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Socioeconomic status and asthma: A bidirectional Mendelian randomization study

Liang Peng, MD[a,b] and Wei-Ping Wen, MD[a,b,c]*

ABSTRACT

Background: Asthma is closely associated with lower socioeconomic status (SES), while the causal relationship between asthma and SES is undetermined. We aim to examine bidirectional relationships between asthma and SES using two-sample bidirectional Mendelian randomization (MR) for assessing potential causal inference.

Methods: Education attainment (years of schooling), household income, and Townsend deprivation index (TDI) were 3 indicators of SES considered in our study. The genetic summary data for SES and asthma were retrieved from publicly available genome-wide association studies (GWASs) conducted in participants of European ancestry. The MR estimates from each genetic instrument were combined using random effects inverse variance weighted (IVW) meta-analysis, with alternate methods (eg, MR-Egger, weighted median). Horizontal pleiotropy was assessed by sensitivity analyses. Analyses were performed using the package TwoSampleMR in R.

Results: The genetically instrumented years of schooling, household income, and TDI were not associated with the risk of asthma. However, according to the IVW method, 1.72 times increase in the odds ratio (OR) for asthma will lead to 0.024 standard deviation (SD) decrease in the years of schooling, 0.026 SD decrease in the household income, and 0.016 SD increase in the TDI. Although the substantial heterogeneity may undermine the reliability of results to some extent, sensitivity analyses further supported the causation of low household income by asthma.

Conclusion: Our study indicated that genetically predicted asthma may play a causal role in lowering the household income. However, the causal role of lower SES in asthma development was not supported by our MR analyses. Considering the heterogeneity in the current study, additional MR studies are needed to validate the results in the future.

Keywords: Asthma, Socioeconomic status, Mendelian randomization, Causal inference, Genome-wide association studies

[a]Department of Otorhinolaryngology Head and Neck Surgery, The First Affiliated Hospital, Sun Yat-sen University, Guangzhou, Guangdong, China
*Corresponding author. Department of Otorhinolaryngology, The First Affiliated Hospital, Sun Yat-sen University, No. 58 Zhongshan 2nd Road, Guangzhou, 510080, China. E-mail: wenwp@mail.sysu.edu.cn
Full list of author information is available at the end of the article

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INTRODUCTION

Asthma is one of the most common chronic respiratory diseases, which affects around 334 million people worldwide.[1] Socioeconomic status (SES) is closely associated with health status and is an important aspect in health research.[2,3] Disparities in the prevalence of asthma across SES have long been recognized.[4,5] A systematic review based on observational studies has concluded that a lower SES is associated with a higher prevalence of asthma.[6] The relationship between SES and asthma is complex and needs to be explained. The causal effects of a lower SES on asthma could be mediated by exposures to air pollution, indoor allergens, and smoking, or by comorbidities, such as obesity, and depression.[7,8] On the other hand, poor health can result in low SES.[3] For example, poorly controlled asthma in youths can impair educational achievements through its effects on cognition, school connectedness, and absenteeism.[9,10] Work-related asthma in adults can lead to work disability and a reduction of income.[11] However, the causal inference from observational data usually suffers from confounding bias or reverse causality.[12,13]

Mendelian randomization (MR) is a method that strengthens causal inference by using genetic variants (ie, single-nucleotide polymorphisms [SNPs]) as instrumental variables (IVs) to mimic a randomized controlled trial.[14,15] The genetic IVs used in MR must meet 3 assumptions: 1) reliably associated with the exposure; 2) associated with the outcome only through the exposure; 3) independent of confounders of the exposure-outcome association.[15] In the era of genome-wide association study (GWAS), the publicly accessible GWAS summary data facilitate the exploration of risk factor-disease association by two-sample MR design.[16] The MR method has been successfully applied in asthma research investigating the relationship between asthma and risk factors, such as obesity,[17] low vitamin D,[18] and early pubertal maturation.[19]

In the present study, we applied bidirectional two-sample MR analyses to identify the causal relationship between SES and asthma.

