# Causal links between socioeconomic status, leisure sedentary behaviours and gastroesophageal reflux disease: a multivariable two–sample Mendelian randomization study

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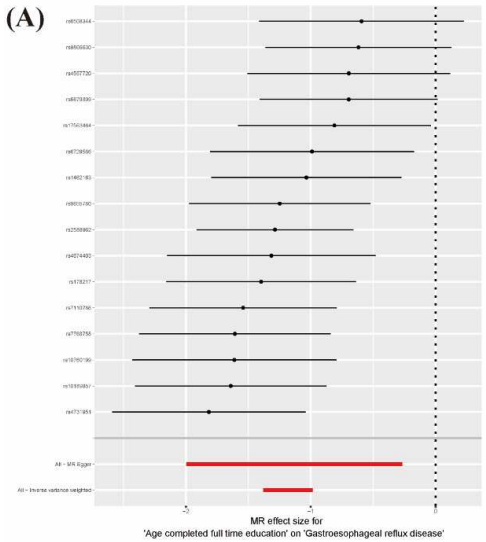
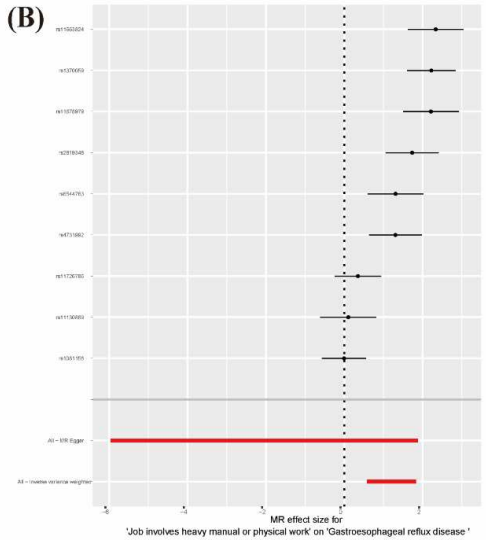
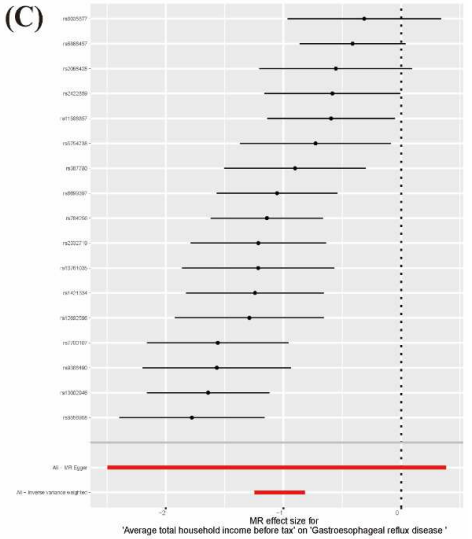
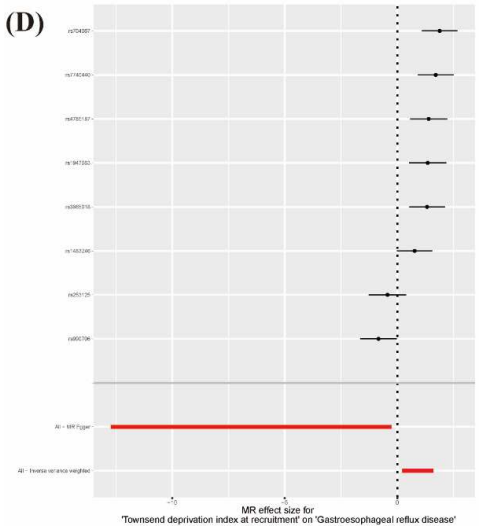
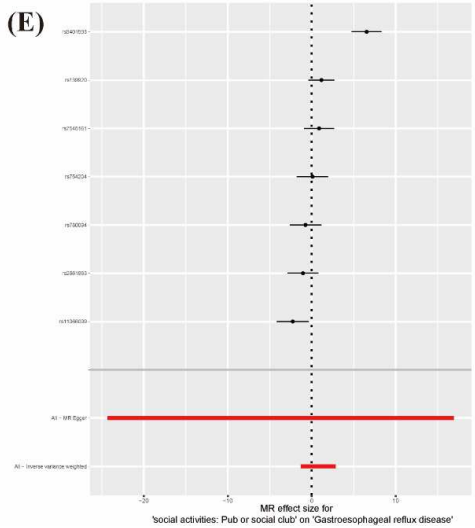

(A)
All - MR Egger
All - Inverse variance weighted
MR effect size for
'Age completed full time education' on 'Gastroesophageal reflux disease'

