



Basic Study

Causal effect of education on type 2 diabetes: A network Mendelian randomization study

Li-Zhen Liao, Zhi-Chong Chen, Wei-Dong Li, Xiao-Dong Zhuang, Xin-Xue Liao

ORCID number: Li-Zhen Liao 0000-0001-5807-2339; Zhi-Chong Chen 0000-0002-8691-6399; Wei-Dong Li 0000-0003-1430-9749; Xiao-Dong Zhuang 0000-0001-6508-8507; Xin-Xue Liao 0000-0001-7631-1866.

Author contributions: Liao LZ and Chen ZC conceived the study and contributed equally to this study; Li WD completed the analyses; Zhuang XD led the writing; Liao XX supervised the study.

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Li-Zhen Liao, Wei-Dong Li, Department of Health, Guangdong Pharmaceutical University, Guangzhou 510275, Guangdong Province, China

Li-Zhen Liao, Wei-Dong Li, Guangdong Provincial Key Laboratory of Pharmaceutical Bioactive Substances, Guangdong Pharmaceutical University, Guangzhou 510006, Guangdong Province, China

Zhi-Chong Chen, Department of Cardiology, The Sixth Affiliated Hospital of Sun Yat-Sen University, Guangzhou 510080, Guangdong Province, China

Xiao-Dong Zhuang, Xin-Xue Liao, Department of Cardiology, The First Affiliated Hospital of Sun Yat-Sen University, Guangzhou 510080, Guangdong Province, China

Corresponding author: Xin-Xue Liao, PhD, Chief Physician, Department of Cardiology, The First Affiliated Hospital of Sun Yat-Sen University, No. 58 Zhongshan 2nd Road, Yuexiu District, Guangzhou 510080, Guangdong Province, China. liaoxinx@mail.sysu.edu.cn

Abstract

BACKGROUND

The causality between education and type 2 diabetes (T2DM) remains unclear.

AIM

To identify the causality between education and T2DM and the potential metabolic risk factors [coronary heart disease (CHD), total cholesterol, low-density lipoprotein, triglycerides (TG), body mass index (BMI), waist circumference (WC), waist-to-hip ratio (WHR), fasting insulin, fasting glucose, and glycated hemoglobin] from summarized genome-wide association study (GWAS) data used a network Mendelian randomization (MR).

METHODS

Two-sample MR and network MR were performed to obtain the causality between education-T2DM, education-mediator, and mediator-T2DM. Summary statistics from the Social Science Genetic Association Consortium (discovery data) and Neale Lab consortium (replication data) were used for education and DIAGRAMplusMetabochip for T2DM.

RESULTS

The odds ratio for T2DM was 0.392 (95%CI: 0.263-0.583) per standard deviation

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increase (3.6 years) in education by the inverse variance weighted method, without heterogeneity or horizontal pleiotropy. Education was genetically associated with CHD, TG, BMI, WC, and WHR in the discovery phase, yet only the results for CHD, BMI, and WC were replicated in the replication data. Moreover, BMI was genetically associated with T2DM.

CONCLUSION

Short education was found to be associated with an increased T2DM risk. BMI might serve as a potential mediator between them.

Key Words: Mendelian randomization; Education; Type 2 diabetes mellitus; Genome-wide association study; Coronary heart disease; Body mass index

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Core Tip: Genetically predicted education was negatively causally associated with type 2 diabetes (T2DM). The odds ratio for T2DM was 0.392 (95%CI: 0.263-0.583) per standard deviation increase (3.6 years) in education. Body mass index might serve as a potential mediator.

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INTRODUCTION

Type 2 diabetes mellitus (T2DM), affecting approximately 415 million people, has become a major global health problem. This number will rapidly increase to 642 million by 2040^[1]. Environmental, genetic, and metabolic risk factors all contribute to T2DM^[2]. Among these, controlling the modifiable risk factors to decrease the T2DM morbidity, turns into a key public health priority^[3]. A previous systematic review and meta-analysis reported that diabetes self-management education can reduce all-cause mortality risk in T2DM patients^[4], indicating that education may help T2DM management. However, the causality between primary education (years of schooling) and T2DM remains unclear. If the causal association exists, the potential pathways involved in the association from education to T2DM have not yet been studied.

