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Association of educational attainment with hypertension and type-2 diabetes: A Mendelian randomization study

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ABSTRACT

BACKGROUNDDue to the long time interval between exposure and outcome, it is difficult to infer the causal relationship between educational attainment (EA) and common chronic diseases. Therefore, we utilized Mendelian randomization (MR) to predict the causal relationships of EA with hypertension and type-2 diabetes (T2DM).

METHODSA two-sample MR analysis was conducted using genome-wide association studies (GWASs) combined with inferential measurements. A GWAS meta-analysis including 1,131,881 European individuals was used to identify instruments for EA. Hypertension and T2DM data were obtained from a Finnish database.

MR analyses were performed using inverse-variance weighted meta-analysis (IVW), weighted median regression, MR−Egger regression, simple mode regression, weighted mode regression and the MR-Pleiotropy RESidual Sum and Outlier test. Sensitivity analyses were further performed using the leave-one-out method to test the robustness of our findings.

RESULTSUsing the MR approach, our results showed that EA was significantly associated with a reduced risk of hypertension (OR = 0.63; P = 2.94×10^{-47}; [95% CI: 0.59, 0.67]) and type-2 diabetes (OR = 0.59; P = 1.25×10^{-16}; [95% CI: 0.52, 0.67]).

CONCLUSIONSThis study showed that EA is causally linked to the risk of chronic diseases, including high blood pressure and T2DM.

1. Introduction

The global burden of chronic diseases is on the rise, accounting for three-fifths of total global deaths(Violan et al., 2014). According to the WHO, this situation is expected to deteriorate over the next decade. Multiple chronic diseases (MCCs) refer to the presence of two or more chronic diseases, with hypertension and T2DM being the most prevalent (Blumel et al., 2020; Busija et al., 2019). Chronic diseases impose significant health and socioeconomic burdens on countries worldwide. Research on various chronic diseases has also been recognized as a priority in the medical field by numerous scholars(Hajat & Kishore, 2018).

To date, several observational studies have demonstrated a strong association between socioeconomic status (SES) and the prevalence of multiple chronic diseases. A study on the prevalence of chronic diseases in people over 60 years of age in China found that higher personal SES is associated with a higher prevalence of multiple chronic diseases, such as type-2 diabetes, hypertension, cardiovascular disease, and cancer(Su et al., 2023). In low- and middle-income countries with higher levels of education, the increased risk of chronic disease may be associated with changes in personal lifestyle behaviors at work, such as sedentary work and fatty diets, as well as having overweight, according to Hosseinpoor

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A.R. et al.(Hosseinpoor et al., 2012). Similarly, a European study revealed that people with headaches or back pain had higher than average incomes and moderate or higher levels of education(Alvarez-Galvez et al., 2022). In contrast, studies have also shown that the prevalence of chronic diseases is generally lower in people of high SES, which may be related to the promotion of physical health by people of high SES through healthier lifestyles, better living conditions and better access to health services(Adamsen et al., 2018; Wang et al., 2019; Wuneh et al., 2019). A study of a multiethnic population in Singapore demonstrated a higher prevalence of cardiometabolic polymorbidity in uncontrolled hypertension patients with low SES(Wang et al., 2022). Similarly, a study of the Canadian population showed that the lower the SES was, the higher the burden of chronic diseases(Mbuya-Bienge et al., 2021). Therefore, according to the current literature, there are still some contradictions in the relationship between SES and the risk of chronic disease, which warrants further exploration.

The measurement of SES encompasses wealth and income levels, educational attainment, and occupational status, as these factors are considered highly relevant in social stratification processes (Howe et al., 2012; Schulreich et al., 2023). EA is one of three factors influencing SES, and it is associated with an increased risk of chronic disease; in addition, EA was the focus of the first large-scale GWAS of a social science phenotype(Lee et al., 2018). It continues to serve as a "model phenotype" for behavioral traits (similar to height for medical traits)(Rietveld et al., 2013). However, determining causality is challenging because of the long observation time between exposure and outcome.

