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Peer Reviewer of *World Journal of Clinical Cases*, Ralph Victor Yap, MD, RN, Assistant Professor, Surgeon, Department of Surgery, Cebu Doctors' University Hospital, Cebu 6000, Philippines. rvyapmd@gmail.com

AIMS AND SCOPE

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ORIGINAL ARTICLE

Clinical and Translational Research

Modifiable factors mediating the effects of educational attainment on gestational diabetes mellitus: A two-step Mendelian randomization study

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Abstract

BACKGROUND

Although there is currently a wealth of evidence to indicate that maternal educational attainment is associated with gestational diabetes mellitus (GDM), the specific modifiable risk factors that mediate the causal relationship between these two variables have yet to be identified.

AIM

To identify the specific modifiable risk factors that mediate the causal relationship between the level of maternal education and GDM.

METHODS

Mendelian randomization (MR) was conducted using data from genome-wide association studies of European populations. We initially performed a two-sample MR analysis using data on genetic variants associated with the duration of education as instruments, and subsequently adopted a two-step MR approach using metabolic and lifestyle factors as mediators to examine the mechanisms underlying the relationship between the level of maternal education and risk of developing GDM. In addition, we calculated the proportions of total causal effects mediated by identified metabolic and lifestyle factors.

RESULTS

A genetically predicted higher educational attainment was found to be associated with a lower risk of developing GDM (OR: 0.71, 95%CI: 0.60-0.84). Among the metabolic factors assessed, four emerged as potential mediators of the education-GDM association, which, ranked by mediated proportions, were as follows: Waist-to-hip-ratio (31.56%, 95%CI: 12.38%-50.70%), body mass index (19.20%, 95%CI: 12.03%-26.42%), high-density lipoprotein cholesterol (12.81%, 95%CI: 8.65%-17.05%), and apolipoprotein A-1 (7.70%, 95%CI: 4.32%-11.05%). These

findings proved to be robust to sensitivity analyses.

CONCLUSION
Our findings indicate a causal relationship between lower levels of maternal education and the risk of developing GDM can be partly explained by adverse metabolic profiles.

Key Words: Educational status; Gestational diabetes mellitus; Metabolism; Lifestyle factors; Mendelian randomization analysis

Core Tip: Studies have shown that the level of maternal education is associated with the risk of developing gestational diabetes mellitus (GDM). In this study, we sought to identify the specific modifiable risk factors that mediate the causal relationship between the level of maternal education and the likelihood of developing GDM. We performed Mendelian randomization analyses based on publicly available data obtained in a number of genome-wide association studies of European populations. Our findings indicate that a genetically predicted higher level of maternal education is associated with a lower GDM risk and that four modifiable metabolic factors contribute to mediating this association, namely, waist-to-hip ratio, body mass index, and the contents of high-density lipoprotein cholesterol and apolipoprotein A-1.

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INTRODUCTION

Gestational diabetes mellitus (GDM) is defined as a type of glucose intolerance that is initially detected during pregnancy [1]. It is a disorder of substantial public health significance worldwide, with prevalence estimates as high as 14%[2]. Moreover, the prevalence of GDM tends to be characterized by marked inter-population variance due to differences in associated risk factors and approaches to screening and diagnosis. GDM is associated with a higher risk of short- and long-term adverse health outcomes in both mothers and their offspring. Specifically, mothers diagnosed with GDM have been established to be more susceptible to the subsequent development of type 2 diabetes[3], metabolic syndrome[4], and cardiovascular disease[5]. Among the offspring of affected mothers, exposure to GDM in utero tends to increase the predisposition to adverse outcomes, not only in the perinatal period but also in later life. These include, although are not limited to, pre-term birth[6], excessive fetal growth[7], neonatal hypoglycemia[8], autism spectrum disorder[9], obesity [10], and cardiometabolic dysfunction[11].

Educational attainment is a robust predictor of socioeconomic achievement and has extensive implications for lifestyle behaviors and health resource utilization throughout life[12,13]. A robust and compelling body of epidemiological evidence indicates that women with a lower level of educational attainment are disproportionately affected by GDM[14]. An accumulating body of epidemiological research supports the potential advantages of mitigating modifiable risk factors, primarily metabolic factors and lifestyle behaviors, for the prevention and management of GDM[15]. However, whether education independently influences the risk of developing GDM and the degree to which modifiable factors mediate such effects remain unknown. Accordingly, elucidating the mediatory pathways linking educational attainment and GDM could enable the identification of targets for public health policies and interventions aimed at reducing the excess GDM risk arising from socioeconomic disadvantage.

