Causal links between socioeconomic status, leisure sedentary behaviours and gastro-oesophageal reflux disease: a multivariable two-sample Mendelian randomisation study

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ABSTRACT

Introduction We implemented a two-sample multivariable Mendelian randomisation (MR) analyses to estimate the causal effect of socioeconomic status and leisure sedentary behaviours on gastro-oesophageal reflux disease (GERD).

Methods Independent single-nucleotide polymorphisms associated with socioeconomic status and leisure sedentary behaviours at the genome-wide significance level from the Medical Research Council Integrative Epidemiology Unit (MRC-IEU) UK Biobank were selected as instrumental variables. Summary-level data for GERD were obtained from a recent publicly available genome-wide association involving 78 707 GERD cases and 288 734 controls of European descent. Univariable and multivariable two-sample MR analyses, using inverse variance weighted method for primary analyses, were performed to jointly evaluate the effect of socioeconomic status and leisure sedentary behaviours on GERD risk.

Results Three socioeconomic status, including educational attainment (OR 0.46; 95% CI 0.30 to 0.69; p<0.001), average total household income before tax (OR 0.65; 95% CI 0.47 to 0.90; p=0.009) and Townsend Deprivation Index at recruitment (OR 1.60; 95% CI 1.06 to 2.41; p=0.026), were independently and predominately responsible for the genetic causal effect on GERD. In addition, one leisure sedentary behaviour, such as time spent watching television, was independently and predominately responsible for genetic causal effect on GERD (OR 3.74; 95% CI 2.89 to 4.84; p<0.001). No causal effects of social activities and driving on GERD were observed.

Conclusions Genetically predicted Townsend Deprivation Index at recruitment and leisure watching television were causally associated with increased risk of GERD, and age at completion of full-time education and average total household income before tax were causally associated with decreased risk of GERD.

WHAT IS ALREADY KNOWN ON THIS TOPIC

⇒ Gastro-oesophageal reflux disease (GERD) is a common gastrointestinal disorder, which causes troublesome symptoms. Previous studies showed low socioeconomic status was associated with an increased risk of GERD, whereas the causal effect of genetically predicted socioeconomic status on GERD remained undetermined.

⇒ Nowadays, an increasing number of people, tend to extend sedentary behaviours in their daily lives, which increased the risk and mortality of chronic diseases. There are limited data on causal association between leisure sedentary behaviours and GERD.

WHAT THIS STUDY ADDS

⇒ Genetically predicted Townsend Deprivation Index at recruitment had a positive causal association with the risk of GERD, while age at completion of full-time education and average total household income before tax had a negative causal association with risk of GERD.

⇒ Mentally passive sedentary behaviours, such as time spent watching television, was independently responsible for genetic causal effect on GERD.

HOW THIS STUDY MIGHT AFFECT RESEARCH, PRACTICE OR POLICY

⇒ Health promotion in socioeconomic status and leisure sedentary behaviours targets would help reduce health inequality and the formulation of feasible strategies to mitigate GERD risk.

INTRODUCTION

Gastro-oesophageal reflux disease (GERD) is a common gastrointestinal disorder that develops due to pathological oesophageal acid exposure and causes troublesome symptoms and complications. Approximately 14% of the global population experiences GERD symptoms at least weekly, and GERD has increased in many Western countries in recent years.[1] The aetiology of GERD maybe multifactorial, including genetic architecture, racial differences, obesity, Western lifestyle and the demise of *Helicobacter pylori*.[2] Although GERD itself is not a fatal condition, it accounts for a substantial proportion of healthcare costs, adversely impacts the quality of life and increases the risk of developing Barrett's oesophagus and oesophageal adenocarcinoma.[2 3] Therefore, early detection and prevention of the causal link between potentially modifiable risk factors for GERD are promising strategies.

The strong association of socioeconomic status and lifestyle with a wide range of chronic diseases has been an enduring feature of population health.[4 5] Nowadays, an increasing number of people tend to engage in sedentary behaviours in their daily lives, including increased time spent watching television, using computer and driving.[6] Moreover, notably, the more time engaged in sedentary behaviours, the higher the risk and mortality of type 2 diabetes, cardiovascular disease and cancer.[7–9] Observational epidemiological studies have attempted to reveal a link between low socioeconomic status and lifestyle factors and an increased risk of gastro-oesophageal reflux symptoms.[5 10 11] Socioeconomic position patterns observed for patients with GERD indicate potential inequity in accessing care. Although there are growing concerns about increasing sedentary behaviours (such as screen time), reliable evidence that leisure sedentary behaviours increase the risk of GERD is lacking. In addition, whether socioeconomic status and certain individual sedentary behaviours are associated with GERD remains undetermined, mainly because the intrinsic problems of unmeasured confounding and reverse causation in observational studies.

