• Mendelian Randomization •

Causal effect of obesity on cataract and mediating roles of metabolites: a Mendelian randomization study

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Received: 2025-07-21 Accepted: 2025-11-25

Abstract

● **AIM:** To investigate the causal effect of obesity on cataract risk and explores the potential mediating roles of metabolites using Mendelian randomization (MR).

● **METHODS:** Summary-level data from large-scale genome-wide association studies to examine the relationship between obesity and cataract were utilized. Obesity-related traits, including body mass index (BMI), waist-to-hip ratio (WHR), and waist circumference (WC). A two-sample MR approach was employed to assess the causal effect of obesity on cataract risk, while potential mediators were identified from suitable genome-wide association studies (GWAS) datasets. Additionally, a metabolic pathway analysis was conducted.

● **RESULTS:** An increase of 1 standard deviation (SD) in BMI, WHR, and WC was associated with a significantly higher risk of cataract (BMI: odds ratio (OR) 1.0017, 95% confidence interval (CI): 1.0001-1.0032, *P*=0.0320; WHR: OR 1.0029, 95%CI: 1.0006-1.0051, *P*=0.0129; WC: OR 1.0020, 95%CI: 1.0001-1.0038, *P*=0.0390]. These associations remained robust after adjusting for confounding factors in multivariable MR analysis. Furthermore, a two-step MR analysis identified eight potential metabolic mediators, with one mediator showing a significant causal role in the relationship between obesity and cataract.

● **CONCLUSION:** This work highlights the importance of addressing obesity as a modifiable risk factor for cataracts, particularly through metabolic pathways.

● **KEYWORDS:** obesity; cataract; Mendelian randomization; body mass index; waist-to-hip ratio; waist circumference

DOI:10.18240/ijo.2026.03.18

Citation: Li C, Wang JM, Yang WH. Causal effect of obesity on cataract and mediating roles of metabolites: a Mendelian randomization study. *Int J Ophthalmol* 2026;19(3):564-574

INTRODUCTION

Cataract remains a leading cause of visual impairment and blindness worldwide, both in developing and developed countries. Although cataract surgery is an effective treatment, over 12 million people worldwide remain blind due to cataract[1-3]. Moreover, no effective pharmacological treatments currently exist for preventing cataract formation. Obesity, a growing public health concern, is linked to various age-related diseases[4-5]. In large-scale epidemiological studies, while measurements of body weight and height are straightforward, assessing fat distribution and fat mass often requires more invasive methods. As a result, body mass index (BMI), calculated from weight and height, is commonly used to assess overall obesity, while waist-to-hip ratio (WHR) and waist circumference (WC) are employed to evaluate fat distribution. These obesity indicators not only reflect body size but also reveal fat distribution patterns, offering a more comprehensive understanding of how obesity contributes to the risk of various diseases. Previous studies have established a connection between obesity and cataract, though the directionality of this association remains inconsistent. Some studies suggest that obesity increases cataract risk[6-7], while others have reported the opposite[8-9]. Other studies have found no association between obesity and cataract[10]. Traditional observational studies are prone to confounding, leaving uncertainty regarding whether obesity directly contributes to cataract development. Furthermore, numerous studies have explored the relationship between metabolites and cataract. Sabanayagam *et al*[11] identified an association between obesity-induced changes in serum metabolites and cortical cataract. Several studies have suggested a potential link between elevated triglycerides or low high-density lipoprotein (HDL) levels and cataract development[12-13]. Clarifying whether these metabolic changes mediate the link between obesity and cataract could improve our understanding of cataract pathophysiology and open new

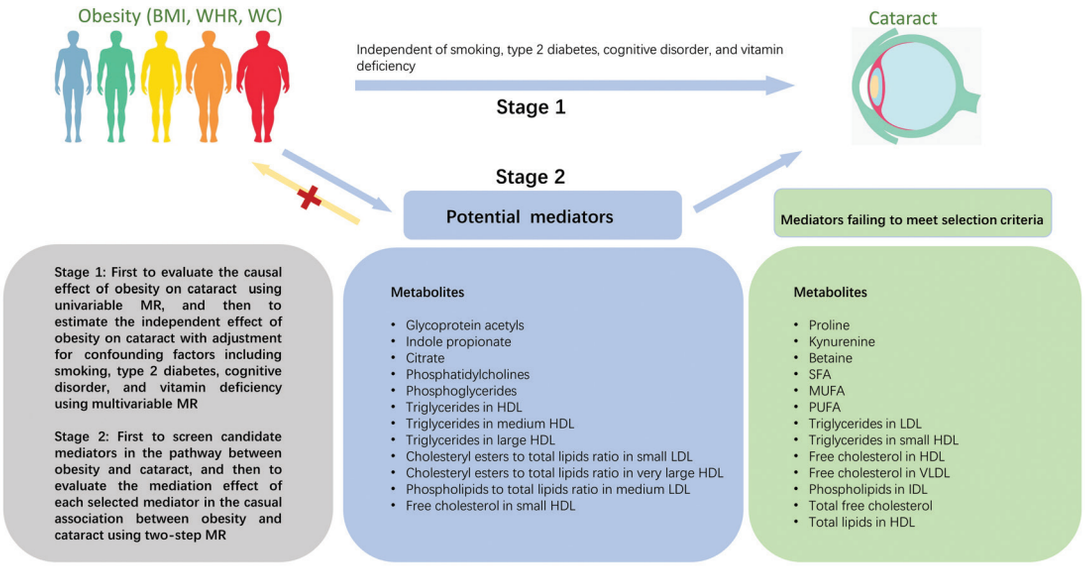

Figure 1 Schematic view of design and three key assumptions of the MR study BMI: Body mass index; WHR: Waist-to-hip ratio; WC: Waist-circumference; MR: Mendelian randomization; SFA: Saturated fatty acids; MUFA: Monounsaturated fatty acids; PUFA: Polyunsaturated fatty acids; HDL: High-density lipoprotein; LDL: Low-density lipoprotein; VLDL: Very low-density lipoprotein.

avenues for prevention and treatment. Despite growing interest in obesity-related diseases, limited research has focused on the intermediary mechanisms linking obesity to cataract.

