Education could be a protective factor against gastro-oesophageal reflux disease: a Mendelian randomization study

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Abstract

Background

Patient education has been shown to be beneficial for a variety of diseases. Similarly, observational studies have shown that education contributes to the prevention and treatment of gastroesophageal reflux disease (GORD). However, this relationship is not supported by strong evidence.

Methods

We used publicly available genetic summary data from two large consortia, the Psychiatric Genomics Consortium, with data from 1,271 single-nucleotide polymorphisms (SNPs) closely associated with educational attainment (EA), and the UK Biobank, including 41 024 patients with GORD and 410 073 control cases. For Mendelian randomization (MR) analysis, we used the inverse-variance weighted method, weighted median method, MR-Egger regression, MR pleiotropy residual sum, and outlier test to retrieve summary data. Analyses were performed using the 'Two Sample MR' package in R.

Results

Our results showed that the potential causal relationship between education and lower risk of GORD was statistically significant (OR 0.979, 95% CI 0.975–0.984, $P = 0.002$). Similar results were obtained using the methods of weighted median and weighted mode. The sensitivity analysis is consistent with the causal explanation. Longer education tended to be associated with lower body mass index, lower risk of hypertension, lower risk of type 2 diabetes, less cigarettes per day and more alcoholic intake per week.

Conclusions

Our analysis shows that education may have a negative causal effect on GORD, which can be a protective factor for the prevention of GORD.

Background

Gastroesophageal reflux disease (GORD) refers to reflux of gastric contents into the oesophagus leading to oesophagitis, often accompanied by recurrent and troublesome heartburn and reflux or GORD specific complications. [1] GORD is one of the most common digestive system diseases in the world, about 20% of the adult population in developed countries troubled by GORD, which consumes a lot of medical care and social resources every year. [2] Patient education has been proved to have a positive impact on a variety of chronic diseases and become an important prevention strategy for some diseases. [3–5]

As we all known, patient education is one of the important prevention strategies of GORD. Recently, a multi-center prospective study showed that GORD education program may be beneficial to some people. [6] However, there are also studies showing contradictory results that patient education does not have any positive impact on patients with GORD. [7] It is difficult to untangle the causal relationship between educational attainment (EA) and GORD, because of the potential bias introduced by unmeasured confounding and reverse causality in observational studies. As far as we know, the potential path from education to GORD has not been studied.

With an increasing number of genome-wide association studies (GWAS), Mendelian randomization (MR) has quickly become a novel epidemiological tool. This approach uses genetic variants as instrumental variables (IVs) to investigate potential causal relationships among different human traits. This method will provide clinicians and researchers with strong evidence of causality, and avoid the bias caused by confusion and reverse causality.[8] This method has been used to study the effect of patient education on some diseases, indicating that education could be a protective factor [9–12]. In our study, two-sample MR will be used to assess the potential causal relationship between patient education and GORD.

Methods

Genetic variants associated with educational attainment

The primary genetic instruments were derived from the summary data of a recent GWAS for educational attainment (EA) in 766,345 people of European descent. [13] A total of 1,271 single-nucleotide polymorphisms (SNPs) were reported to be significantly associated with EA ($P < 5 \times 10^{-8}$, linkage disequilibrium $r^2 < 0.01$) in the Social Science Genetic Association Consortium (SSGAC). These SNPs explain 12% of the variation in educational attainment across individuals [14]. In addition, we performed strict linkage disequilibrium (LD)-clumping restricted to $r^2 < 0.001$, Clumping distance $> 10000\text{kb}$ and retained SNPs at a GWAS threshold of statistical significance to eliminate LD, and finally 310 EA-related SNPs were obtained. Table s1 summarizes the SNPs associated with EA.

GWAS summary data for GORD

The GWAS summary data of GORD were obtained from the MRC-IEU [15]. Totally, there were 41 024 patients with GORD and 410 073 control cases. After removing the SNPs lacking the required information, being palindrome or incompatible allele, a total of 237 SNPs were selected as instrumental variables (IVs) for MR analysis.

GWAS summary data for GORD risk factors

In order to reveal the mediating effect of EA on GORD through other risk factors, inverse variance weighting (IVW) was used to estimate the association between EA and other known risk factors of GORD. Well-accepted risk factors included body mass index(BMI), hypertension, type 2 diabetes, smoking, and alcohol consumption. GWAS summary data for these phenotypes were extracted from the Neale Lab

Consortium, GWAS and Sequencing Consortium of Alcohol and Nicotine Use, and meta-analysis of GWAS. Details of risk factors related GWASs included in MR analysis are given in Table 1.