Mendelian randomisation (MR) design, which uses genetic variants (single-nucleotide polymorphisms (SNPs)) identified from Genome-Wide Association Study (GWAS) as instrumental variables (IVs), has been implemented for probing whether a specific exposure exerts a causal effect on a particular outcome.[12 13] Genetic variants are allocated randomly at conception and also far sooner before disease onset, which means that using genetic variants associated with a particular risk factor could minimise the effects of residual confounding variables and potential bias by reverse causation. Therefore, this study aimed to estimate the causal effect of socioeconomic status and leisure sedentary behaviours on GERD risk using a multivariable two-sample MR approach. This method allowed considering the shared genetic components of socioeconomic status and leisure sedentary behaviours to jointly estimate their causal effects.

METHOD

GWAS data for socioeconomic status and leisure sedentary behaviour-related phenotypes

We separately extracted SNPs strongly associated with socioeconomic status and leisure sedentary behaviours from the Medical Research Council Integrative Epidemiology Unit (MRC-IEU) UK Biobank OpenGWAS data infrastructure. Summary statistics were obtained using the MRC-IEU GWAS database (https://gwas.mrcieu.ac.uk). Socioeconomic status included five traits: educational attainment (defined as age at completion of full-time education), physical work (job involving heavy manual or physical work), household income (average total household income before tax), regional deprivation (Townsend Deprivation Index at recruitment) and social activities. Leisure sedentary behaviours included three traits, such as self-reported time spent using a computer (excluding work use), watching television and driving, with the reported average spent daily time being 1.0 hour (SD 1.2), 2.8 hours (SD 1.5) and 0.9 hour (SD 1.0), respectively. Publicly available summary-level data from two published GWAS of UK Biobank or Neale Lab restricted to European descent were also used to validate the results.[9 14] The design and conduct of this MR study conformed to the Strengthening the Reporting of Observational Studies in Epidemiology Using MR statement.

Selection of genetic instruments for socioeconomic status and leisure sedentary behaviour-related phenotypes

The selected genetic variants should be examined to evaluate whether they satisfy the three MR assumptions.[15] First, we obtained the independent genetic variants (SNPs) with an imputation score ≥0.8 that were strongly associated with socioeconomic status and leisure sedentary behaviours based on the genome-wide significance threshold of $p<5 \times 10^{-8}$. Second, independent SNPs without linkage disequilibrium (LD) were used as IVs according to the PLINK clumping algorithm (LD cut-off of $r^2< 0.001$ within a 10 000-kilobase clumping window). Third, the selected IVs should affect outcomes only through exposure, instead of through other pathways, to avoid the horizontal pleiotropy effect (genetic variant is associated with a covariate independently of the risk factor) between IVs and outcomes.[16] To avoid the pleiotropic effect, we discarded overlapped proxy SNPs associated with more than one phenotype. For example, 'rs11665242' is significantly associated with both educational attainment and household income, and 'rs17789218' is significantly associated with both leisure computer use and watching television, for which these SNPs were discarded. In addition, the MR-pleiotropy residual sum and outlier (MR-PRESSO) method was also used to identify and remove outliers with potential pleiotropic biases at a threshold of $p<0.05$.[17]

GWAS data for GERD outcome

GERD is defined as abnormal oesophageal acid exposure associated with GERD symptoms and/or oesophageal mucosal injury produced by gastro-oesophageal reflux. We collected summary-level data on the associations between SNPs and GERD from the summary-level GWAS results of a recent publication. This GWAS included 78 707 GERD cases and 288 734 controls of European ancestry.[18] We did not select UK Biobank participants on for GERD outcomes, because the independence of data of the SNP–exposure and SNP–outcome association is a crucial prerequisite for the validity of the two-sample MR approach. We harmonised each GWAS summary statistics of exposure-outcome datasets by coded and reference alleles to exclude strand-ambiguous SNPs with a minor allele frequency >0.01.

MR estimates and quality assessment

Here, we summarised the primary MR estimates based on the inverse-variance weighted (IVW) approach. Furthermore, we compared the robustness of the IVW results with those of other MR methods including MR-Egger, weighted median, simple mode and weighted mode estimation. A consistent direction of estimates across all MR methods increased confidence in the causal relationships. Moreover, we conducted a leave-one-out analysis to test the sensitivity of the results, in which we sequentially dropped out one SNP at a time to assess whether the estimates were biased or driven by an outlier.

