratios based on recently published GWAS meta-analysis and myopia summary statistics from the UK Biobank. Our objective was to evaluate the causal relationship between blood metabolites and myopia. This is the first study to explore the causal effects of metabolite levels and ratios on myopia using genetic signals with strong biological confidence from known genes associated with metabolites. Since many metabolites are substrates and products of enzymatic reactions, understanding the genetic determinants of substrate-to-product ratios can provide insights into biological processes that may not be discernible when studying a single metabolite. Identifying genes that control metabolites and their ratios can help pinpoint intervention targets for therapeutic approaches for myopia, thereby integrating metabolism with myopia to better understand its development.

Our findings indicate that genetically determined higher levels of 1-arachidonoyl-GPE have a protective effect on myopia. This novel metabolite, related to the

Table 1. MR Estimates for the Association between Plasma Metabolites and Myopia

Exposure	MR Method	N.SNP	OR	95% CI	P Value	P_FDR	Q_pval	ple_pval	Correct Casual Direction	Steiger_pval
1-arachidonoyl-GPE (20:4n6) levels	IVW	53	0.9953	0.9938−0.9968	1.38E-09	5.80E-06	0.4688	0.8428	True	0
	cML-MA		0.9951	0.9935−0.9967	1.00E-09	5.80E-06				
Linoleoyl-arachidonoyl-glycerol (18:2/20:4) [1] levels	IVW	32	0.9947	0.9922−0.9971	2.24E-05	0.0134	0.1583	0.4061	True	2.48E-217
	cML-MA		0.9942	0.9919−0.9966	1.34E-06	0.0019				
Linoleoyl-arachidonoyl-glycerol (18:2/20:4) [2] levels	IVW	51	0.9958	0.9937−0.9979	7.49E-05	0.0242	0.1200	0.7504	True	0
	cML-MA		0.9951	0.9931−0.9971	1.85E-06	0.0019				
Phosphate to linoleoyl-arachidonoyl-glycerol (18:2/20:4) [2] ratio	IVW	43	1.0048	1.0028−1.0069	3.21E-06	0.0029	0.8844	0.3638	True	6.70E-263
	cML-MA		1.0050	1.0029−1.0071	3.39E-06	0.0029				
Oleoyl-linoleoyl-glycerol (18:1/18:2) [2] to linoleoyl-arachidonoyl-glycerol (18:2/20:4) [1] ratio	IVW	44	1.0037	1.0019−1.0055	5.98E-05	0.0230	0.4113	0.8892	True	0
	cML-MA		1.0038	1.0020−1.0056	3.63E-05	0.0190				
Retinol (vitamin A) to linoleoyl-arachidonoyl-glycerol (18:2/20:4) [2] ratio	IVW	43	1.0042	1.0021−1.0062	6.49E-05	0.0230	0.5128	0.5547	True	1.88E-262
	cML-MA		1.0045	1.0024−1.0067	3.84E-05	0.0190				
Citrulline to dimethylarginine (SDMA + ADMA) ratio	IVW	27	1.0059	1.0031−1.0087	3.07E-05	0.0172	0.4177	0.6751	True	5.64E-150
	cML-MA		1.0058	1.0030−1.0087	4.92E-05	0.0207				
Hexanoylglutamine levels	IVW	56	1.0043	1.0024−1.0063	1.58E-05	0.0102	0.0049	0.1935	True	0
	cML-MA		1.0046	1.0030−1.0063	3.13E-08	8.77E-05				
X-07765 levels	IVW	27	1.0064	1.0032−1.0097	0.0001	0.0338	0.0263	0.6750	True	5.24E-158
	cML-MA		1.0072	1.0044−1.0101	4.73E-07	0.0009				

CI = confidence interval; cML-MA = constrained maximum likelihood and model averaging; FDR = false discovery rate; IVW = inverse variance weighted; MR = Mendelian randomization; OR = odds ratio; SNP = single-nucleotide polymorphism.