Statistical analyses

We use several MR methods to determine MR estimates of EA for GORD. The wald ratio of single SNP was analyzed by random effects inverse variance weighted (IVW) meta analysis. We also used other statistical tests (weighted median and Mr egger regression) to estimate the effects. The results were expressed as odds ratio (OR) and 95% confidence interval (CI), which provided an estimate of the relative risk caused by the increase of each standard deviation (SD) (4.2 years) in the length of education. Moreover, MR analysis makes sense only when it uses IVs that are: (1) associated with the exposure; (2) independent of factors confounding the association of the exposure and outcome; and (3) associated with the outcome only through exposure [16]. However, as many IVs are associated with multiple traits (pleiotropy), this may impact the validity of MR analysis. Therefore, MR-Egger regression was also performed to examine horizontal pleiotropy [17]. To determine the robustness of significant results, a leave-one-out sensitivity analysis was performed, whereby the analysis was reduced by one SNP at a time to determine whether the estimates in IVW analysis could be biased by a single SNP. All MR analysis were performed using R version (4.0.3) with the “Two Sample MR” package [18].

Results

Causal effect from EA to GORD

Genetically predicted higher educational attainment was associated with significantly lower odds of GORD (Table 2). A one standard deviation increase in the duration of Education (4.2 years) was associated with a 2.1% reduction in the risk of GORD (OR 0.979, 95% CI 0.975 – 0.984, $P = 0.002$) by IVW method in conventional MR analysis. In addition, the methods of weighted median and weighted mode were all statistically significant. Figure 1 illustrates forest plot. Furthermore, MR-Egger regression did not find significant interception (intercept $\beta = -0.001$; SE = 0.001, $P = 0.411$) and the funnel plot (Figure 2) was symmetrical, which indicated that no evidence supporting the existence of pleiotropy was found. Regardless of removing any SNPs, there was no fundamental impact on GORD in the leave-one-out analysis, which means that the MR result was robust (Figure 3).

Causal effect from EA on potential GORD risk factors

To identify potential risk factors for the association between EA and GORD, we used IVW analysis to investigate the relationship between EA and GORD risk factors including body mass index, hypertension, type 2 diabetes, smoking and alcohol consumption. Table 3 summarizes the association of EA with these potential risk factors. The MR results indicate that 4.2 years longer education years was associated with 23.8% lower odds of body mass index, 0.3% lower odds of hypertension, 32.4% lower odds of type 2 diabetes, 29.8% lower odds of cigarettes per day and 4.2% higher odds of alcoholic drinks per week.

Discussion

With an MR study design, we found that higher education level was strongly associated with a lower risk of GORD, where 4.2 years of additional education predicted a reduction in the risk of GORD by 2.1%. These results confirm that education can be a protective factor for the prevention of GORD.

In recent decades, GORD has become one of the most important public health problems in the world. [19] Previous studies have indicated that the risk factors of GORD include sleep apnea, unhealthy diet, obesity, psychological factors, current smoking, causes of heart disease, drinking and diabetes. [20–22] However, GORD can be prevented, and changing the above risk factors through education can be an important prevention strategy for GORD. Although the guidelines recommend patient education, there are few previous studies on GORD patient education, and the results are contradictory. In other chronic diseases, patient education has been proved to improve the ability of patients to deal with the disease effectively, reduce the symptoms of patients, and greatly reduce the health-related costs of patients. The present results support those of previous underpowered and inconsistent studies, and also provide stronger evidence for the role of education in GORD.