Mendelian randomization (MR) serves as a strategy for assessing the causality between disease and common risk factors^[5]. Since the genetically determined risk factors occur before the disease onset, MR can avoid the potential bias of reverse causation in retrospective studies. The risk of confounding is also reduced^[6]. In this study, the causality between education and T2DM was analyzed and potential metabolic risk factors were explored from summarized genome-wide association study (GWAS) data. The potential metabolic risk factors included coronary heart disease (CHD), total cholesterol (TC), low-density lipoprotein (LDL), triglycerides (TG), body mass index (BMI), waist circumference (WC), waist-to-hip ratio (WHR), fasting insulin, fasting glucose, and glycated hemoglobin (HbA1c).

MATERIALS AND METHODS

GWAS data summary

Summary data from array-based analysis for single nucleotide polymorphism (SNP) was included. We selected all SNPs associated with education at genome-wide significance ($P < 5 \times 10^{-8}$) in the available GWAS (Supplementary Table 1). The metrics of SNP quality were requested as follows. There was strong evidence of between-study heterogeneity in the SNP-trait association ($P \leq 0.005$). The imputation quality metric (info or r^2) was ≤ 0.90 , and there was Hardy-Weinberg disequilibrium ($P \leq$

0.001). Summary statistics from the Social Science Genetic Association Consortium (SSGAC)^[6] and Neale Lab consortium (<http://www.nealelab.is/blog/2017/9/11/details-and-considerations-of-the-uk-biobank-gwas>) were used for education. Because several large summary statistics from different consortia were available for the same biomarker, we used the earliest and largest summary data (SSGAC) as the discovery data set and the most recent data (Neale Lab) as the replication data set. DIAGRAM plus MetaboChip consortium data were used for T2DM^[7], CARDIoGRAM plus C4D consortium data were utilized for CHD^[8], GLGC consortia data were used for TC^[9], LDL^[9], and TG^[9], Genetic Investigation of Anthropometric Traits consortium data were used for BMI^[10], WC^[11], and WHR^[12], and Mapping and Geographic Information Consortium data were used for fasting insulin^[13], fasting glucose^[14], and HbA1c^[15]. The datasets are presented in **Table 1**.

Two-sample MR and causality evaluation

Our MR study was conducted on the MR-Base platform online (<http://www.mrbase.org>)^[16]. We explored the associations as follows: (1) Causality: The conventional MR approach [inverse variance weighted (IVW)] method, MR Egger method, and weighted median method were used: (a) Causality between genetically determined education and T2DM; (b) Causality between education and metabolic risk factors (CHD, TG, LDL, TC, BMI, WC, WHR, fasting insulin, fasting glucose, and HbA1c); and (c) Causality between metabolic risk factors and T2DM; (2) Heterogeneity: We conducted heterogeneity tests in MR analyses using IVW and MR Egger; (3) Horizontal pleiotropy: The MR Egger intercept was assessed; (4) Leave-one-out analysis; and (5) Funnel plots.

Network MR for “education-mediator-T2DM” analyses

Two-sample MR and network MR were performed to obtain the causality between education-T2DM, education-mediator, and mediator-T2DM^[18]. A network MR analysis consisted of three two-sample MR tests: (1) The causality between education and T2DM; (2) The causality between education and the potential mediators; and (3) The causality between the potential mediators and T2DM.

We could conclude that the specific metabolic risk factor might serve as a mediator between education and T2DM if the causality was estimated in all three steps.

Statistical analysis

The statistical tests were two-sided. The statistical test for the MR analyses was considered statistically significant at $P < 0.05$. All of the calculations were conducted using Stata (College Station, TX, United States) and R language.