Mendelian randomization (MR) offers a powerful tool for establishing causal relationships between exposures and outcomes, using genome-wide association data, comparable to randomized controlled trials (RCTs). However, RCTs are challenging to implement in real-world settings due to logistical and resource constraints, while MR helps overcome confounding and reverse causality. Compared to traditional observational studies, MR offers a more accurate and effective method for causal inference. To bridge this gap, MR analyses were conducted to explore the relationship between BMI, WHR, WC, and the risk of cataract, and corrected the influence of confounding factors such as smoking, type 2 diabetes, cognitive disorder and vitamin deficiency. Our main goal is to identify potential mediators and assess their impact on this causal pathway. MR utilizes genetic variants as instrumental variables (IVs) to establish causality between exposure and outcome. Since genetic variation is randomly assigned at conception, MR studies are immune to reverse causality and can address certain types of confounding, similar to RCTs[14-16]. The two-step MR approach is particularly useful for estimating mediator effects, as it tests causal mediation and corrects for certain measurement errors[17].

MATERIALS AND METHODS

Study Design This study comprised two stages (Figure 1). In the first stage, a two-sample univariable MR using summary-level statistics of genome-wide association studies (GWASs) was conducted to assess the causal effect of BMI, WHR, and WC on cataract risk. Additionally, we employed multivariable MR to assess the independent effect of BMI, WHR, and WC on cataract, while adjusting for confounding factors including smoking, type 2 diabetes, cognitive disorder, and vitamin deficiency. Moving on to the second stage, we initially screened 25 underlying mediators in the relationship between obesity and cataract. Subsequently, we utilized a two-step MR approach to assess the mediating effect of these mediators in the causal relationship pathway.

This MR study rigorously adhered to the STROBE-MR guidelines[18] and implemented different ways to ensure compliance with the three core assumptions of MR. First, the IVs exhibited a strong association with exposure variables (*i.e.*, BMI, WC, WHR). Second, the IVs were proven to be independent of any confounding factors influencing the association between the exposure and the outcome (*i.e.*, cataract). At last, the IVs solely influenced the outcome *via* the exposure variables, excluding any direct or indirect pathways. To conduct our study, summary-level statistics were utilized, sourced from reputable consortia or studies primarily involving individuals of European descent. All original studies referenced in this research had obtained informed consent and ethical approval. This study utilized only publicly available GWAS summary statistics from previously published studies, all of which had obtained appropriate ethical approvals. Since no individual-level data were accessed nor new human subjects recruited, additional ethical review was not required.

Selection, Processing, and Data Sources of IVs Table 1 lists the data sources utilized in our study. Single nucleotide polymorphisms (SNPs) that demonstrated genome-wide significance ($P<5\times10^{-8}$ for BMI, WHR, WC, and each potential mediator) were obtained from the respective GWASs. To select

Table 1 GWAS data sources of the MR study

Phenotype	GWAS ID	Sample size or case/control	Ancestry	Unit	Consortium/cohort
Exposure					
BMI	ieu-a-785	152893	European	SD (kg/m^2)	GIANT
WHR	ieu-a-73	212244	European	SD	GIANT
WC	ieu-a-65	104405	European	SD (cm)	GIANT
Covariate					
Smoking	ieu-b-4877	311629/321173	European		GSCAN
Type 2 diabetes	ebi-a-GCST007516	48286/250671	European		
Cognitive disorder	ieu-b-4837	9997	European		Within family GWAS
Vitamin deficiency	ebi-a-GCST010144	443734	European		
Mediator: metabolites					
Indole propionate	met-a-475	7803	European	$\log_{10}$ units	
Proline	met-a-355	7816	European	$\log_{10}$ units	
Kynurenine	met-a-375	7816	European	$\log_{10}$ units	
Betaine	met-a-362	7806	European	$\log_{10}$ units	
SFA	met-d-SFA	114999	European		
MUFA	met-d-MUFA	114999	European		
PUFA	met-d-PUFA	114999	European		
Phosphatidylcholines	met-d-Phosphatidylc	114999	European		
Phosphoglycerides	met-d-Phosphoglyc	114999	European		
Citrate	met-d-Citrate	115064	European		
Glycoprotein acetyls	met-d-GlycA	115078	European		
HDL-TG	met-d-HDL_TG	115078	European		
LDL-TG	met-d-LDL_TG	115078	European		
M-HDL-TG	met-d-M_HDL_TG	115078	European		
L-HDL-TG	met-d-L_HDL_TG	115078	European		
S-HDL-TG	met-d-S_HDL_TG	115078	European		
S-LDL-CE	met-d-S_LDL_CE_pct	115078	European		
XL-HDL-C	met-d-XL_HDL_C_pct	115053	European		
M-LDL-PL	met-d-M_LDL_PL_pct	115078	European		
S-HDL-FC	met-d-S_HDL_FC	115078	European		
HDL-FC	met-d-HDL_FC	115078	European		
VLDL-FC	met-d-VLDL_FC	115078	European		
IDL-PL	met-d-IDL_PL	115078	European		
Total-FC	met-d-Total_FC	115078	European		
HDL-L	met-d-HDL_L	115078	European		
Outcome					
Cataract	ukb-b-2285	1061/461949	European	SD	MRC-IEU