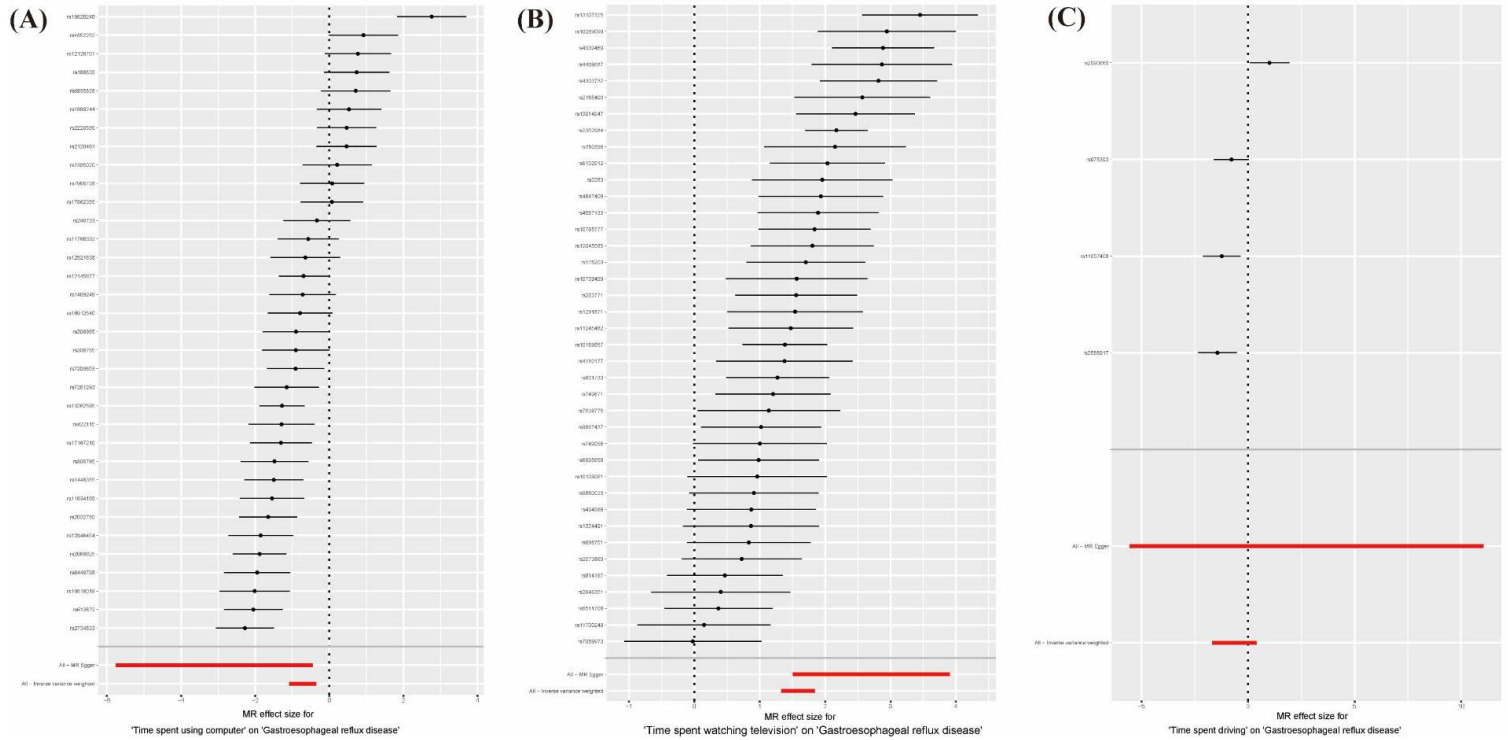

(B)
All - MR Egger
All - Inverse variance weighted
MR effect size for
'Job involves heavy manual or physical work' on 'Gastroesophageal reflux disease '


(C)
All - MR Egger
MR effect size for
'Average total household income before tax' on 'Gastroesophageal reflux disease '


(D)
All - MR Egger
All - Inverse variance weighted
MR effect size for
'Townsend deprivation index at recruitment' on 'Gastroesophageal reflux disease'

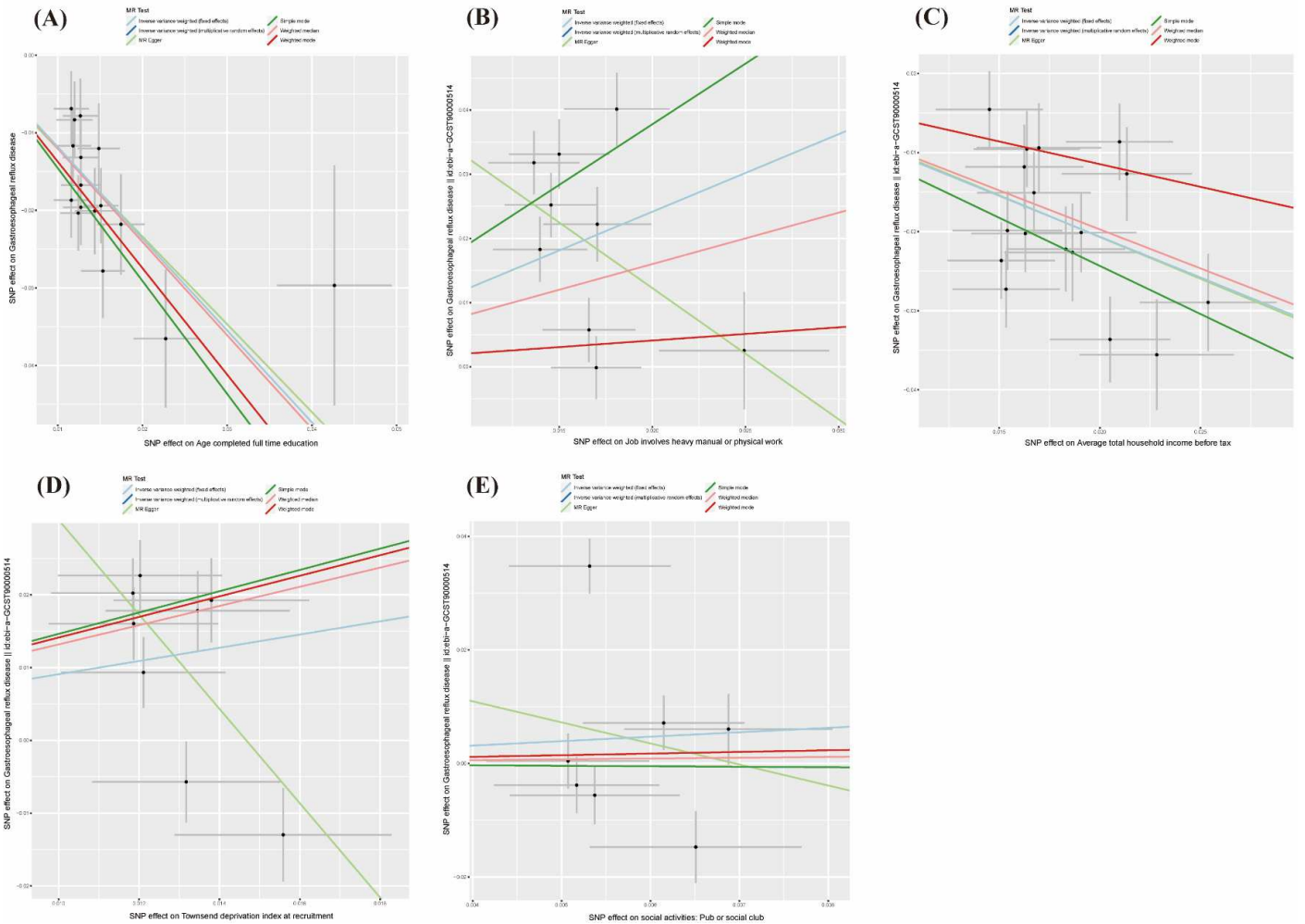

(E)
All - MR Egger
All - Inverse variance weighted
MR effect size for
'social activities: Pub or social club' on 'Gastroesophageal reflux disease'

**Supplementary figures A1** Forest plots of genetically casual association of socioeconomic status with GERD.
Notes: The MR effect size of socioeconomic status were displayed on the X-axis. The different genetic variants for socioeconomic status were listed on the Y-axis. The red point showed the casual effect estimate of socioeconomic status and GERD with valid SNPs utilizing the Egger or inverse variance weighted method, and the red lines indicated the 95% CI of the estimate. (A) Forest plots of genetically casual association of age at completion of full-time education with GERD. (B) Forest plots of genetically casual association of job involving heavy manual or physical work with GERD. (C) Forest plots of genetically casual association of average total household income before tax with GERD. (D) Forest plots of genetically casual association of Townsend deprivation index at recruitment with GERD. (E) Forest plots of genetically casual association of social activities: Pub or social club with GERD.
**Abbreviations:** GERD, gastroesophageal reflux disease; SNP, single nucleotide polymorphism; MR, Mendelian randomization.