MATERIALS AND METHODS

GWAS summary data

Three indicators of SES are considered: the individual level SES is evaluated by education attainment, specifically, the years of schooling; the household level SES is evaluated by the average total household income before tax; the neighborhood level SES is evaluated by the Townsend deprivation index (TDI).[20] The GWAS summary data for education attainment (years of schooling, continuous variable) were retrieved from Okbay's study conducted in 293 723 participants of European descent, with a standard deviation (SD) of 3.71 years.[21] The GWAS summary data for household income and TDI were retrieved from a project conducted by Medical Research Council Integrative Epidemiology Unit (MRC-IEU) using the UK biobank resources.[22] The prospective cohort of the UK biobank includes >500,000 participants, with a survey response rate of around 6%. The household income GWAS included 397 751 participants of European descent; the self-reported household income was collected using a five-point scale corresponding to the total household income before tax, 1 being less than £18 000, 2 being £18 000 – £30 999, 3 being £31 000 – £51 999, 4 being £52 000 – £100 000, and 5 being greater than £100 000. The TDI GWAS included 462 464 participants of European descent; the TDI (continuous variable) was calculated immediately prior to participant joining UK Biobank based on the preceding national census output areas and participants' postcode.

The GWAS summary data for asthma were retrieved from a meta-analysis conducted by the Trans-National Asthma Genetic Consortium (TAGC).[23] We only used the data from European ancestry-specific meta-analysis which included 19 954 asthma cases and 107 715 controls.[23]

Statistical analysis

The SNPs associated with the exposures at genome-wide significance ($p < 5 \times 10^{-8}$) were selected as IVs from the GWAS studies. To ensure the instrumental SNPs were independent, clumping was used to prune SNPs for linkage disequilibrium (LD) with a threshold of LD $R^2 < 0.001$ and a distance of 10 Mb based on the European

ancestry reference data from the 1000 genomes project.[24] Where SNPs for the exposure were not available in the summary statistics of the outcome, we replaced them with proxy SNPs in LD ($R^2 > 0.8$) identified using the European ancestry reference data from the 1000 genomes project.[24] The exposure and outcome datasets were harmonized to ensure that the effect of each SNP on the exposure and the outcome corresponds to the same effect allele.[25] To avoid the reverse causation, Steiger filtering was used to test the causal direction of each SNP on the exposure and outcome and remove the SNPs that had a stronger association with the outcome than exposure.[26] Statistical power for MR was calculated at a standard alpha level of 0.05, using an online calculator based on the method developed by Burgess (https://sb452.shinyapps.io/power).[27]

For each instrumental SNP, the effect size of the exposure on the outcome was calculated using Wald ratio, which is the simplest method for estimating the causal effect of the exposure on the outcome, and is the coefficient of the SNP in the regression of the outcome divided by the coefficient of the SNP in the regression of the exposure.[28] The effect size represented by Wald ratio can be interpreted as the log odds ratio (OR) for asthma per 1 SD increase in the SES, or the SD change for the SES per 1.72 times increase in the OR for asthma. The MR estimate was obtained by performing a random effects inverse variance weighted (IVW) meta-analysis of each Wald ratio.[29] The MR-Egger and weighted median methods were also used to calculate the causal effect as sensitivity analyses.[30,31] Heterogeneity in causal effects amongst instruments was evaluated using Cochran's Q statistic for the IVW and MR-Egger estimates, and Q much larger than its degrees of freedom (number of IVs minus 1) provided evidence for heterogeneity.[32] The funnel plot was also used to detect the presence of heterogeneity, and the asymmetry of funnel plot indicated the presence of heterogeneity.[33] The directional horizontal pleiotropy was evaluated by MR-Egger regression, which allows a non-zero intercept representing an estimate of the directional pleiotropic effect.[30] The MR-Egger intercept test rejecting the null hypothesis indicates the existence of directional horizontal pleiotropy. Leave-one-out analysis was performed to evaluate if the MR estimate is driven or biased by a single SNP that might have a particularly large horizontal pleiotropic effect. To minimize the influences of horizontal pleiotropy, instrumental SNPs that are likely to be associated with confounding factors of the respective exposure-outcome association were identified by PhenoScanner V2 and were excluded in sensitivity analyses.[34] A p-value <0.05 was considered statistically significant. All analyses were performed using the package TwoSampleMR (version 0.5.6) in R (version 3.6.0).[16]