Mendelian randomization (MR) has become an important epidemiological method for assessing causal relationships between exposures and outcomes. MR uses genetic variants, typically single-nucleotide polymorphisms (SNPs) identified from genome-wide association studies (GWASs), as instrumental variables (IVs) to better evaluate exposure-outcome associations[16]. Compared with conventional observational studies, the MR approach is potentially less susceptible to residual confounding, as genetic variants are randomly assigned at meiosis and conception[17]. Hence, MR can substantially enhance the validity and reliability of causal inferences. Additionally, MR minimizes the reverse causation bias as germline genotypes cannot be altered by disease onset or progression[18]. The successful application of MR is dependent on three key assumptions. First, the selected instrumental genetic variables should be strongly associated with the exposure of interest; second, these genetic variables should not be associated with any potential confounders of the exposure-outcome relationship; and third, the genetic variables exclusively influence outcomes *via* exposure[19]. When these assumptions are fulfilled, MR can provide compelling evidence for the causal relationship between exposure and outcome.

In this study, we adopted a two-sample MR approach to assess the causal relationship between maternal educational attainment and the risk of developing GDM. In addition, to guide clinical practice, we conducted MR mediation analyses to examine the extent to which metabolic and lifestyle factors may mediate the effects of educational attainment.

MATERIALS AND METHODS

Study design

We initially performed univariable MR (UVMR) analysis to assess the causal relationship between educational attainment and the risk of developing GDM, in which we conducted a comprehensive screening for potential factors that might mediate this relationship. Subsequently, we employed a two-step MR approach to estimate the mediatory effects of these factors. All data used in this study were derived from publicly available data obtained from studies that had appropriate participant consent and ethical approval. Moreover, the study was conducted in accordance with the Strengthening the Reporting of Observational Studies in Epidemiology guidelines for MR studies[20].

Data sources

Education attainment: Genetic variants for educational attainment were extracted from a GWAS of years of schooling encompassing 1131881 individuals of European descent performed by the Social Science Genetic Association Consortium. Summary statistics were accessible for 766345 of these participants upon the exclusion of those from 23andMe (Table 1).

Metabolic and lifestyle factors: Thirty-two modifiable factors (20 metabolic and 12 lifestyle factors) that we hypothesized might mediate the relationship between education and GDM were selected, and genetic variants for these mediators were extracted from the GWAS data (Table 1). Candidate mediators of the effects of education on GDM were selected according to certain prerequisites. First, the causal relationship between education and a mediator must be unidirectional, given that bi-directionality could compromise the validity of the mediation analyses. Second, the causal association between the mediator and GDM should persist irrespective of whether it is adjusted for education. Third, extant evidence dictates that the relationship between education and a mediator, and that between the mediator and GDM, should be in opposite directions. Ultimately, we identified four metabolic mediators that satisfied all stipulations and these were incorporated into the analyses to assess their mediating influence on the causal relationship between the level of maternal education and the risk of developing GDM.

GDM: Summary statistics for GDM were extracted from the Release 8 data of the GWAS performed by the FinnGen consortium (Table 1), which encompassed 190879 Finnish women, comprising 11279 cases and 179600 controls. GDM cases were defined by code O24.4 in the International Classification of Diseases-9th and 10th revisions.

To avoid biases from population stratification, in the main analysis, summary statistics for exposures, mediators, and outcomes were extracted from the GWAS data conducted predominantly on subjects of European ancestry.

Selection of IVs: To ensure the validity and accuracy of the inferences from this MR study, stringent quality control procedures were employed to select the optimal IVs for exposure, mediators, and outcomes. To obtain powerful IVs, we initially extracted SNPs from the GWAS dataset at a genome-wide significance threshold of $P < 5 \times 10^{-8}$. However, given the extremely limited number of qualified IVs obtained for total, early, and late gestational weight gain (GWG) at this threshold, we subsequently applied a relatively less stringent threshold ($P < 5 \times 10^{-5}$) to obtain a sufficiently large dataset. For genetic variants of interest, we selected a minor allele frequency threshold of 0.01. A fundamental principle of the MR approach is the absence of linkage disequilibrium (LD) between the included IVs, as substantial LD could yield biased results. We accordingly selected genetic variants that achieved independence at LD ($r^2 = 0.001$) and a distance of 10000 kb from the European 1000 Genome Reference Panel. Furthermore, to avoid accidental bias during harmonization, we removed palindromic SNPs, and to avoid the potential influence of horizontal pleiotropy on the MR estimates, we used PhenoScanner to identify and remove SNPs associated with other potential confounders affecting the outcome[21]. Finally, to evaluate the strength of the IVs, we generated *F*-statistics for each SNP, and to minimize potential weak instrument bias, SNPs with *F* values < 10 were deleted[22].