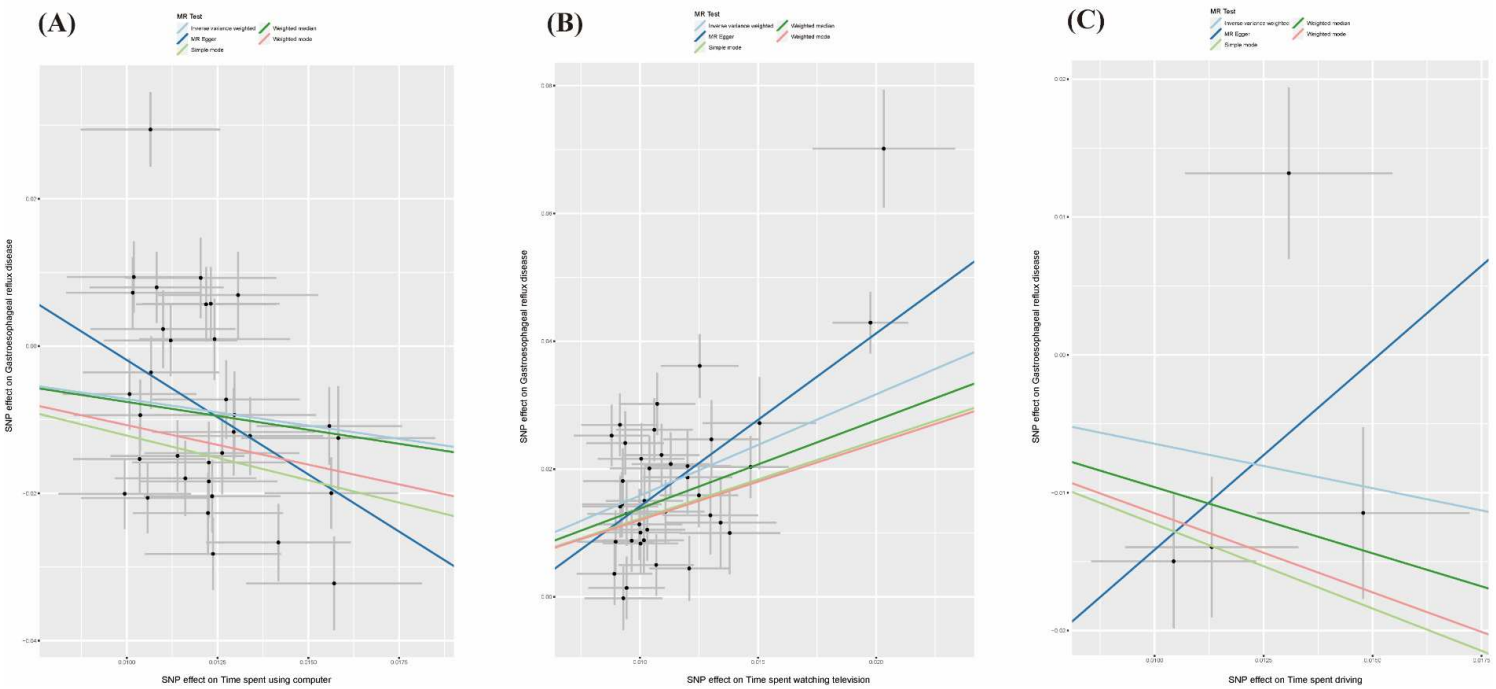



**Supplementary figures A2** Forest plots of genetically casual association of leisure sedentary behaviours with GERD.

Notes: The MR effect size of leisure sedentary behaviours were displayed on the X-axis. The different genetic variants for leisure sedentary behaviours were listed on the Y-axis. The red point showed the casual effect estimate of leisure sedentary behaviours and GERD with valid SNPs utilizing the Egger or inverse variance weighted method, and the red lines indicated the 95% CI of the estimate. (A) Forest plots of genetically casual association of leisure computer use with GERD. (B) Forest plots of genetically casual association of leisure television watching with GERD. (C) Forest plots of genetically casual association of leisure driving with GERD.