RESULTS

Causality between genetically determined education and T2DM

Characteristics of the SNPs are shown in **Supplementary Table 1**. We used the SSGAC consortia for education to explore the causal associations between education and T2DM. In the IVW method, the odds ratio [OR (95%CI)] for T2DM was 0.392 (0.263-0.583) per standard deviation increase (3.6 years) in education (**Table 2** and **Figure 1A**). Results were consistent in weighted median method (OR: 0.406, 95%CI: 0.246-0.672; $P = 0.000$) (**Table 2**). Both IVW and MR Egger estimates indicated no heterogeneity amongst these 17 SNPs ($P = 0.163$ and $P = 0.124$, respectively) (**Table 2**). There was no directional horizontal pleiotropy (MR Egger intercept $P = 0.979$) (**Table 2**). In a leave-one-out analysis, no single instrument was strongly driving the overall effect of education on T2DM (**Figure 1C**). Besides, there was no funnel plot asymmetry (**Figure 1D**). Both the leave-one-out analysis and funnel plot further suggested that no SNPs exhibited horizontal pleiotropy.

To sum up, the genetically predicted education was negatively causally associated with T2DM.

Causality between education and metabolic risk factors

The causality between education and metabolic biomarkers, including CHD, TG, LDL, TC, BMI, WC, WHR, fasting insulin, fasting glucose, and HbA1c, is shown in **Table 3**. Education was causally associated with CHD, TG, BMI, WC, and WHR in the discovery phase. Yet in the replication data, only the results for CHD, BMI, and WC were duplicated.

Table 1 Details of studies and datasets used for analyses

Exposure/Outcome	Cases, <i>n</i>	Controls, <i>n</i>	Sample size	PubMed ID	First author	Consortium	Year	Units
Education (discovery data)	NA	NA	293723	27225129	Okbay	SSGAC	2016	SD (yr)
Education 2 (replication data)	NA	NA	226899	UKB-a:505	Neale	Neale Lab	2017	NA
T2DM	34840	114981	77312	22885922	Morris	DIAGRAM plus MetaboChip	2012	Log odds
CHD	60801	123504	184305	26343387	Nikpay	CARDIoGRAM plus C4D	2015	Log odds
TG	NA	NA	108514	24097068	Willer	GLGC	2013	SD (mg/dL)
LDL	NA	NA	99073	24097068	Willer	GLGC	2013	SD (mg/dL)
TC	NA	NA	108363	24097068	Willer	GLGC	2013	SD (mg/dL)
BMI	NA	NA	152893	25673413	Locke	GIANT	2015	SD (kg/m ²)
WC	NA	NA	232101	25673412	Shungin	GIANT	2015	SD (cm)
WHR	NA	NA	60586	23754948	Randall	GIANT	2013	SD (ratio)
Fasting insulin	NA	NA	38238	20081858	Dupuis	MAGIC	2010	Log pmol/L
Fasting glucose	NA	NA	58074	22581228	Manning	MAGIC	2012	mmol/L
HbA1c	NA	NA	46368	20858683	Soranzo	MAGIC	2010	%

BMI: Body mass index; CHD: Coronary heart disease; GIANT: Genetic Investigation of Anthropometric Traits; HbA1c: Glycated hemoglobin; LDL: Low-density lipoprotein; MAGIC: Mapping and Geographic Information Consortium; NA: Not available; SSGAC: Social Science Genetic Association Consortium; TC: Total cholesterol; T2DM: Type 2 diabetes mellitus; TG: Triglycerides; WC: Waist circumference; WHR: Waist-to-hip ratio.

Table 2 Causal associations between genetically determined education and type 2 diabetes mellitus

Trait	Method	nSNP	OR	95%CI	P value	Heterogeneity P	MR Egger intercept P
Education-T2DM	MR Egger	17	0.381	0.047	3.093	0.381	0.124
	Weighted median	17	0.406	0.246	0.672	0.000	0.979
	Inverse variance weighted	17	0.392	0.263	0.583	0.000	0.163

MR: Mendelian randomization; OR: Odds ratio; nSNP: Number of single-nucleotide polymorphisms; T2DM: Type 2 diabetes mellitus.

Causality between metabolic risk factors and T2DM

Based on the above results, CHD, BMI, and WC might serve as potential mediators between education and T2DM. Thus, we further evaluated whether these three potential mediators were associated with T2DM using MR analyses. Only BMI (but not CHD or WC) was positively associated with T2DM (Table 4). Hence, BMI might serve as a potential mediator between education and T2DM.