Statistical analysis

UVMR: The UVMR method was used to assess the total impact of the exposure (educational attainment) on the outcomes (GDM and the selected mediators). The primary method of analysis used in this MR study was inverse variance weighted (IVW), which combines Wald ratios *via* a random-effects meta-analysis[23].

Mediation MR analyses

We conducted a two-stage MR analysis to investigate whether any modifiable factors mediated the causal relationship between educational attainment and the risk of GDM. In the initial stage, we employed IVW as the primary approach to estimate the causal effects of educational attainment on each potential mediator (β1), and in the second stage, we assessed the causal effects of each mediator on GDM risk after adjusting for the genetic influence of the IVs on education (β2) using regression-based multivariable MR (MVMR)[24]. The individual mediatory effect of each mediator was then calculated by multiplying the results from the two stages (β1 × β2)[25]. The proportion of the total effect of educational attainment on the risk of GDM mediated by each mediator was estimated by dividing the indirect effect by the total effect. Standard errors were derived using the delta method, based on the effect estimates obtained from the two-sample MR analysis[26].

Sensitivity analyses: To validate the robustness of the IVW results in UVMR analyses, we employed MR-Egger[27], weighted median[28], and MR-pleiotropic residual sum and outliers (MR-PRESSO) methods[29]. In addition, we used MVMR Egger sensitivity to validate the robustness of the IVW results in the MVMR analyses. Each approach is dependent on different hypothetical models to evaluate the causal effects. The MR-Egger method provides estimates adjusted for pleiotropy[27], whereas the weighted median approach allows for causal effect estimation when 50% of the

Table 1 Summary of the genome-wide association study data used in the mendelian randomization analyses

Phenotype	Datatype	Sample size	Population	Consortium/cohort
Exposure				
Education	Continuous	766345	European	SSGAC
Outcome				
GDM	Binary	190879	European	FinnGen
Metabolic factors				
BMI[1]	Continuous	681275	European	GIANT
BF%	Continuous	65831	European	Meta
Waist circumference	Continuous	231353	European	GIANT
WHR[1]	Continuous	212244	European	GIANT
Total GWG	Continuous	10555	European	EGG
Early GWG	Continuous	7704	European	EGG
Late GWG	Continuous	7681	European	EGG
Hypertension	Binary	342439	European	FinnGen
Systolic blood pressure	Continuous	757601	European	UK Biobank
Diastolic blood pressure	Continuous	757601	European	UK Biobank
LDL-C	Continuous	440546	European	UK Biobank
HDL-C[a]	Continuous	403943	European	UK Biobank
Triglyceride	Continuous	441016	European	UK Biobank
Apolipoprotein A-1[1]	Continuous	393193	European	UK Biobank
Apolipoprotein B	Continuous	439214	European	UK Biobank
Serum urate	Continuous	110347	European	GUGC
Serum iron	Continuous	23986	European	GISC
Ferritin	Continuous	23986	European	GISC
Transferrin	Continuous	23986	European	GISC
Transferrin saturation	Continuous	23986	European	GISC
Lifestyle factors				
Strenuous sports or other exercises	Continuous	350492	European	UK Biobank
Moderate to vigorous physical activity	Continuous	377234	European	UK Biobank
Sedentary behavior	Continuous	91105	European	UK Biobank
Smoking initiation	Binary	1232091	European	GSCAN
Smoking cessation	Binary	547219	European	GSCAN
Smoking heaviness	Continuous	337334	European	GSCAN
Alcohol drinking	Continuous	941280	European	GSCAN
Coffee consumption	Continuous	375833	European	UK Biobank
Insomnia	Binary	1331010	European	UK Biobank
Sleep duration	Continuous	446118	European	UK Biobank
Long sleep duration	Binary	339926	European	UK Biobank
Short sleep duration	Binary	446118	European	UK Biobank

[1]Candidate mediators met all criteria of mediator selection.