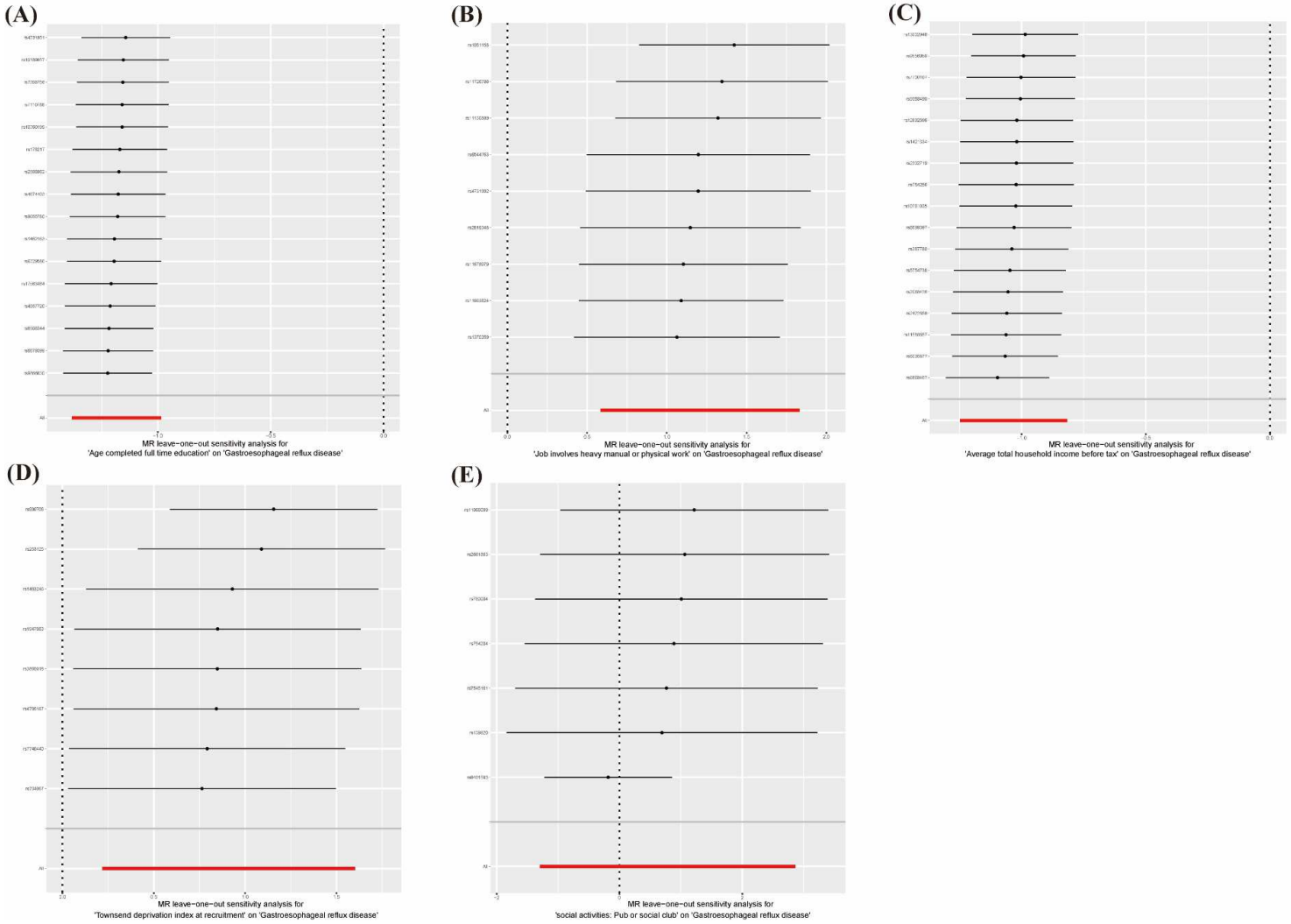

(A)
MR Test
SNP effect on Gastroesophageal reflux disease
SNP effect on Age completed full time education
(B)
MR Test
SNP effect on Gastroesophageal reflux disease || id:ebi-a-GCST90000514
SNP effect on Job involves heavy manual or physical work
(C)
MR Test
SNP effect on Gastroesophageal reflux disease || id:ebi-a-GCST90000514
SNP effect on Average total household income before tax
(D)
MR Test
SNP effect on Gastroesophageal reflux disease || id:ebi-a-GCST90000514
SNP effect on Townsend deprivation index at recruitment
(E)
MR Test
SNP effect on Gastroesophageal reflux disease || id:ebi-a-GCST90000514
SNP effect on social activities: Pub or social club

**Supplementary figures A3** Scatter plots of genetic association of socioeconomic status and GERD risk using five conventional MR methods.
Notes: Scatter plot including the MR estimates between socioeconomic status and GERD, in which a threshold of $P < 1 \times 10^{-8}$ was used for the selection of variants. The variants' effect on socioeconomic status were displayed on X-axis, the variants effect on GERD were displayed on the Y-axis. The gradient of each line represents the MR estimate for the corresponding model and the error bars represent standard errors of effect sizes. (A) Scatter plot of SNPs effects on age at completion of full-time education versus their effects on GERD. (B) Scatter plot of SNPs effects on job involving heavy manual or physical work versus their effects on GERD. (C) Scatter plot of SNPs effects on average total household income before tax versus their effects on GERD. (D) Scatter plot of SNPs effects on Townsend deprivation index at recruitment versus their effects on GERD. (E) Scatter plot of SNPs effects on social activities: Pub or social club versus their effects on GERD. GERD, gastroesophageal reflux disease; SNPs, single nucleotide polymorphisms; MR, Mendelian randomization.

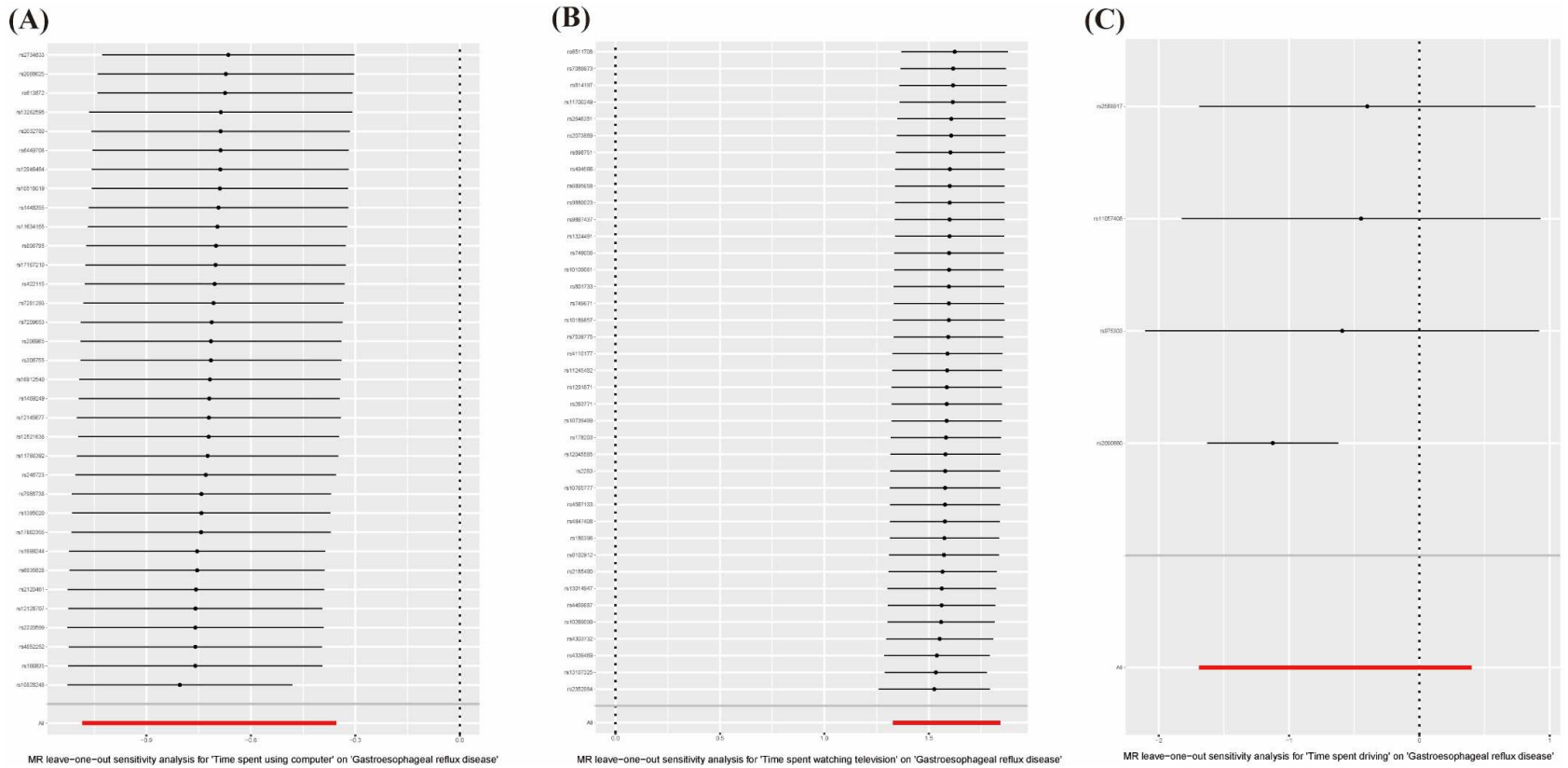



**Supplementary figures A4** Scatter plots of genetic association of leisure sedentary behaviours and GERD risk using five conventional MR methods.