Clinical research methods mainly include observational research and experimental research. Randomized controlled trials (RCTs) are often considered the gold standard for inferring medical causation; however, the feasibility of trials is mainly affected by ethical and financial issues. Although observational studies can be analyzed directly using publicly accessible databases, observational studies are generally considered to establish only associations, not causation. In recent years, with the accumulation of an increasing amount of large-scale GWAS data, research using MR to assess causal inference has become increasingly extensive. MR uses genetic variants that have strong associations with exposure factors, such as EA, as instrumental variables to infer causal relationships between exposures and outcomes, such as disease risk. Since the genetic variation associated with exposure follows the Mendelian rule of "random distribution of parental alleles to offspring" at conception, genetic variation is not affected by traditional confounding factors such as environment, socioeconomic status, and behavioral factors, and genetic variation remains unchanged after birth, indicating that the association with the outcome is chronologically rational (Wang & Shen, 2020). Therefore, MR can minimize the confusion of environmental factors and avoid bias caused by reverse causation.

In this analysis, to determine the causal relationship between EA and hypertension and type-2 diabetes, we uses MR methodology to obtain publicly available aggregate statistics and outcomes from a GWAS of EA to infer whether there is evidence of a causal relationship between educational attainment and reduced risk of hypertension and type-2 diabetes, thereby providing foundational information for clinical RCT studies. In addition, these results provide a theoretical basis for clinical and public health decision-making.

2. Materials and METHODS

2.1. Study design

This study was a secondary analysis of previously published data, and therefore, no additional ethical approval was needed.

We conducted a two-sample MR analysis based on publicly available summary-level data from the Social Science Genetic Association Consortium (SSGAC) and the Integrative Epidemiology Unit (IEU) Open GWAS project to determine whether EA is causally related to hypertension and T2DM. The first step in MR analysis is the selection of instrumental variables. The genetic instrumental variables (IVs) selected for MR analysis must meet the following three assumptions (Bowden et al., 2015): (1) correlation assumption: genetic variants as IVs must have robust and strong correlation with EA; (2) independence assumption: genetic variation cannot be associated with any other confounding factors; and (3) exclusivity hypothesis: genetic variants can affect hypertension and type-2 diabetes only through EA but not through any direct or alternative pathway (see Fig. 1). Possible violations of the core assumptions of instrumental variables include weak instruments, horizontal pleiotropy, linkage disequilibrium (LD), population stratification, and collider bias. A weak instrumental variable refers to a genetic variation that does not have a strong correlation with exposure factors or that genetic variation can only partially explain the phenotype. Therefore, weak instrumental variables tend to overestimate the causal relationship between exposure and outcome in single-sample MR studies. To reduce the bias caused by weak instrumental variables, two measures can be taken: one is to evaluate the strength of association between instrumental variables and exposure factors by using regression models and calculating the F-statistic of instrumental variables greater than 10 (Zheng et al., 2017). The second is to increase the interpretation of phenotypes by constructing allele scores to integrate the effects of multiple genetic variants as instrumental variables (Burgess & Thompson, 2013). The pleiotropy of genetic variation refers to the fact that research results are affected by pathways other than genetic variation, exposure and outcome. This pleiotropy may lead to the failure of the assumption of independence and exclusion. To avoid pleiotropy, the MR−Egger test can be used. If the intercept is 0, it means that no directional pleiotropy was detected for that instrumental variable. However, the premise of using this method must first satisfy the assumption that the effect of pleiotropy of genetic variation on the outcome is independent of the effect of genetic variation on the exposure factor, so the accuracy and test power of statistical results are reduced (Bowden, Del Greco, et al., 2016). In addition, the weighted median estimator method can also be used in sensitivity analysis to test and correct for genetic variation pleiotropy(Bowden, Smith, et al., 2016). LD refers to the nonrandom association between alleles at different genetic loci. Similar to pleiotropy of genetic variation, bias caused by LD can be effectively controlled by using genetic variation with clear biological function as an instrumental variable or by setting two parameters, r^2 and kb, with the help of statistical methods (Zheng et al., 2017). Population stratification refers to the presence of differences in the frequencies of genetic variants among populations with different genetic backgrounds, leading to spurious associations between genetic variants and outcomes. In MR studies, it is the most direct way to include people with the same genetic background to avoid population stratification bias. However, it also indicates that it is necessary to expand the sample size to carry out multicenter GWAS (Haworth et al., 2019). Collider bias means that when exposure and outcome can independently affect a risk factor, adjusting for that risk factor may cause Collider bias. For example, the bias caused by the elderly population as the research object is called "survivor bias", which is one of the most common types of collider bias. To avoid this effect, the results can be corrected by the inverse-probability weighting method(Smit et al., 2019).