RESULTS

SES → asthma causal inference

The genetically instrumented years of schooling (52 SNPs), household income (34 SNPs), and TDI (14 SNPs) were not associated with the risk of asthma according to the IVW, MR-Egger and weighted median methods (Table 1 and Fig. 1). The Cochran's Q statistics (Table 3) and the funnel plot asymmetry (Fig. 3) indicated strong evidence for heterogeneity amongst SNPs in the years of schooling → asthma MR and household income → asthma MR, suggesting that at least some of the SNPs exhibit horizontal pleiotropy. However, there was no evidence for the presence of directional pleiotropy in the MR-Egger regression analysis (Table 4). In the leave-one-out analyses, no single SNP is strongly driving the MR estimates for the effects of each indicator of SES on asthma (Fig. 4). According to Burgess's method,[27] our studies had sufficient power (>80%) at an alpha level of 0.05 to detect effects of SES on asthma if the true causal effect of years of schooling on asthma had an OR of less than 0.79 per 1 SD increase in years of schooling, the true causal effect of household income on asthma had an OR of less than 0.70 per 1 SD increase in household income, and the true causal effect of TDI on asthma had an OR of more than 1.98 per 1 SD increase in TDI.

In the sensitivity analyses for the years of schooling → asthma MR, 25 instrumental SNPs associated with allergy, eosinophil traits, obesity-related traits, or smoking traits were excluded. Among them, rs766406, rs2456973, and rs9739070 are associated with asthma or allergy. Using the remaining instrumental SNPs, the MR estimates

Exposure	Outcome	Number of SNPs	R^2[a]	IVW		MR-Egger		Weighted median	
				OR (95% CI)	*p*-value	OR (95% CI)	*p*-value	OR (95% CI)	*p*-value
Years of schooling	Asthma	52	0.0082	1.06 (0.73–1.53)	0.765	0.46 (0.05–4.46)	0.503	1.11 (0.77–1.60)	0.574
Household income	Asthma	34	0.0037	1.00 (0.71–1.40)	0.989	0.94 (0.15–5.99)	0.9448	0.80 (0.55–1.17)	0.258
TDI	Asthma	14	0.0010	1.11 (0.54–2.28)	0.825	2.87 (0.004–2213)	0.761	1.57 (0.65–3.79)	0.315

Table 1. Mendelian randomization estimates of the causal effects of socioeconomic status on asthma. *Abbreviations: CI, confidence interval; IVW, inverse variance weighted; OR, odds ratio; SNPs, single-nucleotide polymorphisms; TDI, Townsend Deprivation Index.* [a]*R^2 represents the proportion of variance in the exposure explained by instrumental SNPs*

were still statistically nonsignificant (Supplementary Fig. S1). In the sensitivity analyses for the household income → asthma MR, 16 instrumental SNPs associated with eosinophil traits, obesity-related traits or smoking traits were excluded. Using the remaining instrumental SNPs, the MR estimate calculated by IVW method was statistically significant with nonsignificant heterogeneity (Supplementary Fig. S2). In the sensitivity analyses for the TDI → asthma MR, 6 instrumental SNPs associated with allergy, or obesity-related traits were excluded. Using the remaining instrumental SNPs, the MR estimates were still statistically nonsignificant (Supplementary Fig. S3).

Asthma → SES causal inference

We found that the genetically instrumented asthma (16 SNPs) was associated SES using the IVW and weighted median methods, but not the MR-Egger method (Table 2 and Fig. 2). According to the IVW method, 1.72 times increase in the OR for asthma will lead to 0.024 SD decrease in the years of schooling, 0.026 SD decrease in the household income, and 0.016 SD increase in the TDI (Table 2). Similar results were provided by the weighted median method. However, the MR-Egger method returned statistically nonsignificant results, which may be due to the reduced statistical power compared to the IVW method. The Cochran's Q statistics indicated strong evidence for heterogeneity amongst SNPs in the asthma → years of schooling MR and asthma → household income MR (Table 3), and the funnel plot asymmetry indicated potential heterogeneity amongst SNPs in the asthma → TDI MR (Fig. 3). The substantial heterogeneity may explain the inconsistency among the MR estimates. However, none of these asthma → SES MR was likely to be biased by the directional pleiotropy according to the MR-Egger regression analyses (Table 4). In the leave-one-out analysis, no single SNP is strongly driving the MR estimates for the effects of asthma on each indicator of SES (Fig. 4). Our studies had sufficient power (>80%) to detect effects of asthma on SES if the true causal effect of asthma on years of schooling was 0.055 SD decrease in years of schooling per 1.72 times increase in the OR for asthma, the true causal effect of asthma on household income was 0.047 SD decrease in household income per 1.72 times increase in the OR for asthma, and the true causal effect of asthma on TDI was 0.044 SD increase in TDI per 1.72 times increase in the OR for asthma.