The heterogeneity of SNP estimates in each MR association was evaluated using Cochran's Q and Rucker's Q statistics by combining different genetic variants or SNPs in the IVW model and MR-Egger regression. Cochran's Q and Rucker's Q tests $p>0.05$ indicated no potential heterogeneity. In cases where Cochran's Q and Rucker's Q tests showed heterogeneity, we adopted the results of a random-effects model instead of the fixed-effects model of the IVW method. In the MR-Egger regression, the assumption of no horizontal pleiotropy is relaxed if the intercept is not constrained to zero. The MR-PRESSO method was also used to identify and correct for observed genetic variant

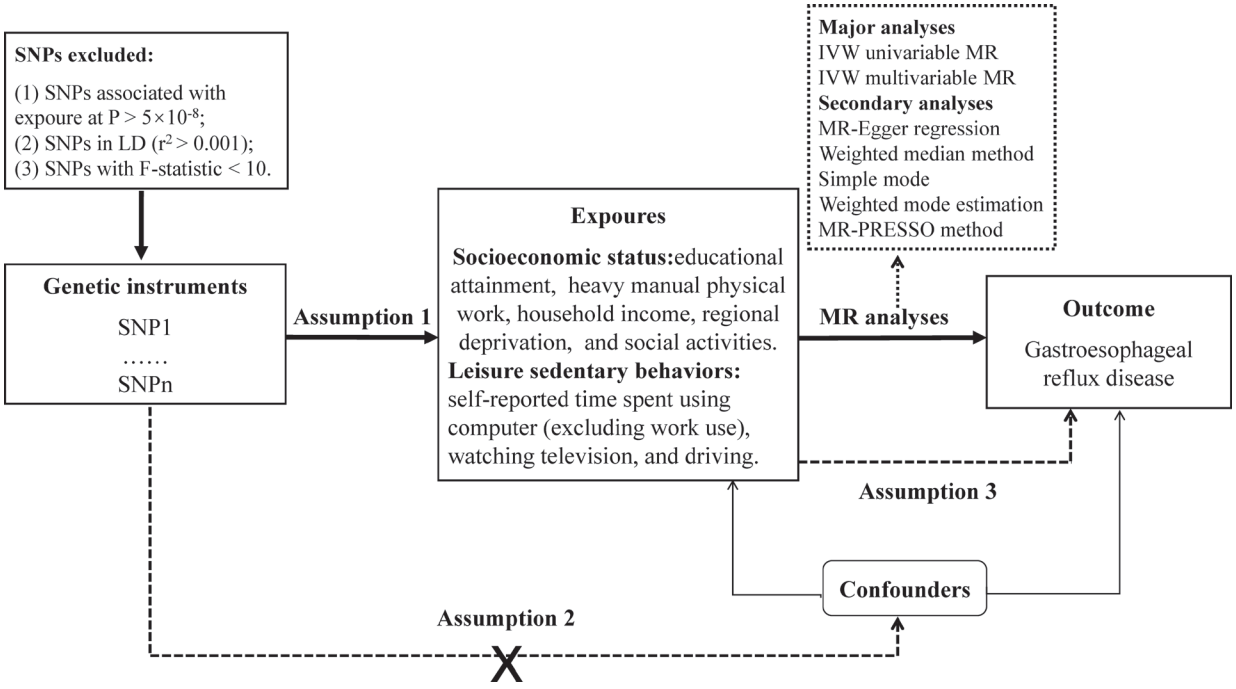

Figure 1 Flow chart of the current MR design. There are three key assumptions of MR design. Assumption 1 is that the selected genetic variants used as instrumental variables should be robustly related to the exposure; assumption 2 is that the used genetic variants should not be associated with any potential confounders and assumption 3 is that the genetic variants for socioeconomic status and leisure sedentary behaviours should affect the risk of the outcome merely through the risk factor, not via alternative pathways. LD, linkage disequilibrium; IVW, inverse-variance weighted; PRESSO, pleiotropy residual sum and outlier; SNP, single-nucleotide polymorphism.

outliers, which helped to reassess the estimates and avoid potential horizontal pleiotropy.

Statistical analyses

We conducted a two-sample univariable MR analyses to investigate the causal effects of genetically predicted socioeconomic status and leisure sedentary behaviours on GERD outcomes. We then, respectively, performed multivariable MR analyses to determine which one or several of the educational attainment, heavy manual or physical work, household income, regional deprivation, social activities, leisure using computer, leisure watching television and driving, accounted for the causal association with GERD risk using the set of overlapping SNPs as genetic instruments. We scaled the OR and CI to 1-unit increase in log-transformed OR of the effect estimates. F statistics were calculated to quantify the strength of selected SNPs using the following formula: $F=R^2*(N-2)/(1-R^2)$. R^2 is the proportion of variances of socioeconomic status or leisure sedentary behaviours explained by the genetic variances or SNPs, and N is the sample size. If F>10, the correlation between IVs and exposure was considered as strong enough to avoid the bias caused by weak IVs. The MR-Egger method identifies and corrects for potential pleiotropy. We performed the power calculations on MR analyses using an online tool (https://shiny.cnsgenomics.com/mRnd/). A sufficient power of over 80% was recommended. We conducted all MR analyses in R software (V.4.0.2; R Foundation for Statistical Computing, Vienna, Austria) using 'TwoSampleMR' and MR-PRESSO packages. All statistical analyses were two tailed.