2.2. GWAS summary data for EA

Total measurements of EA-related SNPs (as IVs) were extracted from the GWAS. To date, the largest GWAS of EA (N = 293,723) identified 74 approximately independent SNPs at genome-wide significance (hereafter, lead SNPs). The database selected for this study expanded the educational attainment GWAS sample (combined discovery and replication) from N = 405,072 to N = 1,131,881 individuals, identifying 1271 lead SNPs. A meta-analysis of 71 independent GWASs of educational attainment, which was defined as the number of years of schooling that the study participants completed. Proxies were identified from the publicly available summary statistics, which excluded samples

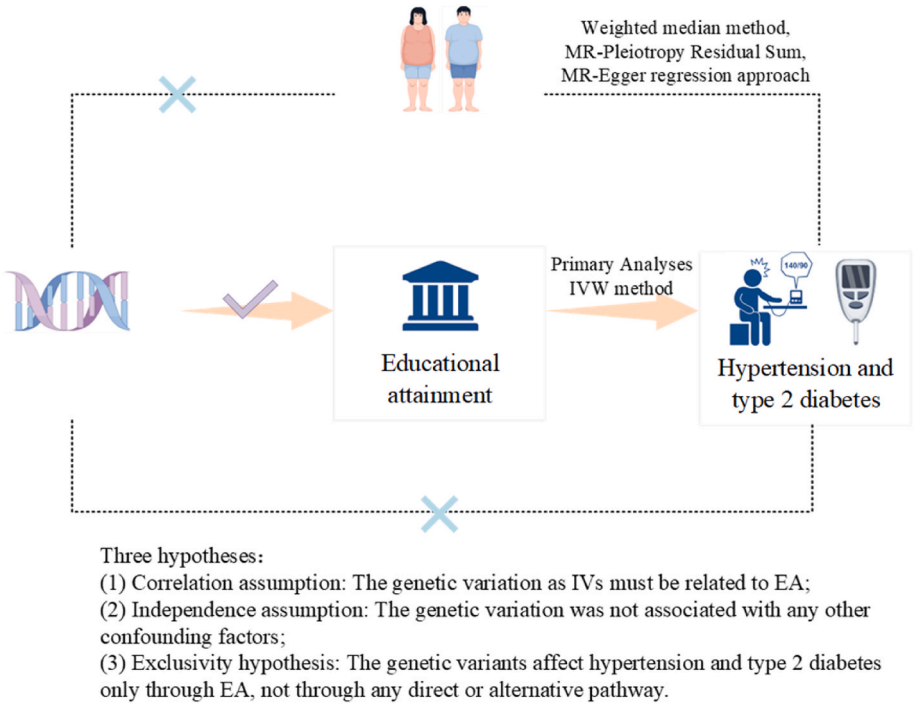

Fig. 1. Three core hypotheses for the causal relationships of EA with hypertension and T2DM.