DISCUSSION

Diabetes has rapidly become a global epidemic and a significant public health concern. Identifying the high-risk populations and addressing the risk factors for diabetes might prove to be an effective diabetes prevention strategy. Traditional risk factors for T2DM include obesity, diet, physical activity, socioeconomic status, *etc.*^[19], some of which are modifiable through behavioral or pharmacological intervention (*e.g.*, obesity, diet, and physical activity). It is of great importance to determine whether traditional risk factors have a causal role in T2DM or are merely bystanders.

Previous studies have reported that education might help T2DM management. A prospective, randomized, single-center study revealed that pharmacotherapeutic education of patients with T2DM could significantly improve 30-d post-discharge

Table 3 Causal association between genetically determined education and metabolic risk factors

Trait	Method	nSNP	Beta	SE	P value	Heterogeneity P	MR Egger intercept P
Discovery (education-metabolic risk factors)							
CHD	MR Egger	71	0.145	0.417	0.729	0.123	0.263
	Weighted median	71	-0.238	0.107	0.026		
	Inverse variance weighted	71	-0.318	0.079	0.000	0.117	
TG	MR Egger	57	-0.183	0.263	0.489	0.112	0.937
	Weighted median	57	-0.192	0.057	0.001		
	Inverse variance weighted	57	-0.204	0.043	0.000	0.130	
LDL	MR Egger	57	-0.274	0.275	0.324	0.316	0.415
	Weighted median	57	0.007	0.063	0.909		
	Inverse variance weighted	57	-0.051	0.045	0.261	0.326	
TC	MR Egger	57	-0.087	0.277	0.755	0.197	0.838
	Weighted median	57	-0.018	0.064	0.775		
	Inverse variance weighted	57	-0.031	0.045	0.500	0.223	
BMI	MR Egger	59	0.013	0.353	0.970	0.000	0.415
	Weighted median	59	-0.209	0.048	0.000		
	Inverse variance weighted	59	-0.272	0.058	0.000	0.000	
WC	MR Egger	59	-0.002	0.404	0.996	0.000	0.429
	Weighted median	59	-0.269	0.056	0.000		
	Inverse variance weighted	59	-0.319	0.066	0.000	0.000	
WHR	MR Egger	58	-0.743	0.461	0.113	0.028	0.346
	Weighted median	58	-0.298	0.097	0.002		
	Inverse variance weighted	58	-0.311	0.076	0.000	0.027	
Fasting insulin	MR Egger	58	-0.269	0.215	0.215	0.010	0.312
	Weighted median	58	-0.039	0.048	0.419		
	Inverse variance weighted	58	-0.053	0.035	0.129	0.014	
Fasting glucose	MR Egger	58	-0.185	0.172	0.287	0.167	0.398
	Weighted median	58	-0.044	0.039	0.257		
	Inverse variance weighted	58	-0.041	0.028	0.152	0.172	
HbA1c	MR Egger	58	0.004077	0.1779	0.9818	0.5674	0.889
	Weighted median	58	-0.009323	0.04094	0.8199		
	Inverse variance weighted	58	-0.02056	0.02908	0.4796	0.6038	
Replication (education-metabolic risk factors)							
CHD	MR Egger	20	-0.985	0.772	0.218	0.196	0.537
	Weighted median	20	-0.474	0.209	0.024		
	Inverse variance	20	-0.511	0.164	0.002	0.222	

TG	weighted						
	MR Egger	13	0.099	1.076	0.928	0.000	0.702
	Weighted median	13	-0.161	0.134	0.229		
BMI	Inverse variance weighted	13	-0.319	0.163	0.051	0.000	
	MR Egger	14	0.830	0.582	0.179	0.079	0.071
	Weighted median	14	-0.381	0.106	0.000		
WC	Inverse variance weighted	14	-0.308	0.095	0.001	0.018	
	MR Egger	14	0.669	0.637	0.314	0.179	0.169
	Weighted median	14	-0.246	0.113	0.030		
WHR	Inverse variance weighted	14	-0.252	0.096	0.009	0.118	
	MR Egger	15	0.235	1.375	0.867	0.010	0.661
	Weighted median	15	-0.511	0.222	0.021		
	Inverse variance weighted	15	-0.375	0.213	0.079	0.014	

BMI: Body mass index; CHD: Coronary heart disease; HbA1c: Glycated hemoglobin; LDL: Low-density lipoprotein; MR: Mendelian randomization; nSNP: Number of Single-nucleotide polymorphisms; TC: Total cholesterol; T2DM: Type 2 diabetes mellitus; TG: Triglycerides; WC: Waist circumference; WHR: Waist-to-hip ratio.