GWAS: Genome-wide association study; MR: Mendelian randomization; BMI: Body mass index; WHR: Waist-to-hip ratio; WC: Waist circumference; SFA: Saturated fatty acids; MUFA: Monounsaturated fatty acids; PUFA: Polyunsaturated fatty acids; HDL: High-density lipoprotein; LDL: Low-density lipoprotein, VLDL: Very low-density lipoprotein; HDL-TG: Triglycerides in HDL; LDL-TG: Triglycerides in LDL; M-HDL-TG: Triglycerides in medium HDL; L-HDL-TG: Triglycerides in large HDL; S-HDL-TG: Triglycerides in small HDL; S-LDL-CE: Cholesteryl esters to total lipids ratio in small LDL; XL-HDL-C: Cholesterol to total lipids ratio in very large HDL; M-LDL-PL: Phospholipids to total lipids ratio in medium LDL; S-HDL-FC: Free cholesterol in small HDL; HDL-FC: Free cholesterol in HDL; VLDL-FC: Free cholesterol in VLDL; IDL-P: Phospholipids in IDL; Total-FC: Total free cholesterol; HDL-L: Total lipids in HDL; SD: Standard deviation; GIANT: Genetic Investigation of Anthropometric Traits; GSCAN: GWAS and Sequencing Consortium of Alcohol and Nicotine use; MRC-IEU: MRC Integrative Epidemiology Unit.

independent genetic variants, SNPs were further grouped based on a linkage disequilibrium threshold of $r^2<0.01$ within a 10 000 kb window.

Obesity (BMI, WHR, and WC) The researchers extracted summary statistics for individuals' genetic variants associated with their BMI from a Meta-analysis of 152 893 European

participants conducted by the Genetic Investigation of Anthropometric Traits (GIANT) Consortium. This study used a two-stage Meta-analysis approach to obtain BMI-associated loci in European adults. In the first stage, a Meta-analysis of 80 GWAS with a total of 234 069 individuals were performed, followed by the incorporation of data from 34 additional studies (n=88 137) in the second stage[19]. For WHR and WC data, a Meta-analysis of 212 244 European participants also conducted by the GIANT Consortium. This study aimed to identify genetic association with WHR and WC-related traits and successfully identified 49 loci associated with WHR and WC from 57 previously or new described GWAS. Additionally, data from up to 67 326 European participants from 44 Metabochip studies were included. The combined Meta-analyses included a vast number of autosomal single nucleotide polymorphisms (SNPs) (up to 2 542 447) and up to 210 088 individuals of European ancestry[20].

Confounding factors The selection of confounding factors for multivariable MR adjustment was based on their well-established dual associations with both obesity and cataract pathogenesis. GWAS summary statistics for confounding factors included smoking from the GSCAN Consortium (311 629 cases and 321 173 controls), type 2 diabetes (48 286 cases and 250 671 controls), cognitive disorder from the family GWAS Consortium (9997 individuals), and vitamin deficiency (443 734 individuals).

Candidate mediators Obesity and cataract are closely related to the metabolites[21-22]. Therefore, we focused on some related candidate mediators, including 25 metabolites, which were closely related to ophthalmic diseases (7803 individuals for indole propionate, 7816 individuals for proline and kynurenine, 7806 individuals for betaine, 114 999 individuals for SFA, MUFA, PUFA, phosphatidylcholines and phosphoglycerides, 115 064 individuals for citrate, 115 078 individuals for glycoprotein acetyls, triglycerides in HDL, low-density lipoprotein (LDL), medium HDL, large HDL and small HDL, cholesteryl esters to total lipids ratio in small LDL, phospholipids to total lipids ratio in medium LDL, free cholesterol in small HDL, HDL and very low-density lipoprotein (VLDL), phospholipids in IDL, total free cholesterol, total lipids in HDL, and 115 053 individuals for cholesterol to total lipids ratio in very large HDL.

Candidate mediators were selected based on prior literature linking them to ophthalmic diseases or metabolic pathways implicated in cataract pathogenesis. For example, lipids and lipoproteins have been associated with cataract in epidemiological studies[12,23-24], while glycoprotein acetyls are markers of systemic inflammation linked to age-related diseases[25]. Amino acids (*e.g.*, proline, kynurenine) and energy metabolism markers (*e.g.*, citrate) were included due to their roles in oxidative stress and protein aggregation in the lens[26-27]. A total of 25 metabolites were chosen to cover key pathways such as glycerophospholipid metabolism, fatty acid metabolism, and amino acid metabolism.

Cataract Genetic instruments associations with cataract were identified through an extensive GWAS Meta-analysis involving 1061 European cataract cases and 461 949 European controls. This comprehensive study, conducted by the MRC-IEU Consortium, provided valuable data on the genetic factors associated with cataract.

Statistical Analysis

Univariable and multivariable MR analyses To conduct univariable MR analyses, we employed five methods to assess the robustness of our results under different assumptions. The main analysis utilized the inverse variance weighted (IVW) method, which is a traditional method that merges the wald ratio estimates of each IV in a Meta-analysis manner[28]. Additionally, we performed sensitivity analyses using the weighted median, MR-Egger, weighted mode, and simple mode methods. To address potential pleiotropic bias, the MR-Egger method was employed. The weighted median estimate is the median of the weighted empirical distribution function of individual SNP ratio estimates. On the other hand, the weighted mode and simple mode clustered the SNPs based on the similarity of their causal effects and estimated the causal effect from the largest cluster. To assess heterogeneity, we conducted the Cochran Q test. Furthermore, we used MR-Egger regression intercept test to identify the horizontal pleiotropy. The strength of instruments was measured using F-statistics, and an F statistic >10 suggests strong instruments[29]. Additionally, we mainly used multivariable inverse variance weighted (MV-IVW) for multivariate MR analysis.