GDM: Gestational diabetes mellitus; BMI: Body mass index; BF: Body fat; WHR: Waist-to-hip ratio; GWG: Gestational weight gain; LDL-C: Low-density lipoprotein cholesterol; HDL-C: High-density lipoprotein cholesterol; SSGAC: Social Science Genetic Association Consortium; GIANT: Genetic Investigation of Anthropometric Traits; EGG: Early Growth Genetics Consortium; GUGC: Global Urate Genetics Consortium; GISC: Genetics of Iron Status Consortium; GSCAN: GWAS & Sequencing Consortium of Alcohol and Nicotine use.

SNPs are invalid[28], and the MR-PRESSO technique is used to detect and correct outliers, thereby yielding MR estimates that are robust to heterogeneity after removing the identified outliers[29]. We performed MR-Egger regression intercept analysis to assess horizontal pleiotropy, and also assessed heterogeneity using the IVW and MRI-Egger methods based on Cochran's Q statistic.

All MR analyses were conducted using the TwoSampleMR, MRPRESSO, MR, and MVMR packages in R (version 4.1.3). To account for multiple testing in the UVMR analyses, we applied a Bonferroni corrected significance level of P value < 1.52×10^{-3} (= 0.05/33). For MVMR analysis, we set the statistical significance at a P value < 0.05.

RESULTS

Effects of education on GDM

In the UVMR analyses, the results of IVW revealed that a genetically predicted higher level of maternal education attainment (OR: 0.71, 95%CI: 0.60-0.84) was associated with a lower risk of GDM (Table 2). MR-Egger and MR-PRESSO sensitivity analyses confirmed the robustness of the IVW results. There was adequate instrument strength (F-statistics > 10) among the genetic variants assessed for educational attainment (Table 2). The IVs selected based on educational attainment were characterized by sustained heterogeneity and no pleiotropy (Supplementary Tables 1 and 2).

Effects of education on different mediators

We identified four candidate mediators for inclusion in the mediation MR analyses, namely, waist-to-hip ratio (WHR), body mass index (BMI), high-density lipoprotein cholesterol (HDL-C), and apolipoprotein A-1 (Table 1). In UVMR analyses, each genetically predicted single standard deviation increase in years of schooling was associated with lower levels of WHR (β: -0.22, 95%CI: -0.29 to -0.16) and BMI (β: -0.16, 95%CI: -0.21 to -0.11) and higher levels of HDL-C (β: 0.18, 95%CI: 0.15-0.21) and apolipoprotein A-1 (β: 0.13, 95%CI: 0.10-0.16). At least two or three sensitivity analyses confirmed the IVW estimates (Table 2). Genetic IVs for educational attainment exhibited sustained heterogeneity and no pleiotropy (Supplementary Tables 1 and 2). The F-statistics of the IVs were greater than 10, thereby tending to indicate an absence of any substantial weak instrument bias (Table 2). In the reverse MR analyses, we found that there was a causal association between BMI (β: -0.12, 95%CI: -0.14 to -0.10) and HDL-C (β: 0.02, 95%CI: 0.01-0.03) and educational attainment, which were largely driven by horizontal pleiotropy (Supplementary Table 3).

Effects of different mediators on GDM with adjustment for education

In the MVMR results, a higher WHR (OR: 2.31, 95%CI: 1.65-3.23) and BMI (OR: 1.53, 95%CI: 1.32-1.76) were found to be associated with an increased GDM risk after adjustment for education (Table 3). In contrast, higher levels of HDL-C (OR: 0.76, 95%CI: 0.70-0.82) and apolipoprotein A-1 (OR: 0.81, 95%CI: 0.74-0.89) were shown to be associated with a reduced GDM risk having adjusted for education (Table 3). MVMR sensitivity analyses validated the sustained heterogeneity and absence of pleiotropy across the selected genetic variants (Supplementary Table 4).

Mediating effects of mediators in the association between education and GDM

Figure 1 depicts the proportions of the effects of educational attainment on GDM risk explained by each of the four identified mediators. WHR accounted for 31.56% (95%CI: 12.38%-50.70%) of the total influence of educational attainment on the risk of GDM, whereas BMI explained 19.20% (95%CI: 12.03%-26.42%) of the total effect, an HDL-C and apolipoprotein A-1 mediated 12.81% (95%CI: 8.65%-17.05%) and 7.70% (95%CI: 4.32%-11.05%) of the total effect, respectively.