Table 4 Causal association between genetically determined metabolic risk factors and type 2 diabetes mellitus

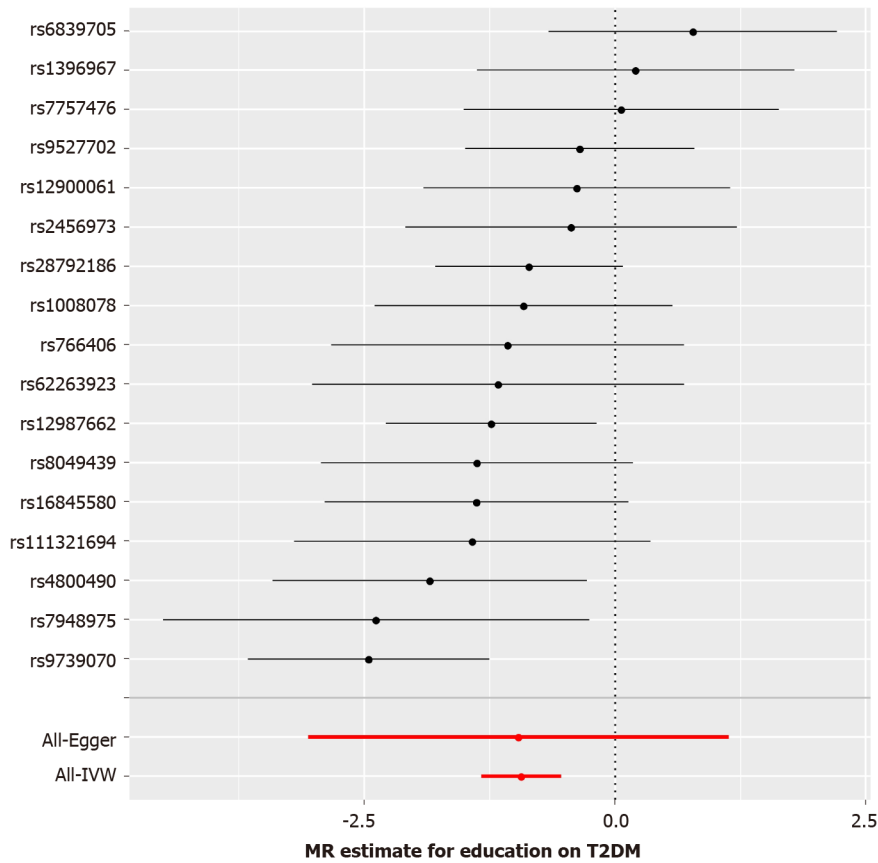
Trait	Method	nSNP	OR	95%CI		P value	Heterogeneity P	MR Egger intercept P
CHD-T2DM	MR Egger	28	0.947	0.697	1.288	0.733	0.000	0.815
	Weighted median	28	1.111	0.996	1.239	0.059		
	Inverse variance weighted	28	1.073	0.954	1.207	0.243	0.000	
BMI-T2DM	MR Egger	72	3.370	1.328	8.556	0.013	0.000	0.240
	Weighted median	72	2.622	2.164	3.178	0.000		
	Inverse variance weighted	72	2.046	1.374	3.048	0.000	0.000	
WC-T2DM	MR Egger	39	11.670	1.590	85.654	0.021	0.000	0.049
	Weighted median	39	2.371	1.788	3.145	0.000		
	Inverse variance weighted	39	1.607	0.879	2.938	0.123	0.000	

BMI: Body mass index; CHD: Coronary heart disease; MR: Mendelian randomization; OR: Odds ratio; nSNP: Number of single-nucleotide polymorphisms; T2DM: Type 2 diabetes mellitus; WC: Waist circumference.