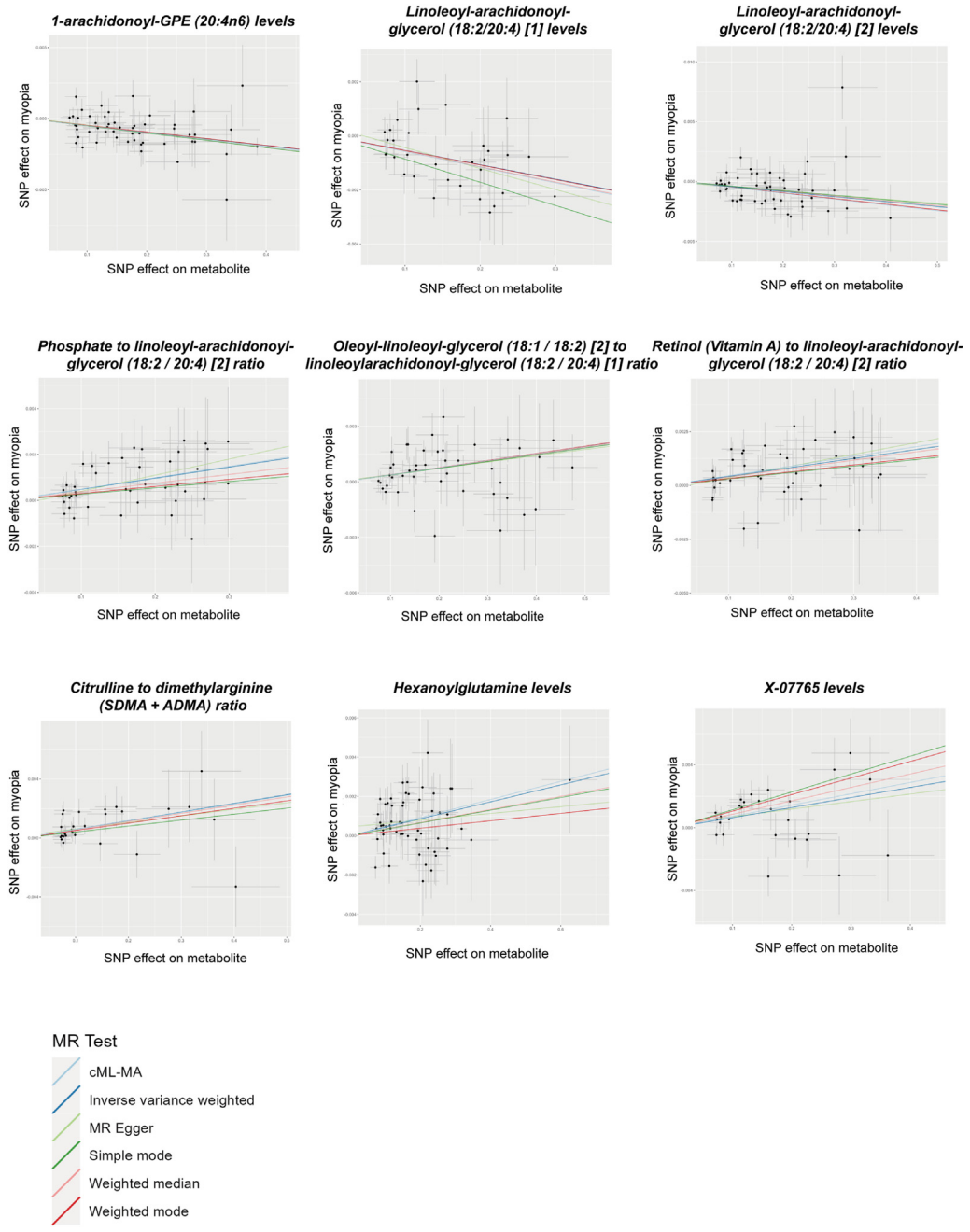

Figure 2. Scatter plots for the causal association between plasma metabolites and myopia. cML-MA = constrained maximum likelihood and model averaging; MR = Mendelian randomization; SNP = single-nucleotide polymorphism.

endocannabinoids system, can produce anandamide through the cleavage of glycerol phosphate ethanolamine by phosphodiesterase.[18,19] Notably, endocannabinoids, which are key bioactive lipid mediators, play an important role in regulating inflammation.[20,21] Inhibition of arachidonate amide hydrolase (fatty acid amide hydrolase) has been shown to reduce inflammation.[22] Besides their systemic effects,[23] endocannabinoids and their receptors are widely expressed in ocular tissues,[23] suggesting they could play important roles in the ocular tissues. For example, endocannabinoids have neuroprotective and therapeutic potential in retinal diseases[24] and promote the dilation of retinal capillaries.[25] This study indicates that 1-arachidonoyl-GPE could be a promising target for the prevention and treatment of myopia.