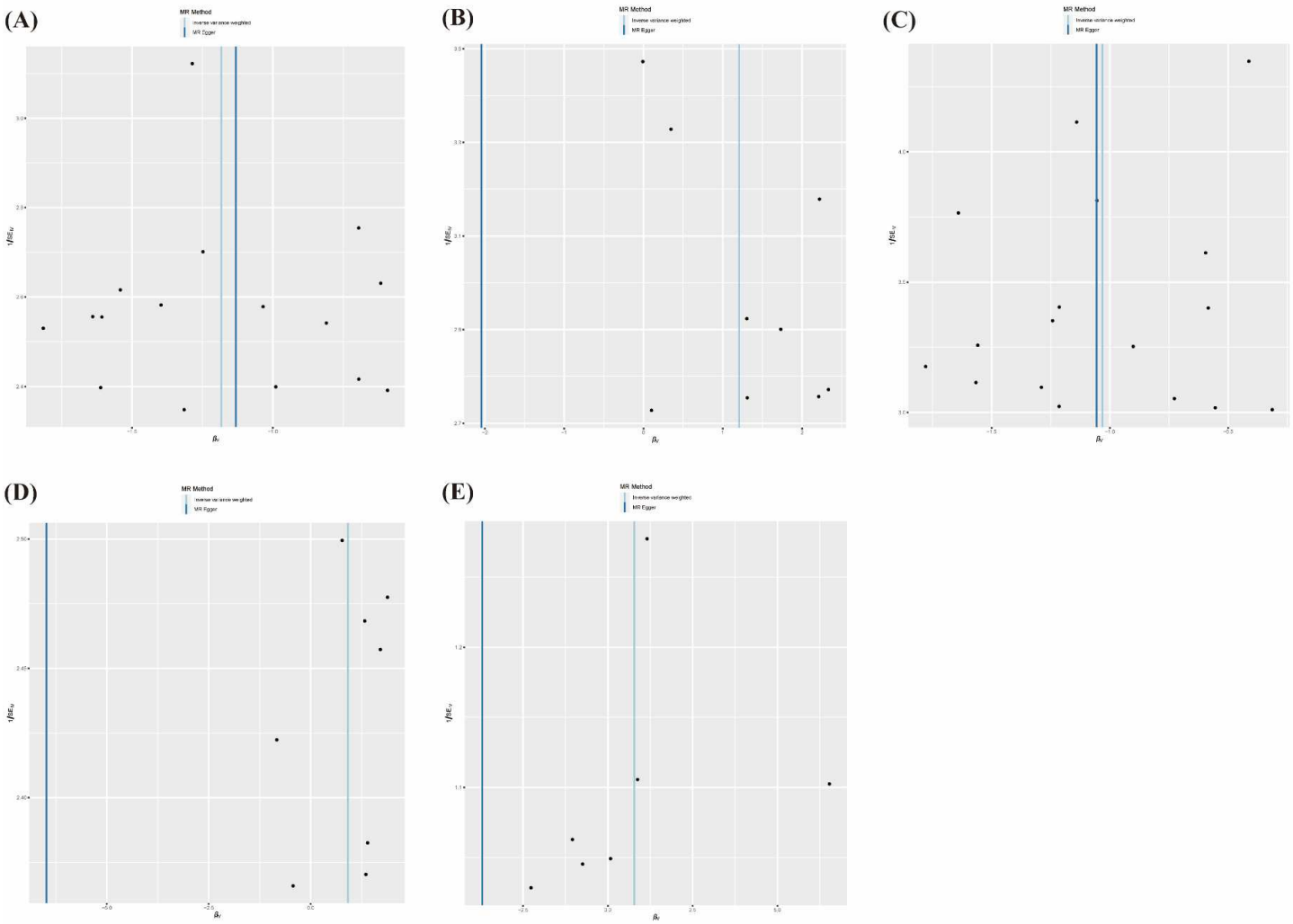
Notes: Scatter plot including the MR estimates between leisure sedentary behaviours and GERD, in which a threshold of $P < 1\times10^{-8}$ was used for the selection of variants. The variants' effect on leisure sedentary behaviours were displayed on X-axis, the variants effect on GERD were displayed on the Y-axis. The gradient of each line represents the MR estimate for the corresponding model and the error bars represent standard errors of effect sizes. (A) Scatter plot of SNPs effects on leisure computer use versus their effects on GERD. (B) Scatter plot of SNPs effects on leisure watching television versus their effects on GERD. (C) Scatter plot of SNPs effects on leisure driving versus their effects on GERD.


(A)
MR leave−one−out sensitivity analysis for
'Age completed full time education' on 'Gastroesophageal reflux disease'
(B)
MR leave−one−out sensitivity analysis for
'Job involves heavy manual or physical work' on 'Gastroesophageal reflux disease'
(C)
MR leave−one−out sensitivity analysis for
'Average total household income before tax' on 'Gastroesophageal reflux disease'
(D)
MR leave−one−out sensitivity analysis for
'Townsend deprivation index at recruitment' on 'Gastroesophageal reflux disease'
(E)
MR leave−one−out sensitivity analysis for
'social activities: Pub or social club' on 'Gastroesophageal reflux disease'