In the sensitivity analyses for asthma → SES MR, 7 instrumental SNPs associated with coronary heart disease, Crohn's disease, or educational traits were excluded. Among them, rs10957979 is associated with the years of educational attainment. Using the remaining instrumental SNPs, the asthma → household income MR estimate calculated by the IVW method remained to be statistically significant with nonsignificant heterogeneity (Supplementary Fig. S4), while the asthma → the years of schooling and the asthma → TDI MR estimates were statistically nonsignificant (Supplementary Figs. S5 and S6).

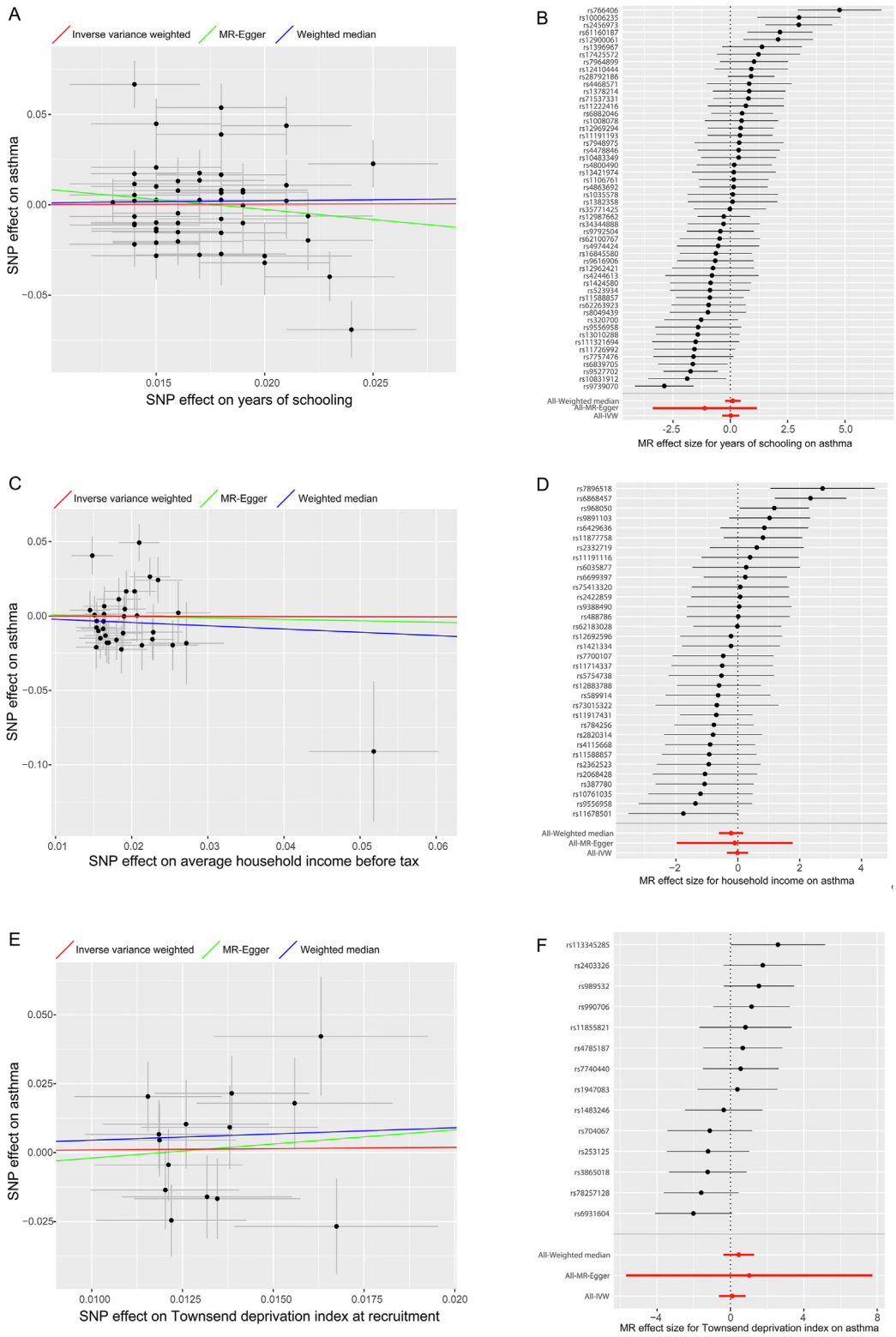

Fig. 1 Mendelian randomization plots for the effects of socioeconomic status on asthma. (A) Scatter plot of single-nucleotide polymorphism (SNP) effects on years of schooling vs. asthma. (B) Forest plot of individual and combined MR effect sizes for years of schooling on asthma. (C) Scatter plot of SNP effects on household income vs. asthma. (D) Forest plot of individual and combined MR effect sizes for household income on asthma. (E) Scatter plot of SNP effects on Townsend deprivation index vs. asthma. (F) Forest plot of individual and combined MR effect sizes for Townsend deprivation index on asthma. The effect sizes shown in this Figure are β coefficients