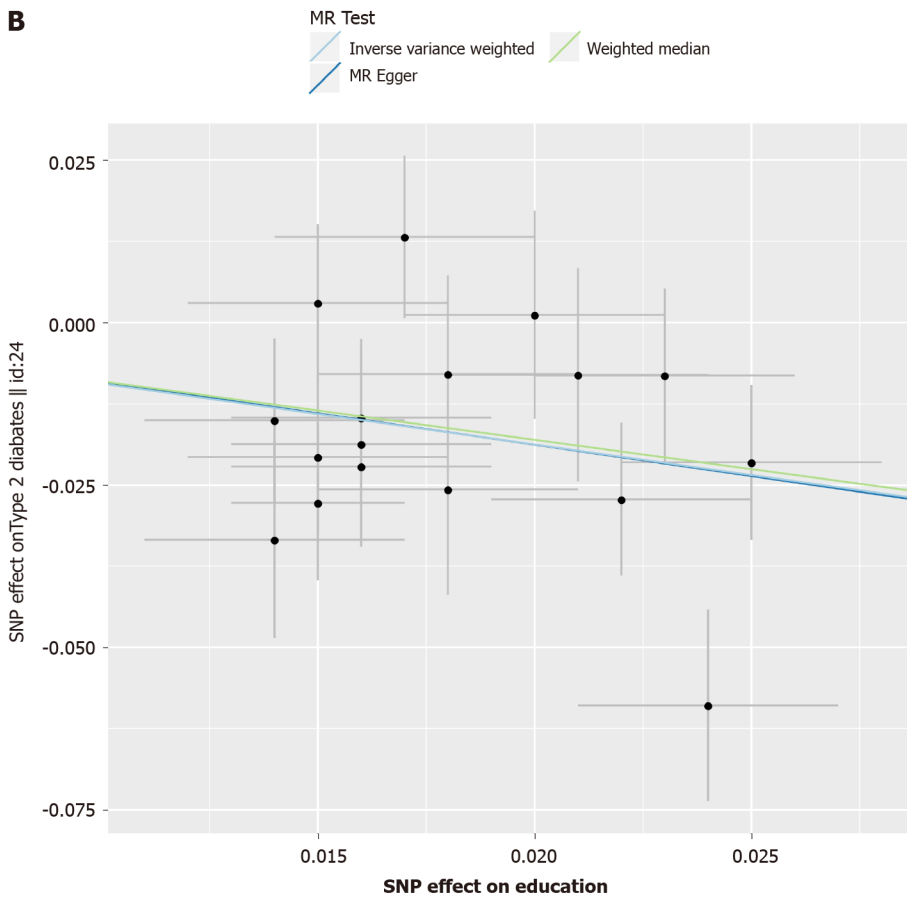
medication adherence without a significant reduction in adverse clinical outcomes^[20]. A systematic review and meta-analysis also demonstrated that educational interventions improved medication adherence among adult patients diagnosed with diabetes^[20]. Moreover, structured education had a positive impact on glucose control and hypoglycemia in T2DM^[22]. However, there has been no direct study exploring the causality between original education and T2DM.

Interestingly, previous findings indicated a causal association between low educational attainment and increased risk of smoking^[23]. Also, observational studies suggested an association between smoking and risk of T2DM^[24,25]. Based on the above reviews, we made a bold assumption that education might be negatively causally associated with T2DM. As we expected, our MR results revealed that the OR (95%CI)