Effect of obesity on cataract We conducted univariable MR analysis to evaluate the overall effect of obesity (BMI, WHR, WC) on cataract, the estimates are presented as odds ratios (OR) with 95% confidence intervals (95%CI). For any detected pleiotropic SNP, the MR-PRESSO outlier test was performed to remove these SNPs and rectify the horizontal pleiotropy[30]. Furthermore, a leave-one-out analysis was also conducted to assess the influence of individual IV on causalities. Considering that certain recognized risk factors for cataract could act as confounders due to their causal role in cataract development and close relationship with obesity[31], we conducted multivariable MR analysis to evaluate the independent effect of obesity on cataract while adjusting for four confounding factors: smoking, type 2 diabetes, cognitive disorder, and vitamin deficiency.

Mediator selection and two-step MR We initially employed univariable MR to assess the causal relationships between these potential mediators and cataract. For those mediators that were

found to have an impact on cataract risk, we investigated the causal relationships between obesity (BMI, WHR, or WC) and these mediators. To account for multiple testing, we calculated an adjusted *P*-value using the Benjamini-Hochberg method of false discovery rate (FDR) correction. We considered IVW results with $P<0.05$ and FDR<0.05 as strong evidence. If the evidence that BMI, WHR or WC influenced the mediators, and these mediators also influenced cataract risk, then these mediators were the ones we choose for further study. We subsequently conducted two-step MR analyses to assess the mediation effect of each mediator in the causal relationship. In step one, we used univariable MR to evaluate the causal effect ($\beta 1$) of genetically identified BMI, WHR and WC on the mediator. In step two, we estimated the causal effect ($\beta 2$) of each mediator on cataract risk using univariable MR. The statistical analyses were conducted by "TwoSampleMR", "MRPRESSO" and "fdrtool" packages in R.

RESULTS

Univariable and Multivariable MR Analysis for the Causal, Independent Effect of Obesity on Cataract The average F statistic values for BMI, WHR, and WC instruments were 63, 48, and 61, respectively. These values indicate that the genetic instruments effectively predict obesity index (BMI, WHR, and WC). In the univariable MR analysis, every 1-standard deviation (SD) increase in genetically determined BMI was associated with a higher risk of cataract [OR (IVW): 1.0017; 95%CI: 1.0001–1.0032; P=0.0320)]; An elevated risk of cataract was observed with each 1-SD increased in WHR [OR (IVW): 1.0029; 95%CI: 1.0006-1.0051; P=0.0129]; each 1-SD higher WC was associated with an elevated cataract risk [OR (IVW): 1.0020; 95%CI: 1.0001–1.0038; P=0.0390]. No outlier SNPs were detected by MR-PRESSO, and the MR-Egger intercept tests provided no evidence for pleiotropy ($P_{\text{BMI-intercept}}$=0.5389; $P_{\text{WHR-intercept}}$=0.3176; $P_{\text{WC-intercept}}$=0.5704), and the Cochran Q statistic showed no heterogeneity ($P_{\text{BMI-heterogeneity}}$=0.8418; $P_{\text{WHR-heterogeneity}}$=0.7011; $P_{\text{WC-heterogeneity}}$=0.8529). The results of the leave-one-out analysis indicated that none of the single SNP drove the findings (Figure 2).

The causal relationship between BMI, WHR, WC and cataract remained statistically significant in the multivariable MR analyses, even after adjusting for smoking, type 2 diabetes, cognitive disorder, and vitamin deficiency. The ORs (95%CIs) for BMI ranged from 1.0015 (1.0001–1.0029) to 1.0020 (1.0006–1.0034); The ORs (95%CIs) for WHR ranged from 1.0025 (1.0005–1.0044) to 1.0034 (1.0012–1.0055); The ORs (95%CIs) for WC ranged from 1.0013 (1.0004–1.0022) to 1.0022 (1.0009–1.0035; Figure 3).

Univariable MR Analysis for the Causal Effects of Candidate Mediators on Cataract Among the 25 potential mediators, twelve were found to have a causal link with an elevated risk of cataracts. Among these, six mediators partially mediate the effect of BMI on cataract, seven mediators partially mediate the effect of WHR on cataract, and three mediators partially mediate the effect of WC on cataract. It is worth noting that glycoprotein acetyls were the common candidate mediator of BMI, WHR, and WC in the influence of cataract risk (Figure 4). There was compelling evidence indicating causal relationships between genetically determined higher levels of phosphatidylcholines (OR: 1.0011; 95%CI: 1.0002–1.0020; P=0.0212), phosphoglycerides (OR: 1.0011; 95%CI: 1.0002–1.0020; P=0.0225), citrate (OR: 1.0014; 95%CI: 1.0000–1.0027; P=0.0487), glycoprotein acetyls (OR: 1.0014; 95%CI: 1.0002–1.0026; P=0.0225), triglycerides in HDL (OR: 1.0011; 95%CI: 1.0002–1.0019; P=0.0127), triglycerides in medium HDL (OR: 1.0011; 95%CI: 1.0002–1.0020; P=0.0159), triglycerides in large HDL (OR: 1.0007; 95%CI: 1.0001–1.0014; P=0.0238), cholesteryl esters to total lipids ratio in small LDL (OR: 1.0010; 95%CI: 1.0000–1.0020; P=0.0489), free cholesterol in small HDL (OR: 1.0013; 95%CI: 1.0002–1.0025; P=0.0213) with cataract risk, while lower indole propionate (OR: 0.9953; 95%CI: 0.9911–0.9996; P=0.0321), phospholipids to total lipids ratio in medium LDL (OR: 0.9984; 95%CI: 0.9971–0.9997; P=0.0162), and cholesterol to total lipids ratio in very large HDL (OR: 0.9991; 95%CI: 0.9983–0.9999; P=0.0308) with cataract risk. The average F statistics for the genetic instruments were 22 or higher, suggesting minimal risk of weak instrument bias. The majority of these findings demonstrated no signs of pleiotropy or heterogeneity between the candidate mediators and cataract.