Exposure	Outcome	Number of SNPs	R^{2a}	IVW		MR-Egger		Weighted median	
				β (SE)	*p*-value	β (SE)	*p*-value	β (SE)	*p*-value
Asthma	Years of schooling	16	0.0089	−0.024 (0.011)	0.026	0.006 (0.035)	0.878	−0.038 (0.010)	<0.001
Asthma	Household income	16	0.0089	−0.026 (0.010)	0.006	0.0002 (0.0323)	0.994	−0.026 (0.009)	0.003
Asthma	TDI	16	0.0089	0.016 (0.005)	<0.001	−0.012 (0.016)	0.474	0.014 (0.007)	0.030

Table 2. Mendelian randomization estimates of the causal effects of asthma on socioeconomic status. *Abbreviations: IVW, inverse variance weighted; SE, standard error; SNPs, single-nucleotide polymorphisms; TDI, Townsend Deprivation Index.* [a]*R^2 represents the proportion of variance in the exposure explained by instrumental SNPs*

Exposure	Outcome	IVW		MR-Egger	
		Cochran's Q statistic	*P*-value	Cochran's Q statistic	*P*-value
Years of schooling	Asthma	144.05	8.23e-11	142.52	7.98e-11
Household income	Asthma	57.47	0.005	57.47	0.004
TDI	Asthma	20.25	0.089	20.12	0.065
Asthma	Years of schooling	50.88	8.63e-06	48.28	1.18e-05
Asthma	Household income	35.93	0.002	34.15	0.002
Asthma	TDI	15.45	0.419	12.09	0.599

Table 3. Results of the heterogeneity test for the Mendelian randomization estimates. *Abbreviations: IVW, inverse variance weighted; TDI, Townsend Deprivation Index*

DISCUSSION

To the best of our knowledge, we conducted the first MR study to investigate the causal effects of asthma on SES, and vice versa. Our bidirectional MR study suggested the causal effects of asthma on the lower SES, including shorter years of schooling, lower household income and

Exposure	Outcome	MR-Egger		
		Intercept	Standard error	*p*-value
Years of schooling	Asthma	0.0146	0.0199	0.467
Household income	Asthma	0.0011	0.0176	0.949
TDI	Asthma	−0.0125	0.0444	0.783
Asthma	Years of schooling	−0.0037	0.0042	0.400
Asthma	Household income	−0.0033	0.0038	0.407
Asthma	TDI	0.0034	0.0019	0.088

Table 4. Assessment of directional pleiotropy by the intercepts of MR-Egger regression. *Abbreviations: TDI, Townsend Deprivation Index*