from 23andme due to data restriction(Li et al., 2021). The study reported 1271 independent SNPs in autosomal chromosomes, explaining 11–13% of the variance in educational attainment. Therefore, in this study, we only used SNPS and pooled data from the SSGAC, and more details of the data analysis can be found in the relevant published materials(Lee et al., 2018). To make IVs strongly correlated with exposure, SNPs with F > 10, $P < 5 \times 10^{-8}$ and LD $r^2 < 0.001$ were selected. The formula for calculating F is as follows: $F = [R^2(1\text{-}R^2)] \times [(n\text{-}k\text{-}1)/k]$; $R^2 = [2 \times \beta^2 \times EAF \times (1\text{-}EAF)]/[2 \times \beta^2 \times EAF \times (1\text{-}EAF) + 2 \times SE^2 \times N \times EAF \times (1\text{-}EAF)]$ (Papadimitriou et al., 2020; Teslovich et al., 2010). (Note: n: Sample size; K: Number of instrumental variables; MAF: effect allele frequency; β: Beta/OR.)

2.3. GWAS summary data for hypertension and T2DM

Hypertension GWAS summary data came from the Neale laboratory. There were 377,207 European hypertension patients (n = 111,581 patients, n = 265,626 control individuals). Hypertension is defined as persistently high systemic arterial blood pressure. Based on multiple readings (blood pressure determination), hypertension is currently defined as when systolic pressure is consistently greater than 140 mmHg or when diastolic pressure is consistently 90 mmHg or more (Unger et al., 2020). T2DM-related GWAS data were obtained for a total of 348,788 Europeans (n = 38,657 patients, n = 310,131 control individuals). T2DM is very broadly defined to include diabetes, which is characterized by insulin resistance or desensitization and elevated blood sugar levels. To ensure that the IVs were not associated with the outcomes, SNPs with $P > 5 \times 10^{-8}$ were selected(Park et al., 2021).

2.4. Heterogeneity and pleiotropy analyses

Sensitivity analysis is key to detecting potential pleiotropy in MR studies, where heterogeneity in MR estimates can be affected by other risk factors. Subjective preliminary judgment of heterogeneity was made by drawing a funnel diagram. Then, we derived heterogeneity markers from the IVW method (Cochran Q-derived $P < 0.05$) to indicate potential heterogeneity. The intercept obtained from the MR–Egger regression is an indicator of horizontal pleiotropy ($P < 0.05$ is considered indicative of directional pleiotropy)(Burgess & Thompson, 2017). The MR-Pleiotropy RESidual Sum and Outlier test was also used to assess and correct horizontal pleiotropy(Ong & MacGregor, 2019). A leave-one-out analysis was used to calculate the MR results of the remaining IVs after removing IVs one by one and evaluate whether the MR results were driven by a single SNP.

2.5. Mendelian randomization analysis

After coordinating the effect alleles between the GWASs of EA, hypertension and T2DM, we used several MR methods, including inverse-variance weighted meta-analysis (IVW), weighted median regression, MR–Egger regression, simple mode regression and weighted mode regression, to estimate EA causality with hypertension and T2DM (Liu et al., 2019).

The IVW method is a comprehensive analysis of the causal effects of each SNP(Burgess et al., 2013). MR–Egger and weighted median methods were used to complement IVW estimates, as these approaches could provide more robust estimates in a broader set of scenarios but are less efficient (wider CIs) (Chen et al., 2020). All statistical analyses were conducted using R (v4.3.1) (the R Foundation) and the R package 'MendelianRandomization' (Yavorska & Burgess, 2017). The power of the test was calculated on the following website: https://shiny.cnsgenomics.com/mRnd/. Statistical significance was set at $\alpha = 0.05$.

3. RESULTS

3.1. Causal effect of EA on hypertension

After extracting exposure and outcome data and performing data screening, data harmonization (i.e., removing the following SNPs for being palindromic with intermediate allele frequencies: rs10931821, rs1245829, rs13085461, rs13130765, rs1320139, rs13402497, rs2478208, rs2517086, rs4899012, rs6687021, rs6969783, rs7040995, rs737945, rs7920624, rs891793, rs9492774), and pleiotropic tests (which excluded 79 SNPs; Supplementary Table 1 and Fig. 1), a total of

312 IVs were used for the MR analysis. The results of the IVW test showed that EA was significantly correlated with hypertension (OR = 0.63; $P = 2.94 \times 10^{-47}$; [95% CI: 0.59, 0.67]). The scatter plot is shown in Fig. 2. The statistical power result is 1 (see Table 1).