DISCUSSION

This MR study provides compelling novel evidence of the causal protective effect of educational attainment on GDM susceptibility. To elucidate the factors associated with this effect, we further assessed potential intermediaries in the path from education to GDM and identified four modifiable risk factors as causal mediators, which, ranked in terms of proportional mediation in the association between education and GDM, were WHR (31.56%), BMI (19.20%), HDL-C (12.81%), and apolipoprotein A-1 (7.70%). Our findings accordingly highlight the causal protective role of education and the substantial mediatory influence of several prevalent metabolic factors on the pathogenesis of GDM.

These findings build on previous work by providing further evidence to indicate that attainment of a higher level of education is a protective factor against the likelihood of developing GDM. Accumulating evidence from observational and MR studies indicates that a higher level of education is protective against hyperglycemia[14,30]. Educational attainment represents a modifiable and malleable factor with an enduring influence on financial status, access to social

Table 2 Univariable mendelian randomization estimating the causal effect of education on candidate mediators and gestational diabetes mellitus

Phenotype	Method	nSNPs	*F*-statistics	Beta	95%CI	*P* value
Outcome						
GDM	IVW	294	49.21	-0.34	-0.51 to -0.18	3.80E-05
	MR Egger	294		-0.41	-1.04 to 0.22	0.21
	Weighted Median	294		-0.38	-0.59 to -0.16	5.47E-04
	MR-PRESSO	294		-0.34	-0.51 to -0.18	4.95E-05
Mediators						
WHR	IVW	145	47.46	-0.22	-0.29 to -0.16	2.76E-12
	MR Egger	145		-0.36	-0.63 to -0.08	0.01
	Weighted Median	145		-0.23	-0.32 to -0.15	1.16E-07
	MR-PRESSO	145		-0.22	-0.29 to -0.16	9.50E-11
BMI	IVW	106	44.47	-0.16	-0.21 to -0.11	1.97E-10
	MR Egger	106		-0.17	-0.43 to 0.09	0.19
	Weighted Median	106		-0.15	-0.19 to -0.10	7.27E-09
	MR-PRESSO	106		-0.16	-0.21 to -0.11	5.26E-09
HDL-C	IVW	245	46.18	0.18	0.15 to 0.21	1.75E-34
	MR Egger	245		0.15	0.03 to 0.27	0.02
	Weighted Median	245		0.17	0.13 to 0.21	2.81E-20
	MR-PRESSO	245		0.18	0.15 to 0.21	3.38E-27
Apolipoprotein A-1	IVW	266	48.41	0.13	0.10 to 0.16	8.03E-19
	MR Egger	266		0.05	-0.06 to 0.17	0.34
	Weighted Median	266		0.11	0.08 to 0.15	3.07E-10
	MR-PRESSO	266		0.13	0.10 to 0.16	1.19E-16

nSNPs: Number of single-nucleotide polymorphisms; GDM: Gestational diabetes mellitus; WHR: Waist-to-hip ratio; BMI: Body mass index; HDL-C: High density lipoprotein cholesterol; IVW: Inverse variance weighted; MR-PRESSO: Mendelian randomization-pleiotropic residual sum and outliers.

Table 3 Multivariable mendelian randomization assessing the causal association between each mediator and gestational diabetes mellitus with adjustment for education from inverse variance weighted results

Mediators	nSNPs	Beta	SE	OR	95%CI	*P* value
WHR	154	0.84	0.17	2.31	1.65 to 3.23	1.00E-06
BMI	420	0.42	0.07	1.53	1.32 to 1.76	5.59E-09
HDL-C	381	-0.28	0.04	0.76	0.70 to 0.82	1.59E-10
Apolipoprotein A-1	358	-0.21	0.05	0.81	0.74 to 0.89	6.08E-06

nSNPs: Number of single-nucleotide polymorphisms; WHR: Waist-to-hip ratio; BMI: Body mass index; HDL-C: High density lipoprotein cholesterol.

capital, and the adoption of healthy lifestyles over the course of an individual's lifespan[31]. Moreover, although formal education typically concludes in early adulthood, adopting a lifelong learning perspective provides opportunities to continually acquire knowledge and contributes to enhancing cognitive abilities and promoting long-term health throughout adult life[31]. Thus, our findings offer key insights into prioritizing educational policies and reducing educational inequities as effective precautionary measures against GDM and its related disease burden.