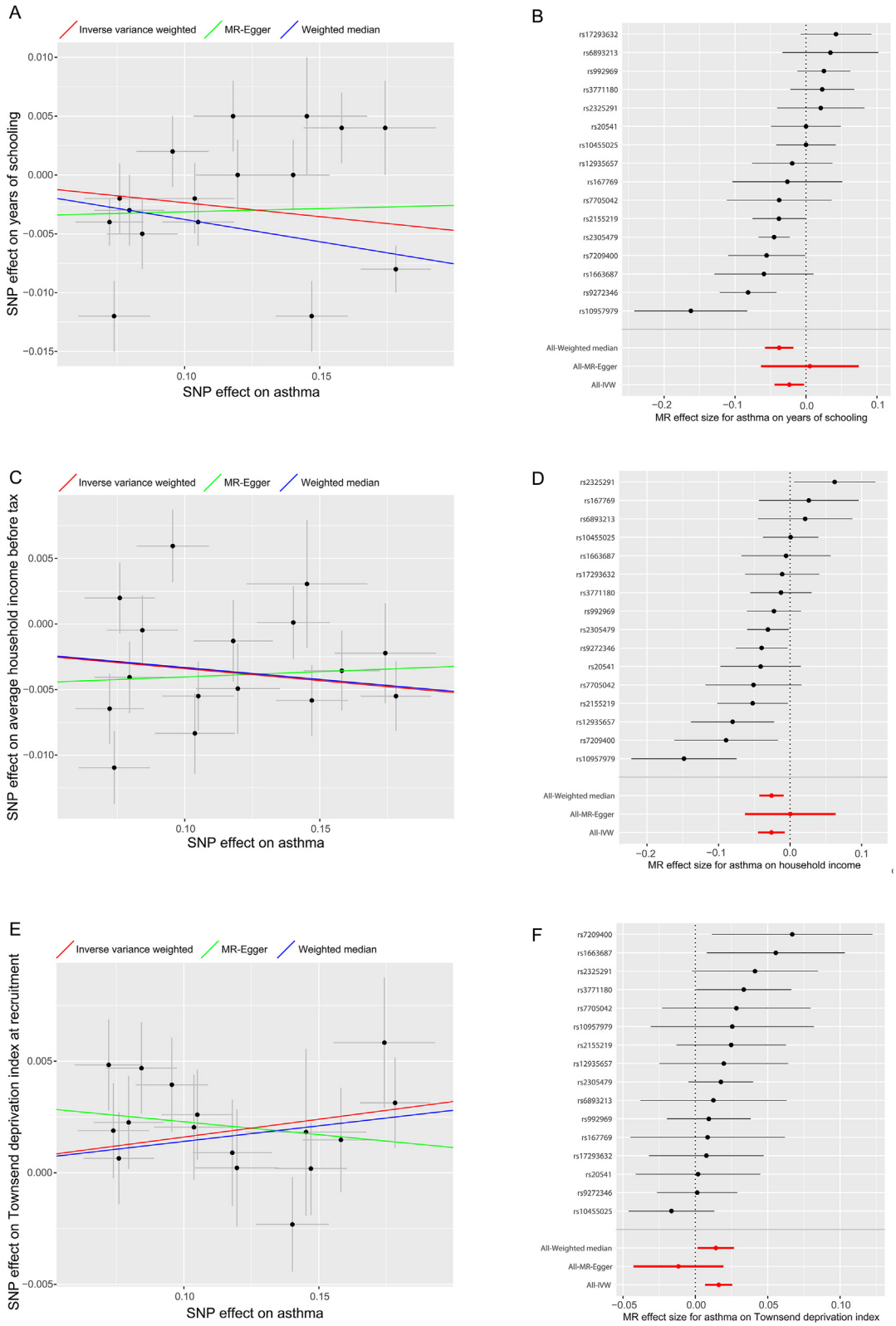

Fig. 2 Mendelian randomization plots for the effects of asthma on socioeconomic status. (A) Scatter plot of single-nucleotide polymorphism (SNP) effects on asthma vs. years of schooling. (B) Forest plot of individual and combined MR effect sizes for asthma on years of schooling. (C) Scatter plot of SNP effects on asthma vs. household income. (D) Forest plot of individual and combined MR effect sizes for asthma on household income. (E) Scatter plot of SNP effects on asthma vs. Townsend deprivation index. (F) Forest plot of individual and combined MR effect sizes for asthma on Townsend deprivation index. The effect sizes shown in this Figure are β coefficients