Univariable MR Analysis for the Causal Effects of BMI, WHR, and WC on Mediators We performed two-step MR analyses on twelve candidate mediators, which included glycoprotein acetyls [OR (BMI): 1.1285; 95%CI:1.0486–1.2144; P=0.0012; OR (WHR): 1.1458; 95%CI: 1.0091–1.3010; P=0.0357; OR (WC): 1.1257; 95%CI: 1.0161–1.2471; P=0.0235], phosphatidylcholines [OR (BMI): 0.8555; 95%CI: 0.7660–0.9556; P=0.0057; OR (WHR): 0.9147; 95%CI: 0.7408–1.0475; P=0.0348], phosphoglycerides [OR (BMI): 0.8705; 95%CI: 0.7815–0.9697; P=0.0118], indole propionate [OR (WHR): 0.8705; 95%CI: 0.7815-0.9697; P=0.0420], citrate [OR (WC): 1.1257; 95%CI: 1.0161–1.2471; P=0.0235], free cholesterol in small HDL [OR (BMI): 0.9078; 95%CI: 0.8264–0.9972; P=0.0436], phospholipids to total lipids ratio in medium LDL [OR (BMI): 1.0616; 95%CI: 1.0001–1.1268; P=0.0497], triglycerides in large HDL [OR (BMI): 0.9165; 95%CI: 0.8621-0.9742; P=0.0052; OR (WC): 0.9117; 95%CI: 0.8581–0.9686; P=0.0028], triglycerides in HDL [OR (WHR): 1.2045; 95%CI: 1.0061–1.4420; P=0.0427] triglycerides in medium HDL [OR (WHR): 1.2042; 95%CI: 1.0087–1.4377;

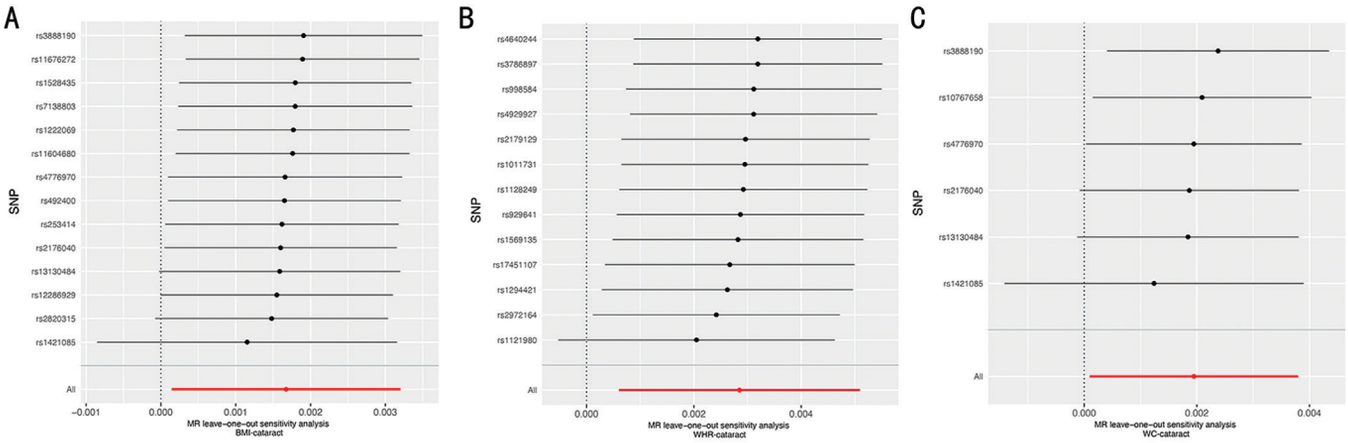

Figure 2 Leave-one-out plots for the causal association between BMI, WHR, WC, and cataract A: BMI-cataract; B: WHR-cataract; C: WC-cataract. BMI: Body mass index; WHR: Waist-to-hip ratio; WC: Waist circumference; MR: Mendelian randomization; SNPs: Single nucleotide polymorphisms.

BMI	cataract	OR (95%CI)	*P* value
Unadjusted		1.0017 (1.0001-1.0032)	0.0320
Adjusted for smoking		1.0016 (1.0004-1.0029)	0.0121
Adjusted for type 2 diabetes		1.0015 (1.0001-1.0029)	0.0312
Adjusted for cognitive disorder		1.0017 (1.0006-1.0029)	0.0026
Adjusted for vitamin deficiency		1.0020 (1.0006-1.0034)	0.0044
WHR	**cataract**	**OR (95%CI)**	***P* value**
Unadjusted		1.0029 (1.0006-1.0051)	0.0129
Adjusted for smoking		1.0025 (1.0005-1.0044)	0.0124
Adjusted for type 2 diabetes		1.0034 (1.0012-1.0055)	0.0023
Adjusted for cognitive disorder		1.0028 (1.0008-1.0048)	0.0071
Adjusted for vitamin deficiency		1.0027 (1.0006-1.0047)	0.0103
WC	**cataract**	**OR (95%CI)**	***P* value**
Unadjusted		1.0020 (1.0001-1.0038)	0.0390
Adjusted for smoking		1.0018 (1.0003-1.0033)	0.0223
Adjusted for type 2 diabetes		1.0021 (1.0006-1.0037)	0.0072
Adjusted for cognitive disorder		1.0013 (1.0004-1.0022)	0.0059
Adjusted for vitamin deficiency		1.0022 (1.0009-1.0035)	0.0007

Figure 3 Univariable and multivariable MR estimates for the causal, independent effect of BMI, WHR, and WC on cataract BMI: Body mass index; WHR: Waist-to-hip ratio; WC: Waist circumference; OR: Odds ratio; CI: Confidence interval; MR: Mendelian randomization.