The funnel plot is basically symmetrical (see Fig. 3). MR–Egger regression analysis suggested no directional horizontal pleiotropy (intercept estimate = 0.0012, $P = 0.44$). In addition, the weighted mode and the use of a weighted median-based method were used to estimate the causality of EA on hypertension, further demonstrating the effect of its significance on hypertension and making our findings more reliable (Table 2).

Leave-one-out analysis methods can identify SNPs that may affect the causality of the relationship between the exposure and outcome (Supplementary Fig. 2). The results of the analysis showed that the predicted values of exposure factor EA and outcome hypertension risk did not change substantially after each SNP was excluded.

A total of 312 IVs were used for MR analysis. The scatter plot shows individual causal estimates from each of the 312 genetic variants, with the X-axis associated with educational attainment and the Y-axis associated with hypertension risk. The solid line shows the causal estimate of the risk of hypertension by EA.

3.2. Causal effect of EA on T2DM

After extracting exposure and outcome data and performing data screening, data harmonization (i.e., removing the following SNPs for being palindromic with intermediate allele frequencies: rs10931821, rs1245829, rs13085461, rs13130765, rs1320139, rs13402497, rs2478208, rs2517086, rs4899012, rs6687021, rs6969783, rs7040995, rs737945, rs7920624, rs891793, rs9492774), pleiotropic tests (which excluded 68 SNPs; see Supplementary Table 2 and Fig. 3), a total of 314 IVs were used for MR analysis. The results of the IVW test showed that EA was significantly correlated with T2DM (OR = 0.59; $P = 1.25 \times 10^{-16}$; [95% CI: 0.52, 0.67]). The scatter plot is shown in Fig. 4. The statistical power result is 1.

The funnel plot is basically symmetrical (see Fig. 5). MR–Egger regression analysis suggested no directional horizontal pleiotropy (intercept estimate = −0.0004, $P = 0.14$). In addition, the use of a weighted median-based method was used to estimate the causality of EA on T2DM, further demonstrating the effect of its significance on T2DM, supporting the robustness of our findings (Table 3).

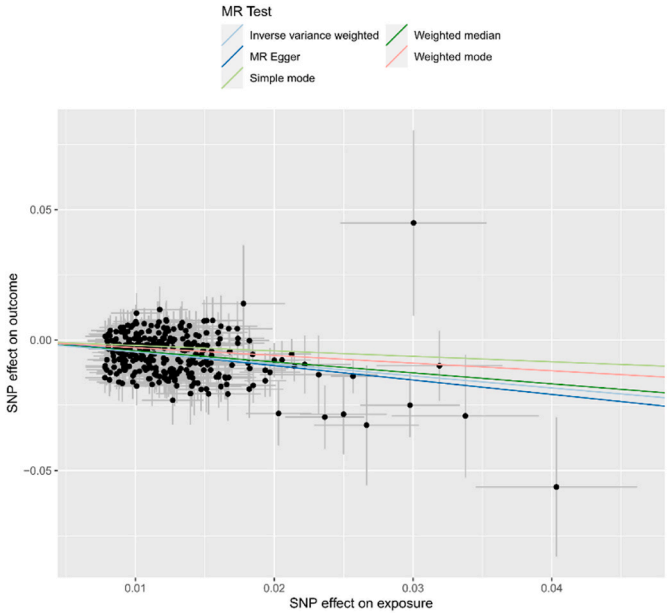

Fig. 2. Scatter diagram.