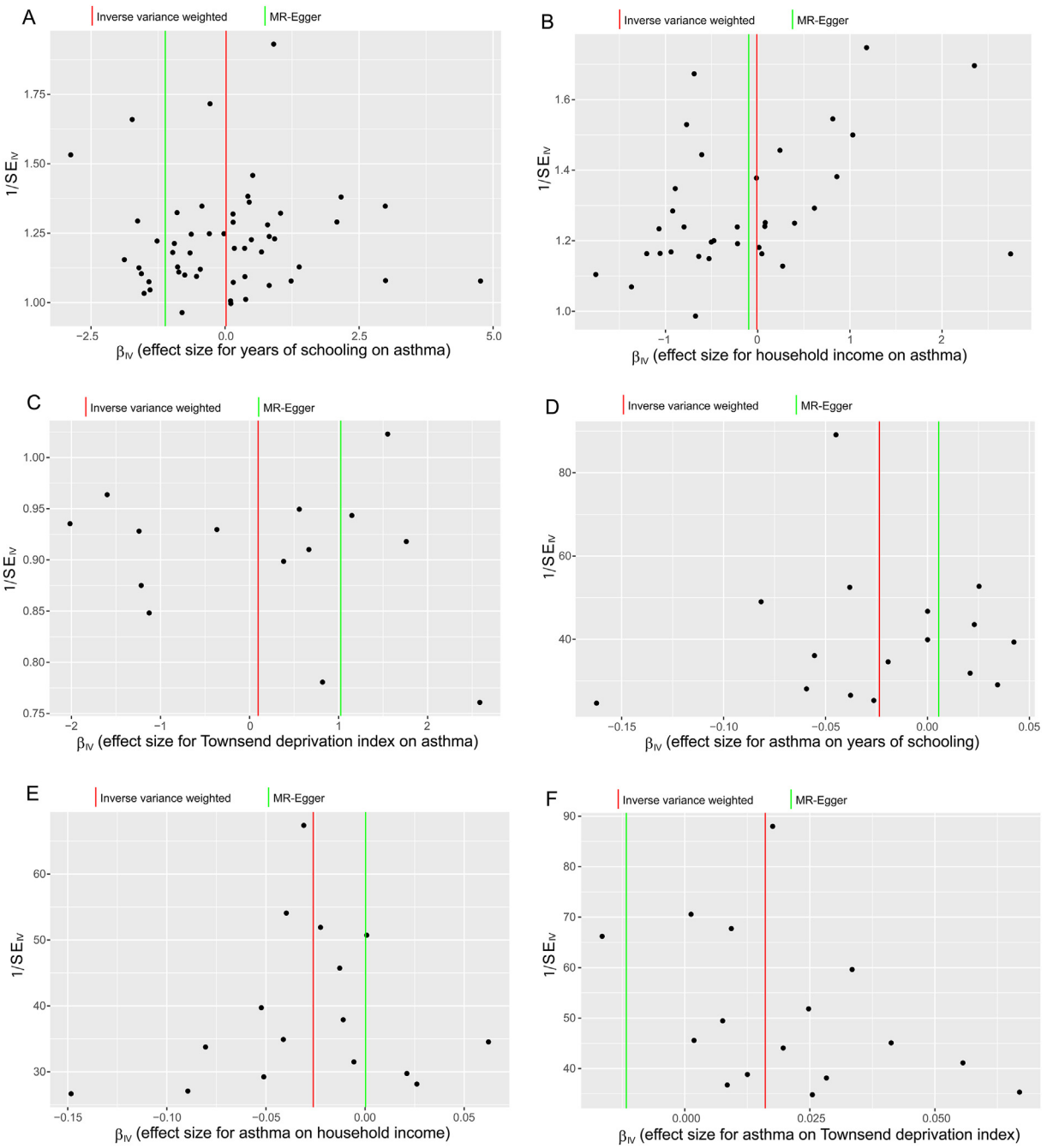

Fig. 3 Funnel plots for the assessment of heterogeneity amongst single-nucleotide polymorphisms. (A) Funnel plot for years of schooling → asthma Mendelian randomization (MR). (B) Funnel plot for household income → asthma MR. (C) Funnel plot for Townsend deprivation index → asthma MR. (D) Funnel plot for asthma → years of schooling MR. (E) Funnel plot for asthma → household income MR. (F) Funnel plot for asthma → Townsend deprivation index MR

greater degree of material deprivation in the neighborhood. However, our study did not support the causal effects of lower SES on the incidence of asthma. Since the F-statistic of each IV was >10, the null results of SES → asthma MR analyses may not be due to the weak instrument bias.[35] It should be noted that there was substantial heterogeneity in analyses which may bias the results. To reduce the heterogeneity, we excluded instrumental SNPs that were more likely to exert horizontal pleiotropy in sensitivity analyses. We found that the asthma → household income MR estimate calculated by the IVW method remained to be statistically