A



B



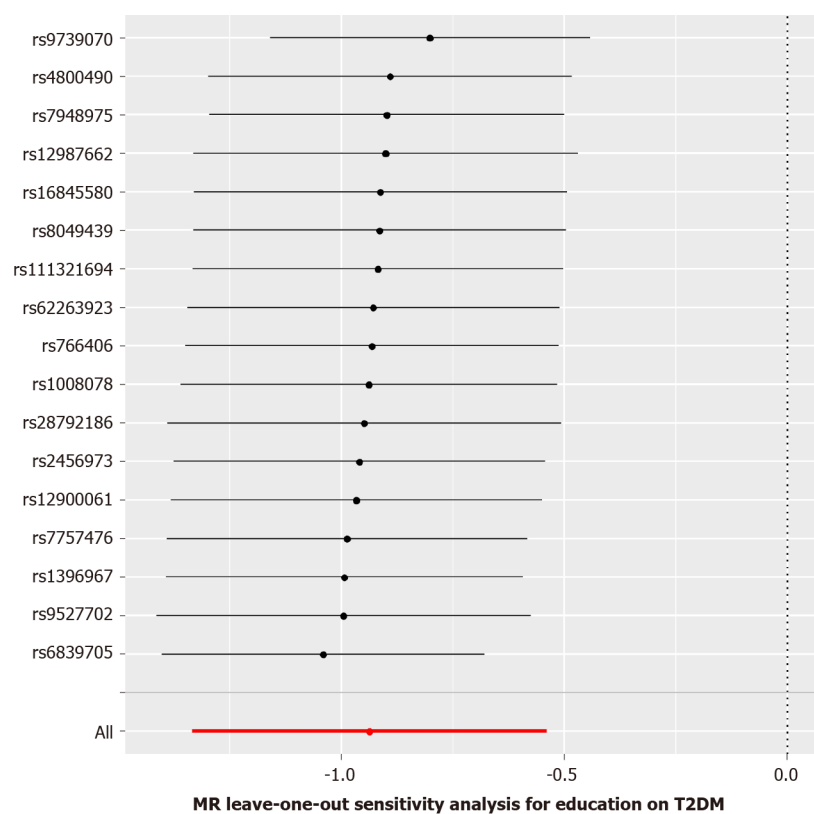
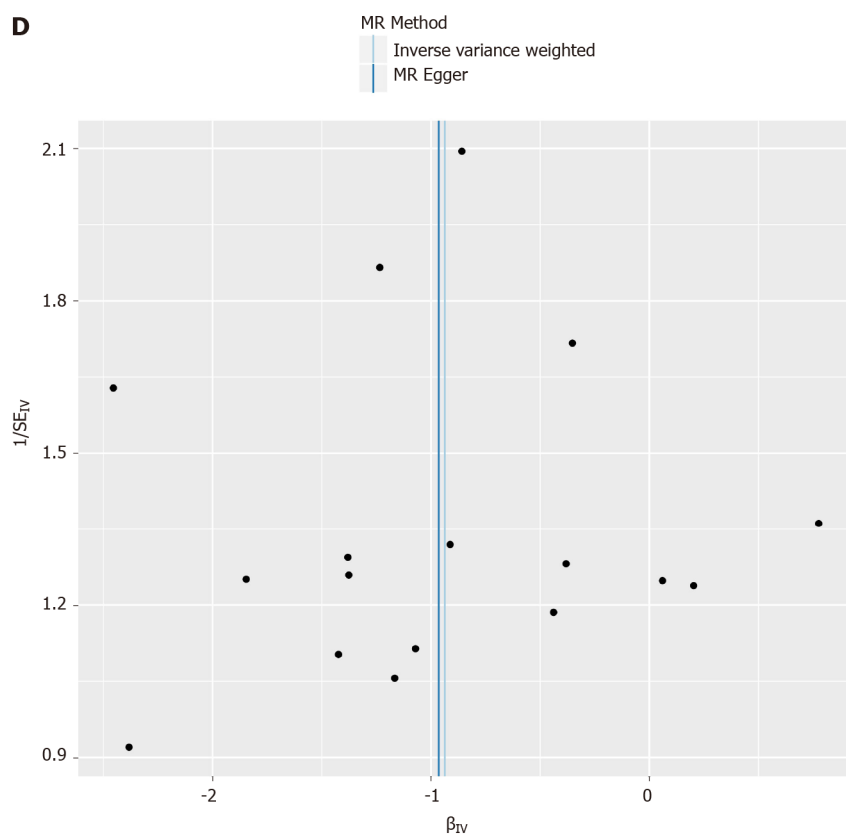
C**D**

Figure 1 Mendelian randomization study of the effect of education on type 2 diabetes mellitus. A: Mendelian randomization estimate for education on type 2 diabetes mellitus (T2DM); B: Effect sizes of the single-nucleotide polymorphism (SNP)-education associations [x-axis, SD (3.6 years) units] and the SNP-T2DM associations (y-axis, log odds of T2DM); C: Leave-one-out sensitivity analysis; D: Funnel plot of the causality between education and T2DM. MR: Mendelian randomization; OR: Odds ratio.

for T2DM was 0.392 (0.263-0.583) per standard deviation increase (3.6 years) in education, indicating that the genetically predicted education was negatively causally associated with T2DM. Since education was shown to be a protective factor against T2DM, and it was modifiable, longer education years among the population are recommended for T2DM prevention.