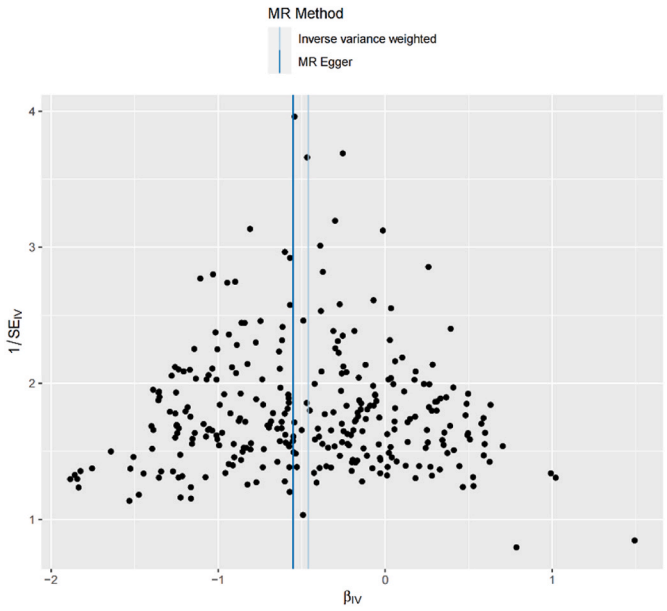

Fig. 3. Funnel plot.

We performed leave-one-out analyses to identify potential influencing SNPs that could bias the causal association (Supplementary Fig. 4). We found that the risk estimates of genetically predicted EA and risk of T2DM did not change substantially after excluding any single SNP.

A total of 314 IVs were used for MR analysis. The scatter plot shows individual causal estimates from each of the 314 genetic variants, with the X-axis associated with EA and the Y-axis associated with T2DM risk. The solid line shows the causal estimate of the risk of T2DM by EA.

4. Discussion

We used two-sample MR to select databases with the largest sample size possible to investigate the associations of EA with hypertension and type-2 diabetes. Only data from official databases were used, which makes our data more reliable and useful. We found clear causal effects of years of education on the development of hypertension and T2DM and an OR value of less than 1, indicating that EA was a protective factor against those two conditions(Bland & Altman, 2000).

Earlier studies on education and disease found that uneducated Brazilian adults had higher levels of diabetes, hypertension, and heart disease than those with college education or more, and among them, diabetes prevalence was approximately twice as high as that of those with higher education, with an even greater gap among women(Beltran-Sanchez & Andrade, 2016). It is worth noting that further studies are needed to confirm the causal relationship between sex and hypertension and type-2 diabetes at the genetic level. Using a national longitudinal study, Kan Sun et al. found that participants with a primary school education or less exhibited a worse risk of newly diagnosed hypertension and blood pressure control compared with those with a junior high school education or above (Sun et al., 2022). Studies on the epidemiology of hypertension in China found that patients' lack of education often led to poor disease management(Wang et al., 2023). This may be related to the fact that higher educated populations are more likely to be health conscious and therefore have a lower prevalence of hypertension. Meghan Zacher showed that older adults with lower education were not only more likely to have hypertension and uncontrolled blood pressure than older adults with higher education, but systolic blood pressure was also higher across almost the entire blood pressure distribution(Zacher, 2023). The study by Lee H and Holly C. Felix et al. showed an inverse association between educational level and

Table 1
The GWAS details incorporated in the MR analysis.

Data source	Phenotype	Participants	GWAS ID/Database name	Year	Population	Category
SSGAC	Educational attainment	1131881	GWAS_EA.to10K	2018	European	Continuous
IEU	Hypertension	377,207	finn-b-I9_HYPTENSESS	2021	European	Binary
IEU	T2DM	348,788	finn-b-T2D_WIDE	2021	European	Binary

Table 2
MR analysis results between EA and hypertension.

Method	OR	95% CI	p value
MR Egger	0.58	0.45–0.73	9.60×10^{-6}*
Weighted median	0.66	0.60–0.72	1.27×10^{-17}*
Inverse variance weighted	0.63	0.59–0.67	2.94×10^{-47}*
Simple mode	0.81	0.57–1.16	2.53×10^{-1}
Weighted mode	0.74	0.57–0.98	3.49×10^{-2}*

Note: OR, odds ratio; CI, confidence interval. *$P < 0.05$.