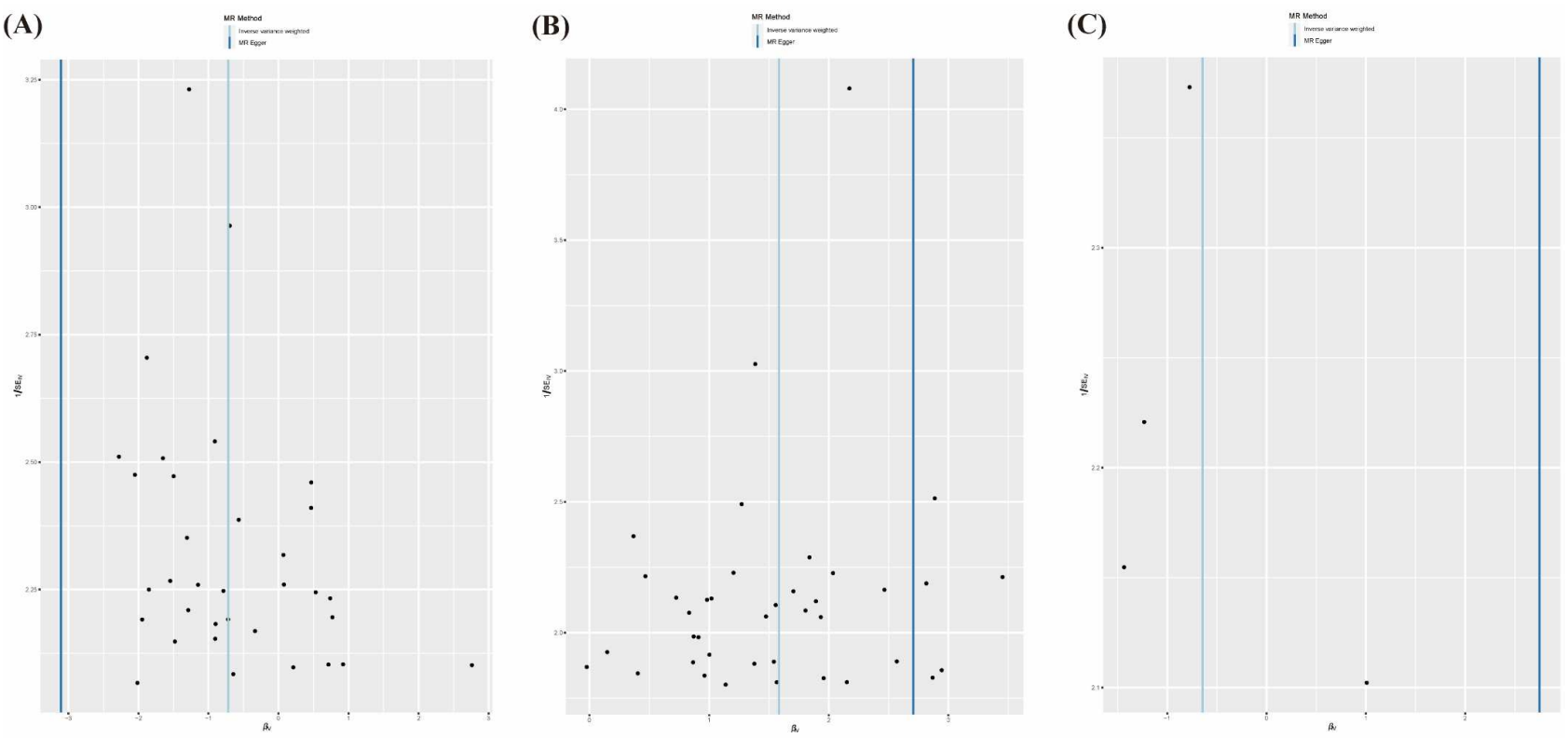
**Supplementary figures A5** Leave-One-Out analyses for variants associated with socioeconomic status on GERD.
Notes: The influence of single variant on the overall MR analysis of GERD was indicated by sequential removal of each genetic variant respectively in age at completion of full-time education (A), job involving heavy manual or physical work (B), average total household income before tax (C), Townsend deprivation index at recruitment (D), and social activities: Pub or social club (E).




**Supplementary figures A6** Leave-One-Out analyses for variants associated with leisure sedentary behaviours on GERD.
Notes: The influence of single variant on the overall MR analysis of GERD was indicated by sequential removal of each genetic variant respectively in leisure computer use (A), leisure television watching (B), and leisure driving (C).


(A)
(B)
(C)
(D)
(E)
MR Method
Inverse variance weighted
MR Egger

**Supplementary figures A7** Funnel plots for the effects of socioeconomic status on GERD.
Notes: The causal effect of individual variant against the overall estimate in the MR analysis on age at completion of full-time education (A), job involving heavy manual or physical work (B), average total household income before tax (C), Townsend deprivation index at recruitment (D), and social activities: Pub or social club (E) and GERD was depicted. Vertical lines denote overall estimates by the inverse variance weighted method.




**Supplementary figures A8** Funnel plots for the effects of leisure sedentary behaviours on GERD.

Notes: The causal effect of individual variant against the overall estimate in the MR analysis on leisure computer use (A), leisure television watching (B), and leisure driving (C) and GERD was depicted. Vertical lines denote overall estimates by the inverse variance weighted method.

**Supplementary tables A1** Information on GWASs for exposure and outcome

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

*The statistical power to detect the associations in the Mendelian randomization analyses.

GWAS, genome-wide association study; SNPs, single-nucleotide polymorphisms; NCP: Non-Centrality-Parameter; MRC-IEU, MRC Integrative Epidemiology Unit.

**Supplementary tables A2** SNPs excluded from the outlier corrected MR-PRESSO analyses and Steiger-filter test between socioeconomic status or leisure sedentary behaviour-related phenotypes and GERD

| **Job involves heavy manual or physical work** | | | |
|---|---|---|---|
| **Outlier SNP** | **Outcome** | **Status** | **Methods** |
| rs1081158 | GERD | Outlier/Horizontal pleiotropy | MR_PRESSO (Outlier test/Global test) |
| rs11663824 | GERD | Outlier/Horizontal pleiotropy | MR_PRESSO (Outlier test/Global test) |
| rs11726786 | GERD | Outlier/Horizontal pleiotropy | MR_PRESSO (Outlier test/Global test) |
| rs1370059 | GERD | Outlier/Horizontal pleiotropy | MR_PRESSO (Outlier test/Global test) |
| **Townsend deprivation index at recruitment** | | | |
| **Outlier SNP** | **Outcome** | **Status** | **Methods** |
| rs253125 | GERD | Outlier/Horizontal pleiotropy | MR_PRESSO (Outlier test/Global test) |
| rs704067 | GERD | Outlier/Horizontal pleiotropy | MR_PRESSO (Outlier test/Global test) |
| rs990706 | GERD | Outlier/Horizontal pleiotropy | MR_PRESSO (Outlier test/Global test) |
| **Social activities: Pub or social club** | | | |
| **Outlier SNP** | **Outcome** | **Status** | **Methods** |
| rs11066099 | GERD | Outlier/Horizontal pleiotropy | MR_PRESSO (Outlier test/Global test) |
| rs9401593 | GERD | Outlier/Horizontal pleiotropy | MR_PRESSO (Outlier test/Global test) |
| **Time spent using computer** | | | |
| **Outlier SNP** | **Outcome** | **Status** | **Methods** |
| rs10828248 | GERD | Outlier/Horizontal pleiotropy | MR_PRESSO (Outlier test/Global test) |
| rs12128707 | GERD | Outlier/Horizontal pleiotropy | MR_PRESSO (Outlier test/Global test) |
| rs166835 | GERD | Outlier/Horizontal pleiotropy | MR_PRESSO (Outlier test/Global test) |
| rs2068625 | GERD | Outlier/Horizontal pleiotropy | MR_PRESSO (Outlier test/Global test) |
| rs2734833 | GERD | Outlier/Horizontal pleiotropy | MR_PRESSO (Outlier test/Global test) |
| rs4852252 | GERD | Outlier/Horizontal pleiotropy | MR_PRESSO (Outlier test/Global test) |

| **Time spent watching television** | | | |
|---|---|---|---|
| **Outlier SNP** | **Outcome** | **Status** | **Methods** |
| rs13107325 | GERD | Outlier/Horizontal pleiotropy | MR_PRESSO (Outlier test/Global test) |
| rs4339469 | GERD | Outlier/Horizontal pleiotropy | MR_PRESSO (Outlier test/Global test) |
| **Time spent driving** | | | |
| **Outlier SNP** | **Outcome** | **Status** | **Methods** |
| rs2090660 | GERD | Outlier/Horizontal pleiotropy | MR_PRESSO (Outlier test/Global test) |

**Abbreviations:** SNPs, single-nucleotide polymorphisms; MR-PRESSO, Mendelian randomization pleiotropy residual sum and outlier; GERD, gastroesophageal reflux disease.