RESULTS

Study overview

An overview of the rationale, design and procedures of current MR study is shown in figure 1. Table 1 shows the characteristics of all the GWAS data for exposure and outcomes. Full information

Table 1 Information on GWASs for exposure and outcome

Exposure or outcome	Sample size	Year	Identified SNPs, n	Variance explained	Statistical power*	NCP	F-statistic
Age at completion of full-time education	307 897	2018	40	0.19%	100%	45.6	368.8
Job involves heavy manual or physical work	263 615	2018	25	0.12%	100%	308.0	442.5
Average total household income before tax	307 897	2018	47	0.18%	100%	67.5	663.6
Townsend Deprivation Index at recruitment	462 464	2018	18	0.06%	100%	59.5	221.6
Social activities: pub or social club	461 369	2018	18	0.05%	100%	32.3	184.8
Time spent watching television	437 887	2018	112	0.39%	100%	3556.6	1439.6
Time spent using computer	360 895	2018	82	0.36%	100%	77.3	1328.6
Time spent driving	310 555	2018	7	0.04%	11%	0.5	148.0
Gastro-oesophageal reflux disease	602 604	2021	2 320 781	NA	NA	NA	NA

*The statistical power to detect the associations in the Mendelian randomisation analyses.
GWAS, Genome-Wide Association Study; MRC-IEU, Medical Research Council Integrative Epidemiology Unit; NA, not available; NCP, non-centrality parameter; SNPs, single-nucleotide polymorphisms.

is shown in online supplemental table A1. This study evaluated the causal effects of nine genetically predicted socioeconomic status or leisure sedentary behaviour-related phenotypes on GERD. After removing SNPs with LD, palindromic SNPs and duplicated SNPs, we selected 7–112 instrumental SNPs for each trait. Among these, 40 independent and significant SNPs were associated with educational attainment (n=307 897), 25 associated with heavy manual or physical work (n=263 615), 47 associated with household income (n=307 897), 18 associated with regional deprivation (n=462 464) and 18 associated with social activities (n=461 369); 112 associated with leisure television watching (n=437 887), 82 associated with leisure computer use (n=360 895) and 7 associated with driving (n=310 555). The F statistics were all higher than 10, ranging from 148.0 to 1439.6, and the statistical power was calculated as >80% (except for time spent driving, which showed statistical power of 11%), indicating a low risk of weak instrument bias in the MR analyses. The lists of instrumental SNPs of socioeconomic status or leisure sedentary behaviour-related phenotypes finally for GERD, which were obtained from MR analyses, are provided in online supplemental etables 1–8. Genetic variants that were removed by MR Steiger filtering of potential outliers by MR-PRESSO analysis are shown in online supplemental table A2.

Univariable MR analyses of genetically predicted socioeconomic status and leisure sedentary behaviour-related phenotypes on GERD

Univariable MR analyses in the main IVW regression indicated a positive genetic association between job involving heavy manual or physical work (OR 3.35; 95% CI, 1.79 to 6.25; p<0.001) and Townsend Deprivation Index at recruitment (OR 2.48; 95% CI 1.24 to 4.96; p=0.01) and the risk of GERD (figure 2). In addition, educational attainment (OR 0.31; 95% CI 0.25 to 0.37; p<0.001) and household income (OR 0.36; 95% CI 0.29 to 0.44; p<0.001) showed inversely genetic association with GERD risk (figure 2). However, no significant genetic association was detected between social activities and GERD risk (OR 2.18; 95% CI 0.27 to 17.52) (figure 2). Regarding leisure sedentary behaviours, significantly positive genetic association between leisure television watching and GERD risk was detected (OR 4.68; 95% CI 3.58 to 6.31; p<0.001) (figure 3). In addition, leisure computer use was associated with lower GERD risk (OR 0.49; 95% CI 0.34 to 0.70; p<0.001) (figure 3). No significant genetic association was detected between leisure driving and GERD risk (OR 1.15; 95% CI 0.37 to 3.56) (figure 3). Similarly, causal estimates were consistent among the weighted median, simple mode, weighted mode and MR-PRESSO analyse