A further salient finding of this study was our identification and quantification of the mediatory roles of certain metabolic factors in the relationship between education and GDM. On the basis of the application of stringent criteria, we identified four causal mediators, among which BMI and WHR appeared to be the principal mediators of the effects of

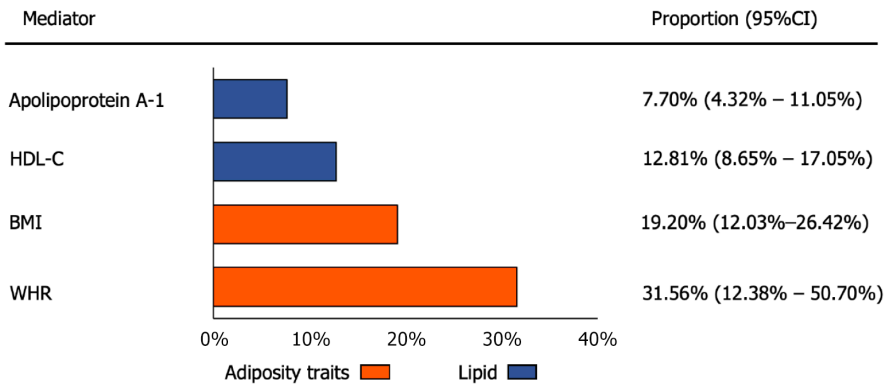

Figure 1 Mendelian randomization estimates of proportional mediation by candidate mediators in the causal relationship between educational attainment and gestational diabetes mellitus. HDL-C: High-density lipoprotein cholesterol; BMI: Body mass index; WHR: Waist-to-hip ratio.

education on the risk of developing GDM. These findings are consistent with previous epidemiological and MR evidence indicating that obesity, measured primarily *via* BMI and WHR, is strongly associated with GDM, thereby indicating that interventions targeting obesity may have the desired effects in low-education scenarios[32,33]. Of the other two identified mediators, HDL-C and apolipoprotein A-1 were shown to be associated with 12.81% and 7.70% of the causal effect of education on the risk of GDM, respectively. Notably, obesity and dyslipidemia are major public health issues that often co-occur and have common biological underpinnings, including immune inflammation and abnormal neuroendocrine regulation and energy metabolism[12,34]. Thus, given the inter-relationships among these four mediators, we suspect that there may be a certain degree of overlap in the proportional mediatory effects of these factors.

Our MR findings of no causal links between genetically predicted GDM and several metabolic and lifestyle factors would tend to indicate that significant relationships detected in observational studies may partly stem from residual confounding or a reverse causation bias, including adiposity traits (body fat percentage, waist circumference[33], total, early, and late GWG[35]), lipids (low-density lipoprotein cholesterol[36], and apolipoprotein B[37]), physical activity and sedentary behaviors[38] (moderate to vigorous physical activity levels and sedentary behavior), sleep-related traits[39,40] (insomnia, sleep duration, long sleep duration, and short sleep duration), and smoking and dietary behaviors[41] (smoking initiation, smoking cessation, smoking heaviness, alcohol consumption[42], and coffee consumption[43]).

To the best of our knowledge, this MR study is the first to establish the causal effects of education on the likelihood of developing GDM, and to identify causal intermediaries in the path between education and GDM. The study has several notable strengths. First, it uses SNPs as genetic instruments to mitigate confounding and reverse causation. Second, the robustness of the IVW estimates was demonstrated by performing multiple MR sensitivity analyses under different assumptions regarding genetic pleiotropy[44]. Third, our application of stringent criteria for mediator selection minimized the reverse causation of mediators on education, thereby ensuring the credibility and rationale of our proposed model explaining the mediating influence. However, despite these strengths, the study does have certain limitations. First, the heterogeneity of the SNPs may have introduced bias and influenced the robustness of our MR findings. Second, the GWAS data used for analyses were obtained from a European population, limiting the generalizability of our results to other ethnicities pending further study. Finally, sample overlap between GWASs may have biased the MR estimates toward observational association estimates[45].

CONCLUSION

In this MR study, we succeeded in elucidating the causal protective influence of educational attainment on the risk of developing GDM and identified four causal mediators underlying the impact of education, namely, WHR, BMI, HDL-C, and apolipoprotein A-1. Our findings in this study provide novel insights into the mechanisms underlying the association between educational attainment and GDM susceptibility.

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FOOTNOTES

Author contributions: Ma MY provide an idea, find data, data analysis, and manuscript checking; Zhao YS write the first draft and data visualization; all authors have read and agreed to publish the manuscript; all authors participated in data interpretation, revisions, and

approved the final version submitted for publication.

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