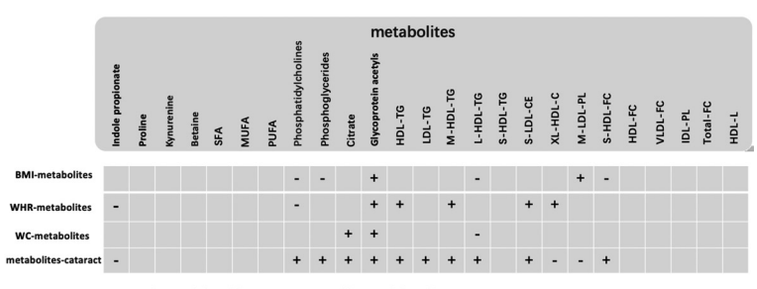

Figure 4 Evidence for the selection of mediators in the association between BMI, WHR, WC, and cataract BMI: Body mass index; WHR: Waist-to-hip ratio; WC: Waist-circumference; SFA: Saturated fatty acids; MUFA: Monounsaturated fatty acids; PUFA: Polyunsaturated fatty acids; HDL: High-density lipoprotein; LDL: Low-density lipoprotein; VLDL: Very low-density lipoprotein; HDL-TG: Triglycerides in HDL; LDL-TG: Triglycerides in LDL; M-HDL-TG: Triglycerides in medium HDL; L-HDL-TG: Triglycerides in large HDL; S-HDL-TG: Triglycerides in small HDL; S-LDL-CE: Cholesteryl esters to total lipids ratio in small LDL; XL-HDL-C: Cholesterol to total lipids ratio in very large HDL; M-LDL-PL: Phospholipids to total lipids ratio in medium LDL; S-HDL-FC: Free cholesterol in small HDL; HDL-FC: Free cholesterol in HDL; VLDL-FC: Free cholesterol in VLDL; IDL-PL: Phospholipids in IDL; Total-FC: Total free cholesterol; HDL-L: Total lipids in HDL; IVW: Inverse variance weighted.

Table 2 MR estimates for the causal effects of BMI, WHR and WC on mediators and the causal effects of mediators on cataract

Exposure	Mediator	β1 (95%CI)	β2 (95%CI)	β (mediation)
BMI	Glycoprotein acetyls	0.1209 (0.0475–0.1943)	0.0014 (0.0002–0.0026)	0.00016926
WHR	Glycoprotein acetyls	0.1361 (0.0091–0.2631)	0.0014 (0.0002–0.0026)	0.00019054
	HDL-TG	0.1861 (0.0061–0.3660)	0.0011 (0.0002–0.0019)	0.00020471
	M-HDL-TG	0.1858 (0.0086–0.3631)	0.0011 (0.0002–0.0020)	0.00020438
	S-LDL-CE	0.1540 (0.0068–0.3011)	0.0010 (0.0001–0.0020)	0.000154
WC	Glycoprotein acetyls	0.1184 (0.0159–0.2208)	0.0014 (0.0002–0.0026)	0.00016576
	Citrate	0.0689 (0.0121–0.1257)	0.0014 (0.0001–0.0027)	0.00009646

BMI: Body mass index; WHR: Waist-to-hip ratio; WC: Waist-circumference; HDL-TG: Triglycerides in HDL; M-HDL-TG: Triglycerides in medium HDL; S-LDL-CE: Cholesteryl esters to total lipids ratio in small LDL; MR: Mendelian randomization.

P=0.0398], cholesterol to total lipids ratio in very large HDL [OR (WHR): 1.1216; 95%CI: 1.0307–1.2205; P=0.0078] and cholesteryl esters to total lipids ratio in small LDL [OR (WHR): 1.1664; 95%CI: 1.0068–1.3514; P=0.0403], which were causally influenced by BMI, WHR, WC and continued to have casual effects on cataract after controlling for confounding variables (Figure 4). Most of these results showed no evidence of pleiotropy and heterogeneity between candidate mediators and cataract. Table 2 shows the causal effect of BMI, WHR, and WC on mediators (β1) and the causal effect of mediators on cataract (β2) and $\beta_{mediation}$. The interactive causal associations of mediators between obesity (BMI, WHR, WC) and cataract are summarized in Figure 5.

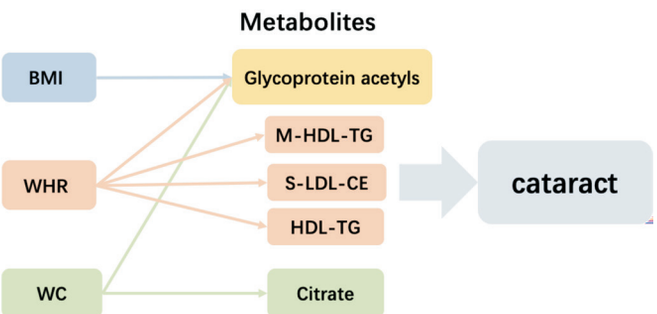

Figure 5 Directed acyclic graph of the proposed causal interactions between metabolites in the pathway between BMI, WHR, WC, and cataract The arrows indicate the direction of causality from BMI, WHR, and WC, through mediators identified in this MR study, to cataract. MR: Mendelian randomization; BMI: Body mass index; WHR: Waist-to-hip ratio; WC: Waist-circumference; HDL: High-density lipoprotein; LDL: Low-density lipoprotein; HDL-TG: Triglycerides in HDL; M-HDL-TG: Triglycerides in medium HDL; S-LDL-CE: Cholesteryl esters to total lipids ratio in small LDL.