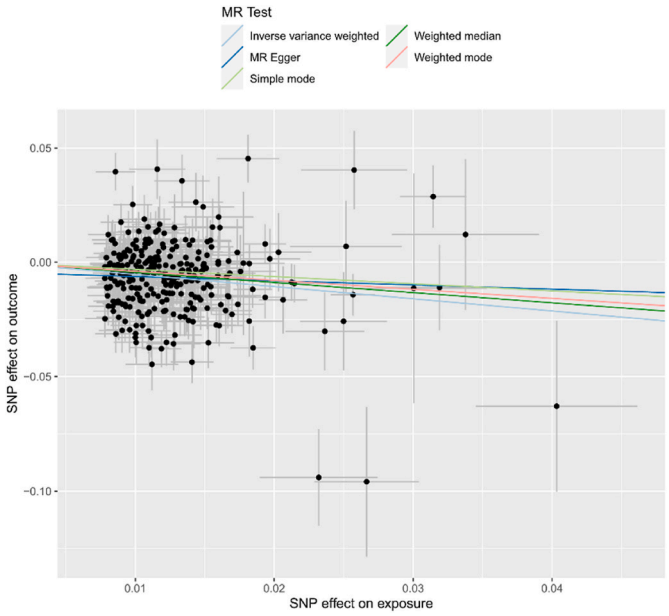

Fig. 4. Scatter diagram.

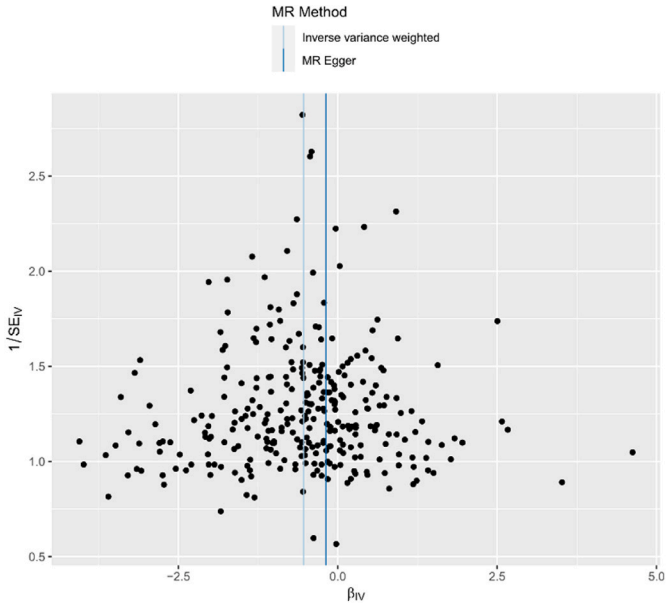

Fig. 5. Funnel plot.

Table 3
MR analysis results between EA and T2DM.

Method	OR	95% CI	p value
MR Egger	0.83	0.51–1.34	4.53×10^{-1}
Weighted median	0.64	0.56–0.74	3.92×10^{-10}*
Inverse-variance weighting	0.59	0.52–0.67	1.25×10^{-16}*
Simple mode	0.73	0.47–1.23	1.57×10^{-1}
Weighted mode	0.67	0.47–0.97	3.43×10^{-2}*

Note: OR, odds ratio; CI, confidence interval. *$P < 0.05$.