**Supplementary tables A3** Causal associations between genetically predicted socioeconomic status and leisure sedentary behaviours with risk of GERD in validation datasets

| Methods | nSNP | OR | 95% CI | P value |
|---|---|---|---|---|
| **Age at completion of full-time education** | | | | |
| MR Egger | 159 | 0.26 | 0.17–0.4 | <0.001 |
| Weighted median | 159 | 0.28 | 0.25–0.32 | <0.001 |
| Inverse variance weighted (multiplicative random effects) | 159 | 0.26 | 0.23–0.28 | <0.001 |
| Inverse variance weighted (fixed effects) | 159 | 0.26 | 0.24–0.28 | <0.001 |
| Simple mode | 159 | 0.30 | 0.21–0.43 | <0.001 |
| Weighted mode | 159 | 0.29 | 0.2–0.42 | <0.001 |
| **Average total household income before tax** | | | | |
| MR Egger | 15 | 0.03 | 0–0.65 | 0.043 |
| Weighted median | 15 | 0.19 | 0.13–0.28 | <0.001 |
| Inverse variance weighted (multiplicative random effects) | 15 | 0.18 | 0.12–0.26 | <0.001 |
| Inverse variance weighted (fixed effects) | 15 | 0.18 | 0.14–0.22 | <0.001 |
| Simple mode | 15 | 0.17 | 0.09–0.35 | <0.001 |
| Weighted mode | 15 | 0.18 | 0.08–0.38 | 0.001 |
| **Job involves heavy manual or physical work** | | | | |
| MR Egger | 7 | 1.32 | 0.94–1.86 | 0.174 |
| Weighted median | 7 | 1.07 | 0.92–1.25 | 0.372 |
| Inverse variance weighted (multiplicative random effects) | 7 | 1.01 | 0.84–1.23 | 0.884 |
| Inverse variance weighted (fixed effects) | 7 | 1.01 | 0.91–1.13 | 0.800 |
| Simple mode | 7 | 1.07 | 0.9–1.27 | 0.490 |
| Weighted mode | 7 | 1.08 | 0.94–1.24 | 0.327 |
| **Social activities: Pub or social club** | | | | |

| | | | | |
|---|---|---|---|---|
| MR Egger | 3 | 0.00 | 0–0.38 | 0.699 |
| Weighted median | 3 | 0.81 | 0.21–3.11 | 0.757 |
| Inverse variance weighted (multiplicative random effects) | 3 | 0.06 | 0–5.84 | 0.223 |
| Inverse variance weighted (fixed effects) | 3 | 0.06 | 0.02–0.15 | 0.000 |
| Simple mode | 3 | 0.82 | 0.23–2.91 | 0.784 |
| Weighted mode | 3 | 0.82 | 0.24–2.82 | 0.778 |
| **Time spent watching television** | | | | |
| MR Egger | 41 | 0.36 | 0.08–1.67 | 0.198 |
| Weighted median | 41 | 0.40 | 0.33–0.49 | <0.001 |
| Inverse variance weighted (multiplicative random effects) | 41 | 0.42 | 0.31–0.56 | <0.001 |
| Inverse variance weighted (fixed effects) | 41 | 0.42 | 0.38–0.46 | <0.001 |
| Simple mode | 41 | 0.36 | 0.23–0.55 | <0.001 |
| Weighted mode | 41 | 0.38 | 0.26–0.57 | <0.001 |
| **Time spent using computer** | | | | |
| Weighted median | 11 | 2.85 | 1.99–4.09 | <0.001 |
| Inverse variance weighted (multiplicative random effects) | 11 | 2.74 | 1.7–4.44 | <0.001 |
| Inverse variance weighted (fixed effects) | 11 | 2.74 | 2.26–3.33 | <0.001 |
| Simple mode | 11 | 3.46 | 1.9–6.30 | 0.002 |
| Weighted mode | 11 | 3.21 | 1.5–6.88 | 0.013 |
| **Time spent driving** | | | | |
| Inverse variance weighted (multiplicative random effects) | 2 | 0.29 | 0.18–1.45 | 0.050 |
| Inverse variance weighted (fixed effects) | 2 | 0.29 | 0.18–1.00 | 0.171 |

**Abbreviations:** SNP, single nucleotide polymorphism; OR, odds ratio; CI, confidence interval; MR, Mendelian randomization. The causal effect of time spent using computer in MR-Egger model was unavailable because of the impact of limited number of IVs and variance explained.

**Supplementary tables A4** Genetic causal effects of genetically predicted socioeconomic status or leisure sedentary–related traits on GERD based on IVW multivariable MR model

| Traits | Conjoint nSNP | β | SE | OR | 95%CI | P |
|---|---|---|---|---|---|---|
| **Socioeconomic status** | | | | | | |
| Age at completion of full-time education | 75 | -0.75 | 0.22 | 0.47 | 0.31–0.73 | <0.001 |
| Job involves heavy manual or physical work | 75 | 0.28 | 0.21 | 1.32 | 0.89–1.98 | 0.172 |
| Average total household income before tax | 75 | -0.47 | 0.17 | 0.63 | 0.45–0.87 | 0.005 |
| Townsend deprivation index at recruitment | 75 | 0.42 | 0.21 | 1.53 | 1.02–2.33 | 0.04 |
| **Leisure sedentary behaviors** | | | | | | |
| Time spent watching television | 116 | 1.33 | 0.12 | 3.8 | 2.97–4.85 | <0.001 |
| Time spent using computer | 116 | -0.22 | 0.12 | 0.81 | 0.63–1.03 | 0.08 |

**Notes:** We reperformed the IVW multivariable MR model by only including specific traits which had statistical differences in univariable MR analyses as a sensitivity analysis.

**Abbreviations:** GERD, gastroesophageal reflux disease; IVW, inverse-variance weighted; MR, Mendelian randomization; SNPs, single-nucleotide polymorphisms; SE, standard errors; OR, odds ratio; CI, confidence interval.