Characteristics/Methods	nSNP	OR (95% CI)	P value
a. Age completed full time education			
MR Egger	16	0.32 (0.14−0.77)	0.022
Weighted median	16	0.30 (0.22−0.41)	<0.001
Inverse variance weighted (fixed effects)	16	0.31 (0.25−0.37)	<0.001
Inverse variance weighted (random effects)	16	0.31 (0.25−0.37)	<0.001
Simple mode	16	0.23 (0.13−0.41)	<0.001
Weighted mode	16	0.25 (0.15−0.44)	<0.001
MR−PRESSO	16	0.31 (0.25−0.44)	<0.001
b. Job involving heavy manual or physical work			
MR Egger	9	0.13 (0.01−6.54)	0.341
Weighted median	9	2.23 (1.50−3.30)	<0.001
Inverse variance weighted (fixed effects)	9	3.35 (2.69−4.16)	<0.001
Inverse variance weighted (random effects)	9	3.35 (1.79−6.25)	<0.001
Simple mode	9	6.62 (2.58−16.96)	0.006
Weighted mode	9	1.23 (0.73−2.06)	0.459
MR−PRESSO (outlier−corrected)	5	3.83 (1.96−7.48)	0.017
c. Average total household income before tax			
MR Egger	18	0.35 (0.08−1.47)	0.171
Weighted median	18	0.37 (0.29−0.48)	<0.001
Inverse variance weighted (fixed effects)	18	0.36 (0.31−0.41)	<0.001
Inverse variance weighted (random effects)	18	0.36 (0.29−0.44)	<0.001
Simple mode	18	0.29 (0.17−0.51)	0.002
Weighted mode	18	0.56 (0.34−0.94)	0.042
MR−PRESSO	18	0.34 (0.29−0.44)	<0.001
d. Townsend deprivation index at recruitment			
MR Egger	8	0.01 (0.01−0.78)	0.088
Weighted median	8	3.74 (2.27−6.16)	<0.001
Inverse variance weighted (fixed effects)	8	2.48 (1.87−3.30)	<0.001
Inverse variance weighted (random effects)	8	2.48 (1.24−4.96)	0.010
Simple mode	8	4.32 (2.54−7.71)	0.001
Weighted mode	8	4.11 (2.25−7.52)	0.002
MR−PRESSO (outlier−corrected)	5	3.69 (2.73−4.99)	0.001
e. Social activities: Pub or social club			
Weighted median	7	1.15 (0.41−3.44)	0.798
Inverse variance weighted (fixed effects)	7	2.18 (1.11−4.29)	0.023
Inverse variance weighted (random effects)	7	2.18 (0.27−17.52)	0.461
Simple mode	7	0.92 (0.22−3.63)	0.911
Weighted mode	7	1.33 (0.37−4.82)	0.676
MR−PRESSO (outlier−corrected)	5	1.19 (0.51−2.81)	0.716

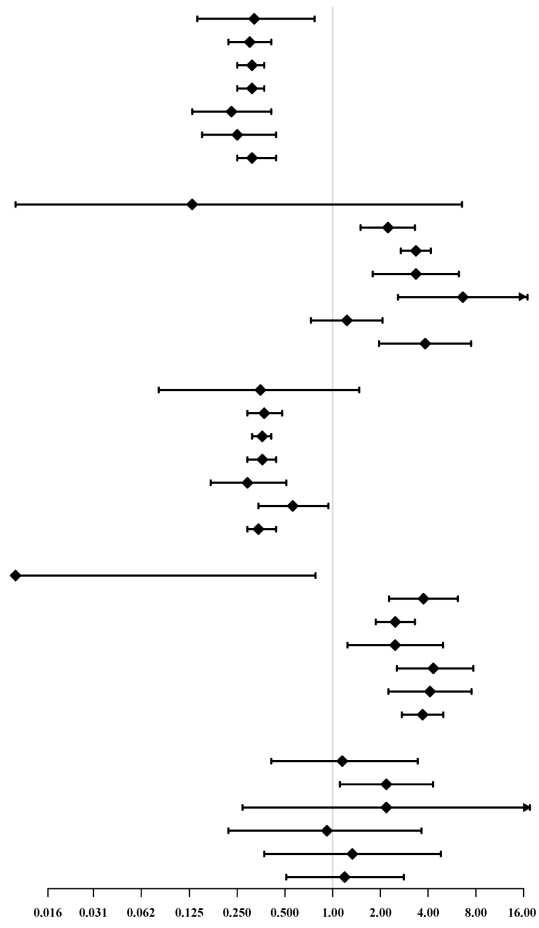

Figure 2 Forrest plots for associations of genetically predicted socioeconomic status with risk of gastro-oesophageal reflux disease. The causal effect estimation of social activities using MR-Egger method was not available because of the impact of limited number of IVs and variance explained. No potential outlier was detected for age at completion of full-time education and average total household income before tax by the MR-PRESSO (outlier-corrected) test. IVs, instrumental variables; PRESSO, pleiotropy residual sum and outlier; SNPs, single-nucleotide polymorphisms.