As there was no full description of the underlying mechanisms possibly connecting education to T2DM, we investigated this relationship. As for the possible mediators from education to T2DM, ten representative modifiable metabolic risk factors were chosen for further MR analysis. Our results indicated that education was causally associated with CHD, TG, BMI, WC, and WHR in the discovery phase. Yet, in the replication data set, only the results for CHD, BMI, and WC were duplicated. Therefore, there were negative causal associations between genetically determined education and CHD, BMI, and WC, which were considered to be the potential mediators between education and T2DM.

A previous study revealed that genetic predisposition towards 3.6 years of additional education was associated with a one-third lower risk of CHD, indicating that low education was a causal risk factor in the development of CHD^[26], which was in accord with our finding. Another MR analysis also suggested that there might be a negative causal effect of education on BMI^[27]. Our results provide more evidence supporting that more education years might help the public better control BMI, which is beneficial for blood glucose regulation and T2DM prevention. There was no direct causal study exploring the effect of education on WC. A randomized clinical trial revealed that nutrition therapy and a multimedia diabetes education program positively impacted achieving metabolic control goals in T2DM, including HbA1C, glucose decrease, TG, and weight loss. Yet, the WC change was still not statistically different^[28]. Another study reported that diet-related and lifestyle-related school-based education could reduce central adiposity in pre-teenagers^[29]. We analyzed whether the different effects of education on WC might be due to various educational programs or diverse populations used in the studies.

Since our MR investigation indicated that CHD, BMI, and WC might be potential mediators from less education years to increased risk of T2DM, we further evaluated whether these three potential mediators were associated with T2DM by MR analysis. Only BMI was positively associated with T2DM. In summary, BMI might serve as a mediator between education and T2DM.

BMI is a well-described risk factor for T2DM^[30], and several large-scale MR studies have addressed its positive causal association with T2DM^[31-33]. Our results also demonstrated that higher BMI could lead to higher risk of T2MD. Combined with the effects of education on BMI and T2MD, for most developing countries where the majority of population receives short education years, we recommend longer education time and a BMI control program for public T2DM prevention.

CONCLUSION

Short education was found to be associated with an increased T2DM risk. BMI might serve as a potential mediator between them.

ARTICLE HIGHLIGHTS

Research background

The causality between education and type 2 diabetes mellitus (T2DM) remains unclear.

Research motivation

In this study, a network Mendelian randomization (MR) framework was applied to determine the causality between education and T2DM from summarized genome-wide association study data.

Research objectives

We used a network MR to identify the causality between education and T2DM and the potential metabolic risk factors [coronary heart disease (CHD), total cholesterol, low-density lipoprotein, triglycerides, body mass index (BMI), waist circumference (WC), waist-to-hip ratio, fasting insulin, fasting glucose, and glycated hemoglobin] from

summarized genome-wide association study data.

Research methods

Two-sample MR and network MR were performed to obtain the causality between education-T2DM, education-mediator, and mediator-T2DM. Summary statistics from the Social Science Genetic Association Consortium (discovery data) and Neale Lab consortium (replication data) were used for education. DIAGRAM plus Metabochip consortium data were utilized for T2DM.

Research results

In the IVW method, the odds ratio (95%CI) for T2DM was 0.392 (0.263-0.583) per standard deviation increase (3.6 years) in education, without heterogeneity or horizontal pleiotropy. Education was genetically associated with CHD, triglycerides, BMI, WC, and waist-to-hip ratio in the discovery phase, yet only the results for CHD, BMI, and WC were confirmed in the replication data. Moreover, BMI was positively associated with T2DM.

Research conclusions

Short education was found to be associated with increased T2DM risk. BMI might serve as a potential mediator between them.

Research perspectives

For most developing countries, the majority of the population receive short education years. Longer education time is recommended as is a BMI control program, for public T2DM prevention.

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