Our study also associates myopia with diacylglycerol (DAG) metabolism, which is consistent with findings by Dai et al, who demonstrated disordered DAG levels in the serum of patients with high myopia, suggesting its potential role in inducing oxidative stress and subsequent proinflammatory

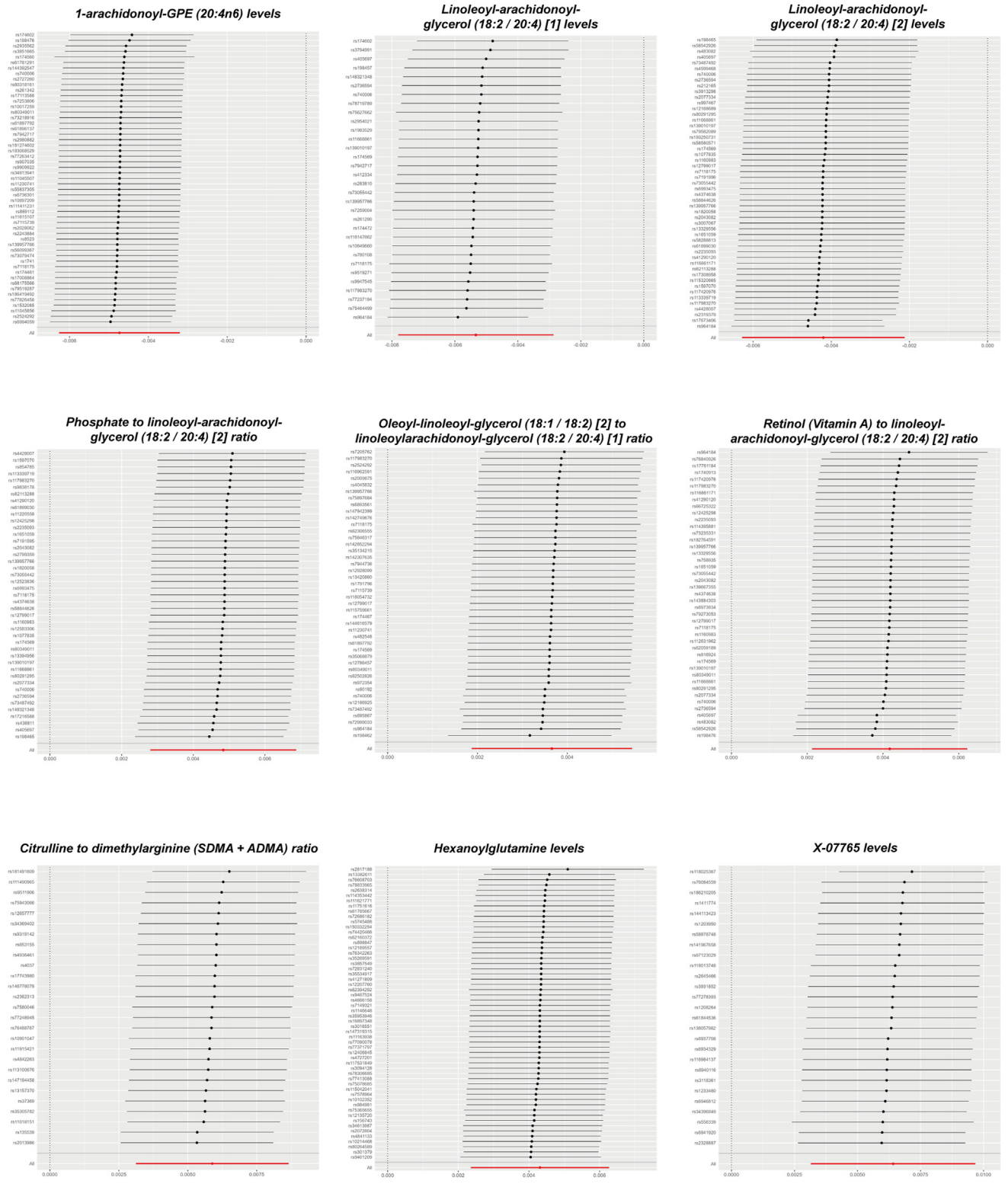

Figure 3. :Leave-one-out plots for the causal association between plasma metabolites and myopia.