The mechanisms underlying the association between education and GORD are still unclear. At present, Studies point out the following possible explanations. Higher education may be associated with a healthier lifestyle, a more satisfying career and better access to health care. [23–25] People with higher education tend to avoid the risk factors associated with GORD, such as smoking, drinking, physical inactivity, improper diet and obesity, and are usually informed of their harmful effects on health. [26–27]

In addition, the results can represent lifetime risk of GORD due to education because of the stability of genetic variants. It is reported that education may have a negative causal effect on BMI ($b = -0.84$); 95% CI = $-1.77, 0.09$) [28], indicating that education may be a protective factor in preventing obesity. Since obesity is an established cause of GORD and is obviously related to education, it may be a key intermediate factor on the education-GORD pathway. It is reported that higher education level was associated with a decreased rate of total stroke [29]. There might be a protective causal association between education and stroke. It is well known that stroke is a vital cause of GORD [30]. Since stroke is closely associated with education, we may get the conclusion that stroke plays an important role in the education-GORD pathway. Short education was found to be associated with an increased type 2 diabetes [31], which is also related to GORD. However, all those studys including our study did not specifically contribute to the debate on the mechanisms why education impacts GORD.

There are several limitations in our study. Although this MR study has a rigorous framework to detect the causal effect of education on GORD, it also has some limitations. First, the MR analysis lacks validation in more GORD related outcome datasets. Second, GORD related GWAS data were from individuals aged between 37 and 73 years living in the UK. Whether the findings above can be generalized to other populations and age groups remains to be investigated.

Conclusions

In conclusion, our MR study supplied reliable evidence to prove that education could be a protective factor against GORD. Future research should focus on mechanisms of the relationship between EA and GORD.

Abbreviations

GORD: Gastroesophageal reflux disease; SNPs:Single-nucleotide polymorphisms; EA:Educational attainment; MR:Mendelian randomization; GWAS:Genome-wide association studies; IVs:Instrumental variables; SSGAC:Social Science Genetic Association Consortium; LD:Linkage disequilibrium; IVW:Inverse variance weighting; CI:Confidence interval; SD:Standard deviation.

Declarations

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Authors'contributions

(I)Conception and design: CG, JY X, and XW Z; (II) Administrative support: XW Z; (III) Data analysis and interpretation: TH L, WJ L and LJ S; (IV) Manuscript writing: All authors.

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Availability of data and materials

All data and materials during this study are presented within the manuscript.

Ethics approval and consent to participate

Not applicable.

Consent for publication

Not applicable.

Competing interests

The authors declare that they have no competing interests.

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Tables

Table 1. Details of the risk factors related GWASs included in Mendelian randomization

Trait	Sample size	Consortium	Reference
BMI	681,275	A meta-analysis of GWAS	Yengo et al.[3]
Hypertension	361,194	Neale Lab Consortium	http://www.nealelab.is/uk-biobank
Type 2 diabetes	70,127	A meta-analysis of GWAS	Bons-Guarch et al.[4]
Cigarettes per Day	337,334	GWAS and Sequencing Consortium of Alcohol and Nicotine use	Liu et al.[5]
Alcoholic drinks per week	335,394	GWAS and Sequencing Consortium of Alcohol and Nicotine use	Liu et al.[5]

Abbreviations: BMI, body mass index; GWAS, genome-wide association studies.

Table 2. Mendelian randomization estimates of the causality between EA and GORD.

Exposure	Outcome	nSNPs	method	OR	Low 95% CI	Up 95% CI	P
EA	GORD	237	IVW	0.722	0.566	0.921	0.009
			MR-Egger	0.627	0.243	1.623	0.337
			Weighted median	0.701	0.499	0.985	0.041

Abbreviations: n=number; SNP: single-nucleotide polymorphism; OR, odds ratio; CI, confidence interval; EA, educational attainment; GORD, Gastroesophageal reflux disease.

Table 3. Causal effects from 4.2 years of education to common risk factors by IVW method.

Risk factors	nSNPs	OR	Low 95% CI	Up 95% CI	P
BMI	237	0.762	0.720	0.807	≤0.001
Hypertension	300	0.997	0.996	0.998	≤0.001
Type 2 diabetes	297	0.676	0.563	0.811	≤0.001
Cigarettes per day	294	0.702	0.650	0.758	≤0.001
Alcoholic drinks per week	293	1.042	1.011	1.074	0.008

Abbreviations: SNP: single-nucleotide polymorphism; OR, odds ratio; CI, confidence interval; BMI, body mass index.

Figures

Figure 1

Forest plot of SNPs associated with education and their risk of gastroesophageal reflux disease.

Figure 2

Funnel plot of SNPs associated with education and their risk of gastroesophageal reflux disease.

Figure 3

Leave-one-out of SNPs associated with education and their risk of gastroesophageal reflux disease.

Supplementary Files

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- [Tables1SNPsassociatedwitheducationalattainment.docx](#)