Characteristics/Methods	nSNP	OR (95% CI)	P value
a. Time spent watching television			
MR Egger	40	14.96 (4.25−49.75)	<0.001
Weighted median	40	3.97 (3.03−5.24)	<0.001
Inverse variance weighted (fixed effects)	40	4.68 (3.77−5.61)	<0.001
Inverse variance weighted (random effects)	40	4.68 (3.58−6.31)	<0.001
Simple mode	40	3.56 (1.76−6.42)	0.001
Weighted mode	40	3.28 (1.69−6.36)	0.001
MR−PRESSO (outlier−corrected)	38	4.35 (3.45−5.49)	<0.001
b. Time spent using computer			
MR Egger	34	0.05 (0.01−0.71)	0.029
Weighted median	34	0.49 (0.36−0.63)	<0.001
Inverse variance weighted (fixed effects)	34	0.49 (0.42−0.56)	<0.001
Inverse variance weighted (random effects)	34	0.49 (0.34−0.70)	<0.001
Simple mode	34	0.30 (0.16−0.54)	<0.001
Weighted mode	34	0.34 (0.19−0.61)	0.001
MR−PRESSO (outlier−corrected)	28	0.43 (0.32−0.58)	<0.001
c. Time spent driving			
Weighted median	4	1.89 (0.79−4.56)	0.155
Inverse variance weighted (fixed effects)	4	1.15 (0.39−2.49)	0.787
Inverse variance weighted (random effects)	4	1.15 (0.37−3.56)	0.814
Simple mode	4	1.73 (0.43−7.02)	0.457
Weighted mode	4	2.45 (0.88−6.82)	0.108
MR−PRESSO (outlier−corrected)	3	0.52 (0.18−1.49)	0.313

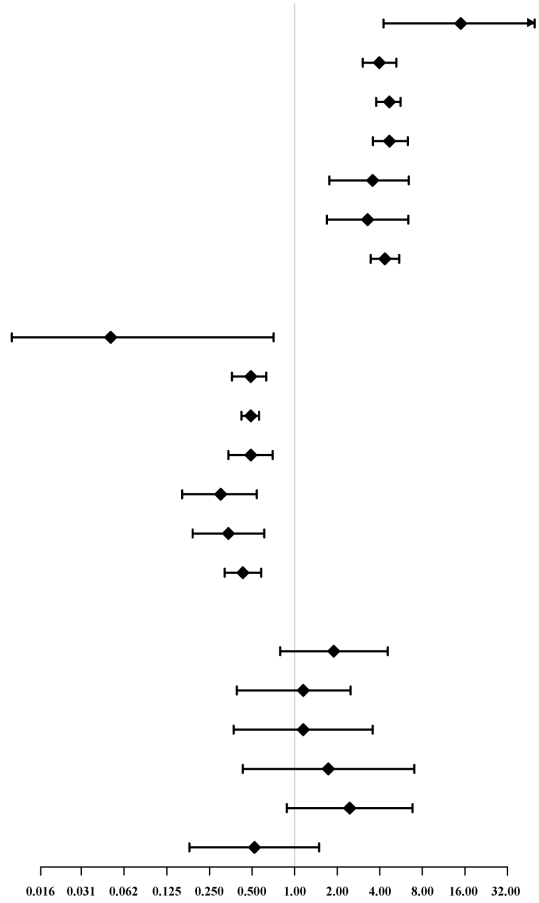

Figure 3 Forrest plots for associations of genetically predicted leisure sedentary behaviours with risk of gastro-oesophageal reflux disease. The causal effect estimation of time spent driving using MR-Egger method was not available because of the impact of limited number of IVs and variance explained. IVs, instrumental variables; PRESSO, pleiotropy residual sum and outlier; SNPs, single-nucleotide polymorphisms.

(figure 2–3). The forest plots and scatter plots were used to visualise the estimate effects, which are presented in online supplemental figures A1–A4 . The validation datasets showed consistent directional association (online supplemental table A3).

Multivariable MR analyses of genetically predicted socioeconomic status and leisure sedentary behaviour-related phenotypes on GERD

We harvested a combination of 82 SNPs associated with socioeconomic status and 118 SNPs associated with leisure sedentary behaviours to conduct multivariable MR analyses (online supplemental etables 9–10). Three socioeconomic statuses, including educational attainment age at completion of full-time education (OR 0.46; 95% CI 0.30 to 0.69; p<0.001), average total household income before tax (OR 0.65; 95% CI 0.47 to 0.90; p=0.009) and Townsend Deprivation Index at recruitment (OR 1.60; 95% CI 1.06 to 2.41; p=0.026) were independently and predominately responsible for the genetic causal effect on GERD risk (table 2). In addition, leisure sedentary behaviours, such as time spent watching television, were independently and predominately responsible for the genetic causal effect on GERD risk (OR 3.74; 95% CI 2.89 to 4.84; p<0.001) (table 2). Heavy manual or physical work and leisure computer use showed a consistent direction of estimated effects in univariable MR analyses, even though no significant genetic association was detected. Furthermore, consistent results were obtained by only including specific traits which had statistical differences in univariable MR analyses into the IVW multivariable MR model (online supplemental table A4).

Bidirectional MR analyses of genetically predicted GERD on socioeconomic status and leisure sedentary behaviour-related phenotypes

We extracted 77 SNPs strongly and independently predicting GERD. Bidirectional MR analyses showed significantly positive genetic association between GERD and job involving heavy manual or physical work (OR 1.21; 95% CI 1.19 to 1.24), Townsend Deprivation Index at recruitment (OR 1.11; 95% CI 1.09 to 1.13), time spent watching television (OR 1.18; 95% CI 1.17 to 1.20) and social activities (OR 1.02; 95% CI 1.01 to 1.03). Significantly negative genetic association was detected between GERD and educational attainment (OR 0.82; 95% CI 0.81 to 0.84), average total household income before tax (OR 0.77; 95% CI 0.75 to 0.78) and time spent using computer (OR 0.93; 95% CI 0.91 to 0.94) (online supplemental table A5).