uncontrolled T2DM(Felix et al., 2021; Lee et al., 2015). Studies have shown that the formation of hypertension and T2DM is closely related to daily life and eating habits. Through higher education, unhealthy dietary habits (such as alcohol consumption, low intake of fruits and vegetables, etc.) and lifestyle (such as lack of regular exercise, smoking, etc.) can be altered to improve the physical quality of patients(Doak et al., 2023). Furthermore, strategies such as education, counseling programs, and food replacement programs in primary care can improve glycemic control in patients with T2DM and diastolic blood pressure (DBP) in patients with hypertension, and NT programs tailored for primary care should be encouraged(Simoes et al., 2022). It can be seen that improving the level of education or taking measures to promote health education can help improve the status quo of chronic disease prevention and treatment, improve the management system of chronic diseases, and reduce the medical and economic burden brought by chronic diseases to society. In recent years, research has shown that community-based education is a way to promote health and reduce disability and death related to substance abuse(Sun & Li, 2023). Additionally, improving self-care measures for patients with chronic diseases can significantly reduce the cost of the disease(Jalilian et al., 2023). An earlier study by Gagliardino, J. J. et al. found that by having a multidisciplinary health care professional in a group of no more than 10 people, educators regularly teach patients through four sections: dietary patterns, disease formation, physical exercise, and related complications. Interaction between educators and participants was allowed, and family members and spouses were encouraged to participate. The findings confirm that lifestyle modification through patient education leads to weight loss and better control of blood glucose, blood pressure, and lipids while reducing treatment costs by 34% per year(Gagliardino et al., 2001). Adolfo L Rubinstein et al., prevention and control of hypertensive disorders through mobile Health (mHealth) in low-resource areas of Argentina. The approach refers to the use of mobile telecommunications and multimedia technologies to deliver health care. Specific methods included 1) semistructured counseling interviews via mobile phones to promote lifestyle change; 2) sending text messages (SMS) with personalized subject-specific goals; 3) using a web-based app to deliver the intervention; 4) a customized SMS desktop where messages are generated and tailored to an individual's stage of change and target behavior; and 5) summary reports. The results demonstrated the effectiveness and cost-effectiveness of a comprehensive intervention program to reduce systolic blood pressure (SBP) and diastolic blood pressure (DBP) in patients with uncontrolled hypertension and their families compared with usual care and improved hypertension control in patients with hypertension across an 18-month period, in addition to improving patient

treatment adherence (Rubinstein et al., 2015). In addition, there are many effective education methods for hypertension and T2DM control, such as the development of electronic health records (EHRs), holding seminars, creating effective experiential education activities, lifestyle skills training based on the PRECEDE model, watching videos, distributing leaflets, and listening to audio books (Duckie et al., 2023; Khani et al., 2023; Nakwafila et al., 2023).

The strengths of this study are reflected in the MR design and use of a larger GWAS for exposure and outcome. Another advantage is that racial bias was avoided because the GWAS participants included in the analysis were all of European descent. However, as stated in the study design section, the uniformity of population selection is a weakness of this MR study, and genetic factors may also violate the MR assumptions. Therefore, within-family analysis to reduce this bias needs further research in the future(Brumpton et al., 2020). In addition, further studies on MR in other ethnic populations, such as Asian, African, and gender groups, are needed to make the conclusions more generalizable. Second, the application of MR analyses in determining disease causality is limited, and the reliability of the results needs to be comprehensively discussed in combination with the results of clinical RCTs. The more consistent the results of multiple studies, the more reliable the conclusions will be. Finally, the translation of MR findings into clinical and public health practice still needs to be evaluated in light of practical problems.

5. Conclusions

In conclusion, genetic evidence based on the MR approach suggests causal effects of EA on hypertension and T2DM. The findings suggest that extending education, for example, by raising the school-leaving age, can reduce the risk of hypertension and T2DM in the population. This reminds us of the need for health care or health-related education reform in chronic disease prevention and control initiatives and the need for public health initiatives (e.g., chronic disease screening, risk factor management) to pay special attention to disadvantaged groups with low educational levels to address the burden of chronic diseases associated with this aging trend.

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Declarations of interest

none.

Ethical Statement

This study was a secondary analysis of previously published data, and therefore no additional ethical approval was required.

CRediT authorship contribution statement

Xin Zhang: Writing – original draft. **Shi-liang Yu:** Data curation. **Luming Qi:** Methodology. **Li-na Xia:** Supervision. **Qing-tang Yang:** Data curation, Writing – review & editing.

Data availability

Data will be made available on request.

Acknowledgments

Summary data of SNPs associated with EA were extracted from SSGAC, and summary level data of SNPs associated with T2DM and hypertension were obtained from GWASs. The authors thank all the investigators for sharing these data.

Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.ssmph.2023.101585.

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