effects.[26] Linoleoyl-arachidonoyl-glycerol (18:2/20:4) [1] and linoleoyl-arachidonoyl-glycerol (18:2/20:4) [2], both part of DAG subclass, showed protective effects against myopia. However, retinol (vitamin A) to linoleoyl-arachidonoyl-glycerol (18:2/20:4) [2] ratio and phosphate to linoleoyl-arachidonoyl-glycerol (18:2/20:4) [2] ratio is a

risk factor for myopia[27,28] but also the second messengers of many signal cascades.[29] The results of this study show that different DAGs have different effects on myopia. This study is the first to demonstrate the impact of the DAGs-related metabolic ratio on myopia, providing new insights into DAG metabolic disorders and myopia.

Vitamin A's role is complex, as results from Zhang et al suggested that high levels of serum vitamin A may be associated with increased prevalence of high myopia,[30] whereas Wolf et al reported lower mean serum vitamin D concentrations in myopic participants.[31] The results of this study suggest as retinol (vitamin A)-related metabolite ratio for risk factors, provides another future research train of thought. The citrulline to dimethylarginine (SDMA + ADMA) ratio also emerged as a risk factor. Barbas-Bernardos et al[32] found that metabolites such as glutamate were significantly higher in the aqueous humor of patients with high myopia. Although the role of dimethylarginine in myopia has not been studied, it has been implicated in conditions like diabetic retinopathy,[33,34] glaucoma,[35] and premature retinopathy.[36] The results of this study provide new ideas and directions for the study of the mechanism of myopia. Hexanoylglutamine and X-07765 were found to have causal but nonprotective effects on myopia, necessitating further research to confirm their roles.

This MR analysis sought to establish a causal relationship between plasma metabolites/metabolite ratios and myopia, minimizing confounding factors and reverse causality. Summary statistics of plasma metabolites and metabolite ratios were obtained from the latest GWAS meta-analysis; 31.9% of the significant genetic variant metabolite associations and 12.9% of the loci reported in this metabolite study were novel, thus ensuring the instrument power and innovation in the MR analysis. The MR-Egger regression intercept term test was used to detect and exclude horizontal pleiotropy. Sensitivity analysis with "leave one out" was used to test the reliability and stability of the analysis results. A sample MR design using nonoverlapping data minimized bias,[37] and FDR correction was applied throughout to limit false positives.

Despite these strengths, the study has limitations that should be noted when interpreting the results. Most participants in the GWAS meta-analysis of myopia were of European ancestry, potentially limiting the generalizability of the findings to other populations. We also recognize the limitation of not conducting reverse-directional MR analyses in our current study. The complexity and volume of GWAS data for plasma metabolites exceeded the capabilities of our current server infrastructure, preventing us from performing these analyses promptly. However, reverse-directional MR is crucial as it helps clarify whether metabolites contribute to myopia or if myopia affects metabolite levels. This insight is vital for enhancing causal inference and bolstering the robustness of our conclusions.

This 2-sample MR study identified several plasma metabolites and metabolite ratios causally associated with myopia and highlighted the importance of plasma metabolites in myopia. These findings suggest potential therapeutic targets for myopia and help to understand its etiology, providing new directions for future research.

Footnotes and Disclosures

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HUMAN SUBJECTS: No human subjects were included in this study. This study utilized data obtained from publicly available databases, ensuring compliance with the ethical principles outlined in the Declaration of Helsinki. As the data were anonymized and collected by the original data providers with appropriate ethical approvals, individual informed consent was not required for this secondary analysis.

No animal subjects were used in this study.

Author Contributions:

Conception and design: Jiang, Xu, Li, Zhao

Data collection: Jiang, Xu

Analysis and interpretation: Jiang, Xu, Li, Zhao

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Overall responsibility: Jiang, Xu, Li, Zhao

Abbreviations and Acronyms:
DAG = diacylglycerol; **FDR** = false discovery rate; **GWAS** = genome-wide association study; **IV** = instrumental variable; **IVW** = inverse variance weighted; **MR** = Mendelian randomization; **SNP** = single-nucleotide polymorphism.

Keywords:
Mendelian randomization, Myopia, Plasma metabolites, Genome-wide association studies, Causal analysis.

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