**Supplementary tables A5** Bidirectional MR analyses of genetically predicted GERD on socioeconomic status and leisure sedentary behaviour-related phenotypes

| Characteristics/Methods | nSNP | OR (95% CI) | P value |
|---|---|---|---|
| **a. Age at completion of full-time education** | | | |
| MR Egger | 77 | 0.77 (0.67–0.89) | <0.001 |
| Weighted median | 77 | 0.86 (0.83–0.88) | <0.001 |
| Inverse variance weighted (multiplicative random effects) | 77 | 0.82 (0.80–0.85) | <0.001 |
| Inverse variance weighted (fixed effects) | 77 | 0.82 (0.81–0.84) | <0.001 |
| Simple mode | 77 | 0.89 (0.83–0.96) | 0.002 |
| Weighted mode | 77 | 0.89 (0.83–0.95) | <0.001 |
| **b. Job involving heavy manual or physical work** | | | |
| MR Egger | 77 | 1.28 (1.06–1.54) | <0.001 |
| Weighted median | 77 | 1.18 (1.14–1.22) | <0.001 |
| Inverse variance weighted (multiplicative random effects) | 77 | 1.21 (1.17–1.26) | <0.001 |
| Inverse variance weighted (fixed effects) | 77 | 1.21 (1.19–1.24) | <0.001 |
| Simple mode | 77 | 1.16 (1.07–1.27) | 0.001 |
| Weighted mode | 77 | 1.15 (1.06–1.24) | <0.001 |
| **c. Average total household income before tax** | | | |
| MR Egger | 77 | 0.77 (0.64–0.93) | 0.009 |
| Weighted median | 77 | 0.79 (0.76–0.82) | <0.001 |
| Inverse variance weighted (multiplicative random effects) | 77 | 0.77 (0.74–0.79) | <0.001 |
| Inverse variance weighted (fixed effects) | 77 | 0.77 (0.75–0.78) | <0.001 |
| Simple mode | 77 | 0.78 (0.70–0.86) | <0.001 |

| | | | |
|---|---|---|---|
| Weighted mode | 77 | 0.79 (0.71–0.89) | <0.001 |
| **d. Townsend deprivation index at recruitment** | | | |
| MR Egger | 77 | 1.01 (0.90–1.14) | 0.86 |
| Weighted median | 77 | 1.10 (1.07–1.12) | <0.001 |
| Inverse variance weighted (multiplicative random effects) | 77 | 1.11 (1.09–1.13) | <0.001 |
| Inverse variance weighted (fixed effects) | 77 | 1.11 (1.09–1.13) | <0.001 |
| Simple mode | 77 | 1.10 (1.03–1.17) | 0.003 |
| Weighted mode | 77 | 1.08 (1.02–1.14) | 0.011 |
| **e. Social activities: Pub or social club** | | | |
| MR Egger | 77 | 0.97 (0.91–1.04) | 0.43 |
| Weighted median | 77 | 1.03 (1.02–1.04) | <0.001 |
| Inverse variance weighted (multiplicative random effects) | 77 | 1.02 (1.01–1.03) | 0.005 |
| Inverse variance weighted (fixed effects) | 77 | 1.02 (1.01–1.03) | <0.001 |
| Simple mode | 77 | 1.05 (1.01–1.09) | 0.009 |
| Weighted mode | 77 | 1.05 (1.02–1.09) | 0.005 |
| **f. Time spent watching television** | | | |
| MR Egger | 77 | 1.38 (1.21–1.58) | <0.001 |
| Weighted median | 77 | 1.15 (1.12–1.18) | <0.001 |
| Inverse variance weighted (multiplicative random effects) | 77 | 1.18 (1.15–1.21) | <0.001 |
| Inverse variance weighted (fixed effects) | 77 | 1.18 (1.17–1.20) | <0.001 |
| Simple mode | 77 | 1.20 (1.11–1.29) | <0.001 |
| Weighted mode | 77 | 1.11 (1.03–1.20) | 0.007 |
| **g. Time spent using computer** | | | |
| MR Egger | 77 | 0.98 (0.82–1.17) | 0.86 |
| Weighted median | 77 | 0.93 (0.91–0.96) | <0.001 |

| | | | |
|---|---|---|---|
| Inverse variance weighted (multiplicative random effects) | 77 | 0.93 (0.90–0.96) | <0.001 |
| Inverse variance weighted (fixed effects) | 77 | 0.93 (0.91–0.94) | <0.001 |
| Simple mode | 77 | 0.87 (0.80–0.94) | 0.001 |
| Weighted mode | 77 | 0.87 (0.80–0.95) | 0.002 |

**Abbreviations:** SNP, single nucleotide polymorphism; OR, odds ratio; CI, confidence interval; MR, Mendelian randomization.

**Supplementary tables A6** Heterogeneity (Cochran's Q, Rucker's Q), pleiotropy (MR-Egger intercept, MR-PRESSO Test) and weak instrument statistics between socioeconomic status or leisure sedentary behaviour-related phenotypes and GERD

| Exposure | Cochran's Q | | | Rucker's Q | | | MR-Egger intercept | | | MR-PRESSO | |
|---|---|---|---|---|---|---|---|---|---|---|---|
| | Q | df | P-value | Q | df | P-value | Intercept | SE | P-value | P-value (Global test) | P-value (Distortion test) |
| **Age at completion of full-time education** | 16.21 | 14 | 0.301 | 16.23 | 15 | 0.367 | 0.00 | 0.01 | 0.906 | # | NA |
| **Job involves heavy manual or physical work** | 47.12 | 7 | < 0.001 | 65.28 | 8 | < 0.001 | 0.05 | 0.03 | 0.144 | < 0.001 | 0.194 |
| **Average total household income before tax** | 38.49 | 15 | 0.001 | 38.49 | 16 | 0.001 | 0.00 | 0.01 | 0.97 | # | NA |
| **Townsend deprivation index at recruitment** | 21.59 | 6 | 0.001 | 41.19 | 7 | < 0.001 | 0.10 | 0.04 | 0.06 | < 0.001 | 0.719 |
| **Social activities: Pub or social club** | 55.11 | 5 | < 0.001 | 57.13 | 6 | < 0.001 | 0.03 | 0.06 | 0.69 | < 0.001 | <0.001 |
| **Time spent watching television** | 108.99 | 37 | < 0.001 | 119.28 | 38 | < 0.001 | -0.01 | 0.01 | 0.07 | < 0.001 | 0.388 |
| **Time spent using computer** | 193.11 | 32 | < 0.001 | 212.13 | 33 | < 0.001 | 0.03 | 0.02 | 0.09 | < 0.001 | 0.435 |
| **Time spent driving** | 12.64 | 2 | 0.002 | 16.76 | 3 | 0.001 | -0.04 | 0.05 | 0.50 | # | 0.552 |

**Notes:** Cochran's Q with one–side P-value of < 0.05 were considered as an indication of heterogeneity and, as a consequence, of pleiotropy in the inverse variance weighted fixed effect model. A significant difference (one-side P < 0.05) between the Cochran's Q and Rucker's Q (Q–Q') was considered to indicate the MR-Egger test to be a better method to study the genetic association between the particular exposure and outcome. MR-PRESSO test and an MR-Egger's intercept of zero, tested using a single side P-value threshold of > 0.05, were considered to provide evidence for absence of pleiotropic bias.

P of distortion test was not available for the analysis of age at completion of full-time education and average total household income before tax due to no outlier detected.

**Abbreviations:** SE, standard errors; MR-PRESSO, Mendelian randomization pleiotropy residual sum and outlier; GERD, gastroesophageal reflux disease.