DISCUSSION

This MR study evaluated a novel assessment of the independent causal impact of obesity on the risk of cataract, determined candidate metabolic mediators, and conducted metabolic pathway analysis involved in its causal relationship and potential mediators. Based on the comprehensive MR analysis using powerful obesity-related genetic tools and various methods, genetically determined 1 SD increase in BMI, WHR, and WC were found to have a causal relationship with a higher risk of cataract. Even after adjusting for confounding variables including smoking, type 2 diabetes, cognitive disorder, and vitamin deficiency, the detrimental effects of BMI, WHR, and WC on cataract still persisted. Although we adjusted for several key confounders in our multivariable MR analysis, we cannot rule out residual confounding from other factors such as diet, physical activity, sunlight exposure, and socioeconomic status. These variables are known to influence cataract risk but were not available in the GWAS data we used. Future studies with more comprehensive genetic and environmental data are needed to address this limitation. Among the 25 mediators, twelve mediators were determined to partially mediate the effect of obesity on cataracts, including glycoprotein acetyls, phosphatidylcholines, phosphoglycerides, free cholesterol in small HDL, phospholipids to total lipids ratio in medium LDL, and triglycerides in large HDL, indole propionate, cholesteryl esters to total lipids ratio in small LDL and in very large HDL, triglycerides in HDL and in medium HDL, and citrate. Enrichment analysis revealed that the metabolic pathway including “Linoleic acid metabolism”, “Alpha-Linolenic acid metabolism”, “Citrate cycle (TCA cycle)”, “Alanine, aspartate and glutamate metabolism”, “Glyoxylate and dicarboxylate metabolism”, “Arachidonic acid metabolism”, “Glycerophospholipid metabolism”, “N-Glycan biosynthesis”, “Steroid biosynthesis”, “Primary bile acid biosynthesis”, and “Steroid hormone biosynthesis” may involve in the causal relationship among obesity and cataract and their potential mediators.

Glycoprotein acetyl reflects the composite changes in the number and complexity of N-glycan side chains on acute-phase response proteins during acute and chronic inflammatory states. Acetylation modifications of glycoproteins may be significantly associated with the development and progression of cataract. As a common post-translational modification of lens proteins, acetylation can participate in the pathological processes of cataracts by affecting the structural stability,

chaperone function, and protein interactions of α- and βγ-crystallins[32-33].

Studies suggest that acetylation may have a dual role: on one hand, acetylation modificationscan enhance protein stability and resist the disruptive effects of otherpathological modifications; on the other hand, excessive acetylation may alter the charge distribution of crystallins, promoting their binding to cell membranes and increasing light scattering. This paradoxical effect may be related to the site specificity and degree of modification. For instance, Lapko *et al*[34] found that acetylation at specific sites on αB-crystallin coexists with carboxymethylation, potentially forming a complex regulatory network.

Our research findings offer fresh perspectives on the impact of obesity on the pathogenic mechanism of cataract and the metabolic pathways linking obesity to cataract. The role of oxidative stress in the development of age-related cataract is significant[35]. Obesity is linked to hyperleptinemia, which can trigger oxidative stress and result in lens oxidative damage[36]. Studies have demonstrated that chronic low-grade inflammation and oxidative stress associated with obesity primarily damage OFF-type retinal ganglion cells, which are more vulnerable to metabolic stress, leading to reduced contrast gain and delayed response saturation[37]. The impaired ganglion cells, may weaken antioxidant support for lens epithelial cells by decreasing neurotrophic factor transport. Furthermore, systemic inflammatory mediators elevated in obesity, along with reactive oxygen species released from ganglion cells, can diffuse through the vitreous/aqueous humor to the lens, activating the sorbitol pathway and reducing adenosine triphosphate levels, ultimately accelerating oxidative aggregation and opacification of lens proteins[7]. A further limitation is that our cataract outcome was defined as a combined group without subtype stratification (*e.g.*, nuclear, cortical, posterior subcapsular). Given the distinct pathogenesis of cataract subtypes, our results may not capture subtype-specific effects. We encourage future MR studies to perform subtype-specific analyses once large-scale GWAS data for cataract subtypes are available.

Ye *et al*[38], Pan *et al*[39], and Ling *et al*[40] have confirmed that obesity is a risk factor for incident cataract. However, other study has suggested a negative correlation between obesity and cataract[41]. Although many studies investigating the relationship between obesity and cataract, the findings are not consistent. The inconsistent results in existing studies may be partially explained by different demographic characteristics, different diagnostic methods for cataract, as well as the influences from potential confounding factors such as underlying systemic diseases, vitamin deficiencies, and lifestyle habits. By minimizing potential confounding effects using the MR method, our study extends previous evidence and demonstrates a causal adverse effect of obesity on cataract, independent of confounding factors including smoking, type 2 diabetes, cognitive disorder, and vitamin deficiency, and emphasizes obesity as an important indicator for predicting and preventing cataract risk. As obesity often leads to abnormalities in metabolites in the body, and metabolites are related to the pathogenesis of cataract, this study investigated the causal mediators that regulate the relationship between obesity and cataract. Previous studies have described the relationship between certain lipid metabolites and cataract. Paunksnis *et al*[42] found that there is a positive correlation between high triglyceride levels and subtypes of cataract in middle-aged women. Similarly, the Beaver Dam Eye Study revealed that low levels of HDL cholesterol were associated with cortical cataract in female patients[43]. In the Framingham Offspring Heart Study, it was observed that low HDL levels and high triglyceride levels were linked to posterior subcapsular cataract in male patients[44]. Animal studies have further demonstrated that low levels of HDL cholesterol can accelerate the development of diabetic cataract induced by LDL cholesterol-induced inflammation and oxidative stress[45]. Additionally, there is a correlation between low levels of HDL cholesterol and cortical cataract[46]. In addition, only a few amino acids and lipoprotein subclasses were confirmed as mediators involved in the causal relationship between obesity and cataract in our study.