MR sensitivity analyses

The leave-one-out association approach showed that the detected estimation effects were not dependent on specific SNP (online

Table 2 Genetic causal effects of genetically predicted socioeconomic status or leisure sedentary behaviour-related phenotypes on GERD based on IVW multivariable MR model

Traits	Conjoint nSNP	β	SE	OR	95% CI	P value
Socioeconomic status						
Age at completion of full-time education	82	−0.78	0.21	0.46	0.30 to 0.69	<0.001
Job involves heavy manual or physical work	82	0.31	0.20	1.37	0.92 to 2.05	0.126
Average total household income before tax	82	−0.43	0.16	0.65	0.47 to 0.90	0.009
Townsend Deprivation Index at recruitment	82	0.47	0.21	1.60	1.06 to 2.41	0.026
Social activities: pub or social club	82	−0.37	0.38	0.69	0.33 to 1.46	0.338
Leisure sedentary behaviours						
Time spent watching television	118	1.32	0.13	3.74	2.89 to 4.84	<0.001
Time spent using computer	118	−0.24	0.13	0.79	0.61 to 1.02	0.06
Time spent driving	118	0.16	0.31	1.17	0.64 to 2.13	0.61

GERD, gastro-oesophageal reflux disease; IVW, inverse-variance weighted; MR, Mendelian randomisation; SNPs, single-nucleotide polymorphisms.

supplemental figures A5–A6). We used MR-Egger's intercept with a p value threshold of >0.05 to assess the horizontal pleiotropy between IVs and outcomes, and indicated no evidence of unbalanced horizontal pleiotropy in the MR-IVW analyses. In addition, except for social activities, the MR-PRESSO global test also showed an absence of horizontal pleiotropy (p for global test >0.05). After removing outliers with potential pleiotropic effects detected by outlier-corrected MR-PRESSO analyses, the associations remained consistent (p for distortion test>0.05). However, Cochran's Q and Rucker's Q indices indicated heterogeneity between socioeconomic status or leisure sedentary behaviour-related phenotypes and GERD (online supplemental table A6). Therefore, we adopted a random-effects IVW model to evaluate the associations and showed consistent causal effects. Funnel plots used to visualise the heterogeneity are presented in online supplemental figures A7–A8.

DISCUSSION

This study examined the independent effects of genetically predicted socioeconomic status and leisure sedentary behaviour-related phenotypes on GERD using multivariable MR analyses. Our results indicated positive causal effects of Townsend Deprivation Index at recruitment and leisure watching television, and negative causal effects of age at completion of full-time education and average total household income before tax on GERD risk.

Numerous modifiable risk factors, including alcohol or coffee consumption, tobacco smoking, non-steroidal anti-inflammatory drugs and/or aspirin use, obesity and psychological factors (eg, stress and depression), have been demonstrated to be associated with GERD.[1 19] However, determining the causal inference in these observational studies was challenging, which were prone to unobserved confounding, misclassification, reverse causality and other biases. Recently, two MR-based studies on potentially modifiable risk factors and GERD were conducted to identify the causal effects. Green *et al*'s MR study provided strong evidence that adiposity-related risk factors for GERD were not overall weight but fat distribution; and a higher waist-hip ratio led to GERD.[20] Interestingly, an other MR study showed the causal roles of adiposity and diabetes in the GERD development, whereas genetically predicted coffee or alcohol consumption, waist circumference and body mass index were not associated with GERD,[21] which was not completely in line with previous observational studies.[22 23] Considering these inconsistent results, more reliable MR studies are required to evaluate the causal role of other modifiable risk factors. To our knowledge, the MR-association between socioeconomic status or leisure sedentary behaviour-related phenotypes and the GERD risk has not been investigated. Therefore, this study builds on existing studies and supplements the evidence in this field.

We observed that socioeconomic status had a broad effect on GERD risk, which is congruent with previous observational cohort studies conducted in Western populations. A recent Melbourne Collaborative Cohort Study of 20 975 Australian participants revealed that low socioeconomic status and educational attainment were associated with a higher risk of GERD.[24] A similar finding was reported in a large population-based study comprising 65 333 participants, where people with low education and materially deprived persons had a higher risk of gastro-oesophageal reflux symptoms compared with highly educated persons and those without economic problems.[11]

Our MR study based on genetic data further strengthened the negative association between educational attainment and household income and GERD risk. One possible explanation is that higher educational attainment and household income may reflect better access to healthcare, subsequent healthier living habits or more proactive care seeking behaviours. Furthermore, our results showed a positive causal association between the Townsend Deprivation Index at recruitment and higher risk of GERD. Townsend Deprivation Index is a composite measure of deprivation based on unemployment, non-home ownership, households without cars and overcrowded households, where a negative value represents high socioeconomic status.[25] Low income, unemployment, renting and attendant psychosocial stress might, in turn, account for vulnerability to mental disorders and GERD the development.[26–28] Notably, although our multivariable MR analyses did not indicate a causal effect of heavy manual or physical work on GERD, a consistent direction of estimates in the univariable MR analyses increased confidence in the causal evidence. Consistent with previous studies, vigorous work and physical activity at work increased the risk of GERD, which may have been induced by an increase in abdominal wall pressure, inhibition of gastric emptying, and interference with gastrointestinal absorption.[29] The results of this study revealed the determinants of socioeconomic inequalities in GERD. Thus, determining the effect of socioeconomic status on GERD may enable the formulation of feasible strategies to mitigate disease risk.

One promising target in preventing and managing GERD is sedentary behaviour, which has been demonstrated to be a potential risk factor for many diseases, including neuropsychiatric disorders, peptic ulcers, cancer and cardiovascular mortality.[7 8 30]

Sedentary behaviours are known as waking behaviours characterised by an energy expenditure ≤1.5 hours of metabolic equivalents, while in a sitting, reclining or lying posture.[31] Previous studies have shown that higher levels of recreational physical activity decrease the risk of GERD, whereas observational studies seeking to establish relationships between prolonged sitting time and GERD have yielded inconsistent results.[32–34] A Korean cohort study suggested that the incidence of erosive oesophagitis decreased as sitting time increased, particularly in non-obese participants.[32] In addition, a study investigating the relationship between gastrointestinal diseases and occupational exposures indicated that sedentary white-collar workers had less gastritis.[35] In contrast, previous research has shown that prolonged sitting time is positively associated with peptic ulcers and other digestive diseases.[36] However, evidence examining the relationship between leisure behaviours behaviours and GERD is limited.

Interestingly, this study showed a significantly positive genetic association between leisure television watching and risk factors for GERD, whereas leisure computer use was protective factor against GERD. These results were in line with a previous study, that considered television watching a mentally passive sedentary behaviours and leisure computer use as mentally active sedentary behaviours.[37] One possible explanation for its detrimental effect is that, compared with other sedentary traits, leisure television watching is related to decreased time spent on physical exercise, lower total energy expenditure and increased snacking behaviours, which may increase the risk of adverse prolonged sitting and adiposity effects.[9 38] Moreover, compared with mentally passive sedentary behaviours, computer use requires more direct communication and social interactions between individuals, which could benefit the functioning of the gastrointestinal system through both local and systemic nervous effects.[37 39] Notably, our results showed that leisure computer use had 'borderline' statistical significance in multivariable MR analyses and presented as consistent direction of estimated effects. Studies with a greater sample size and explanatory power are required to further elucidate the latent mediating effect. However, these discrepant results suggest that sedentary behaviours may present different behavioural domains and emphasise the importance of distinguishing the different domains of sedentary behaviours.

This study has some limitations. First, this study depended largely on self-report phenotypes, which could be susceptible to selection and reporting bias caused by the quality of the questionnaires and possible measurement errors. However, exposure variables were assessed based on well-established and widely used measures. Second, although the IVs in our study were strongly associated with SNPs, common SNPs were not sufficient to explain much of the total variance, varying from 0.04% to 0.39% in complex diseases. It could be the impact of limited number of genetic instruments associated with social activities and time spent driving, which may increase the risk of type I error. Therefore, caution should be exercised when considering exact proxies for exposure. We conducted rigorous IVs filtering procedures to minimise bias, and the estimates of the F statistic (a measure of instrument strength) of the genetic variants indicated few weak instruments. Third, we observed significant heterogeneity in MR analyses. However, our main results were consistent when pleiotropy-resistant MR methods (MR-Egger and IVW) and outlier-corrected MR-PRESSO analyses were used after removing of any potential outliers. Fourth, our study stratified the data to include only individuals of European ancestry, which helped reduce population structure bias. This confinement may not apply to other ethnic groups. Finally, we observed different causal effect estimation using MR-Egger method and other MR method. Indeed, MR-Egger method is less precise in estimation of causal effects, especially with limited number of genetic instruments, and is more used to test the pleiotropy. Thus, the results of causal effect estimation using IVW method as primary MR analyses are more predominate.

CONCLUSION

The current study provided evidence that the genetically predicted Townsend Deprivation Index at recruitment and leisure watching television were causally associated with an increased risk of GERD, and that age at completion full-time education and average total household income before tax were causally associated with a decreased risk of GERD. Reducing the time spent watching television, improving educational attainment and employment status, and maximising social welfare may be beneficial measures to prevent GERD. Further studies using new generations of GWAS and including a more representative population are needed to investigate this result.

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