It is worth mentioning that glycoprotein acetyls are the only common mediator in the causal relationship between the three obesity indicators (BMI, WHR, WC) and cataract. As a composite biomarker of protein glycosylation, glycoprotein acetyls are closely associated with adverse cardiovascular metabolic outcomes, reduced life expectancy, and overall mortality. Furthermore, recent studies have found strong correlations between glycoprotein acetyls and conditions such as gout[47], cognitive impairment[48], and type 2 diabetes, and it may serve as a preferred biomarker for systemic inflammation in type 2 diabetes complications[49]. However, there are currently no reports on the association between glycoprotein acetyls and cataract. Given the associations between gout, type 2 diabetes, cognitive impairment, and the occurrence of cataract, as well as their potential as risk factors for cataract progression, it is likely that glycoprotein acetyls play a role in the mechanisms underlying cataract development. Phospholipids and phosphatidylglycerols may also be involved in the mechanisms of age-related cataract development. An *in vitro* experimental studies have found that in a high-oxygen-induced cataract model, the oxidative degree of lens epithelial cells is more active, and lipases eliminate oxidized unsaturated glycerides, leading to an increasing composition of phosphatidylcholines in cell membranes. This change in

membrane tissue caused by oxidative stress is consistent with the age-related changes in human lens epithelial cells[50]. Citrate, as an ancient metabolite, has extensive utilization in the diagnosis and treatment of ocular disorders. It affects various pathological and physiological processes of cataract, as advanced glycation end products induce irreversible changes in lens structural proteins. Citrate inhibits the formation of advanced glycation end products (AGEs) and the unfolding and aggregation of lens proteins, thereby suppressing the development of cataract[51]. However, there is limited knowledge regarding the association between indole propionate and cataract at present.

Our findings open several promising translational avenues that warrant further investigation. First, these metabolites could serve as valuable biomarkers for early risk stratification in obese populations, enabling personalized prevention strategies tailored to individual metabolic profiles. Second, our results suggest the potential for repurposing existing metabolic therapies—particularly anti-inflammatory agents and lipid-modifying drugs—for cataract prevention, though this application requires rigorous clinical validation to establish efficacy and safety in ocular contexts.

However, it is important to acknowledge the limitations of our study. First, our study is based on an analysis of the metabolome. While blood has traditionally been considered a reliable source of metabolite data, it would be beneficial to conduct further research analyzing changes in metabolites in the lens or aqueous humor, which are the direct pathological sites of cataract. Such research would aid in the identification of more promising biomarkers. Second, to ensure genetic background consistency, this MR study is almost entirely limited to individuals of European ancestry, so caution should be exercised when generalizing our findings to other ethnic populations. To address this, we specifically recommend future validation studies in diverse ethnic cohorts, particularly in Asian and African populations where cataract prevalence patterns differ. Thirdly, although the observed ORs for BMI, WHR, and WC in relation to cataract risk were modest (ranging from 1.001 to 1.003 per 1-SD increase), they reached statistical significance in our large-scale genetic analysis. These effect sizes, while small, may still hold public health relevance given the high global prevalence of obesity. However, their direct clinical applicability at the individual level may be limited, and future research should focus on identifying high-risk subgroups or synergistic effects with other factors. Lastly, although our MR analysis has identified several key metabolites associated with obesity-related cataracts, the functional mechanisms of these molecules still require further experimental validation. Recent advances in lens organoid models have opened new opportunities for such research. Notably, organoids derived from induced pluripotent stem cells now enable genotype-specific investigation of metabolic pathways, which helps bridge our population-level findings with individualized mechanisms. However, current limitations in modeling age-related changes and systemic metabolic interactions highlight the need to integrate animal studies and multi-omics approaches for comprehensive validation of these metabolic mediators.

In conclusion, this MR study provides robust and innovation evidence regarding the causal impact of obesity on the risk of cataract and deepens understanding of the potential pathways mediated by lipoprotein subclasses, fatty acids, amino acids, and other factors linking obesity to cataract. Additionally, we have covered a wide range of genetic variables to investigate the causal association between obesity and cataract. The genetic variables of obesity include data from three GWAS datasets on BMI, WHR, and WC. Our study has conducted a systematic and thorough analysis of the metabolic profiles associated with cataract development. Furthermore, by utilizing the MR approach, this study effectively minimizes the impact of reverse causality and residual confounding variables. The inference of the causal association between obesity and cataract risk in this study is considered reliable due to extensive sensitivity analysis that has ruled out the possibility of pleiotropy.

ACKNOWLEDGEMENTS

Data analysis on obesity and cataract are available through the GWAS database. The authors thank these researchers for their selfless sharing.

Authors' Contributions: Chen L was involved in the analysis and interpretation of data and in writing the original draft of the manuscript. Wang JM was involved in the acquisition of data and the design of the work. Yang WH and Wang JM contributed to the design of the study, project administration, and critically edited the manuscript. All authors contributed to the article and approved the submitted version.

Data Availability Statement: The original contributions presented in the study are included in the article/supplementary material, further inquiries can be directed to the corresponding author.

Foundations: Supported by the National Natural Science Foundation of China (No.82501261); Medical Research Projects of the Jiangsu Provincial Health Commission (No. M2024041).

Conflicts of Interest: Li C, None; **Wang JM,** None; **Yang WH,** None.

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