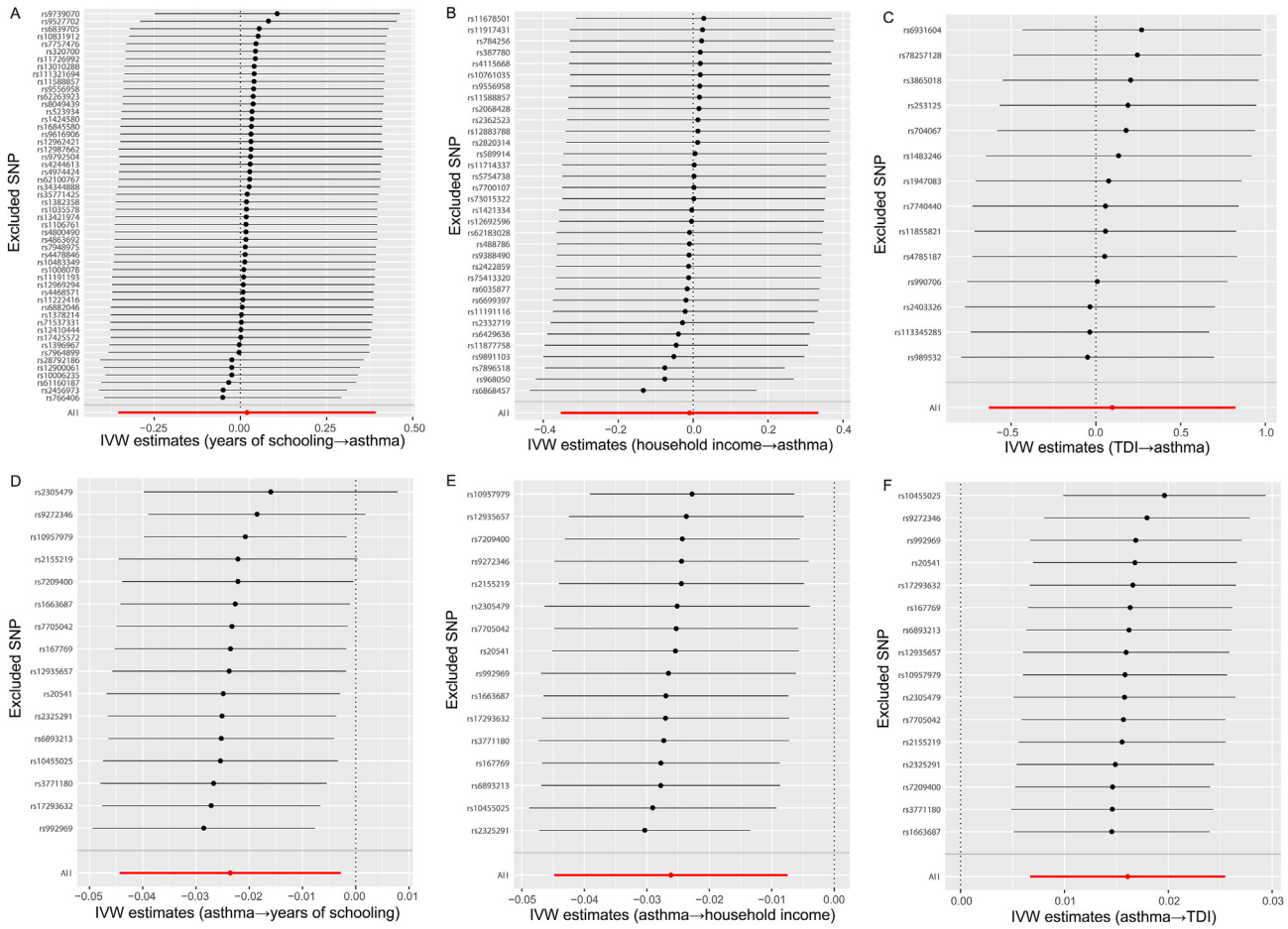

Fig. 4 Forest plots for the leave-one-out analyses. (A) Leave-one-out analysis for years of schooling → asthma Mendelian randomization (MR). (B) Leave-one-out analysis for household income → asthma MR. (C) Leave-one-out analysis for Townsend deprivation index → asthma MR. (D) Leave-one-out analysis for asthma → years of schooling MR. (E) Leave-one-out analysis for asthma → household income MR. (F) Leave-one-out analysis for asthma → Townsend deprivation index MR. The effect sizes shown in this Figure are β coefficients

significant with nonsignificant heterogeneity, suggesting the robustness of the asthma → household income causal inference. Interestingly, the household income → asthma MR estimate calculated by the IVW method was also statistically significant in the sensitivity analyses. It seems that the household income is most closely associated with asthma among the 3 indicators of SES.

Asthma is a complex disease determined by environmental exposures and genetic background.[36] The estimates of asthma heritability range from 35% to 95%.[37] Environmental exposures, such as air pollution, gastrointestinal and respiratory microbiome, tobacco smoke, allergens, viral respiratory-tract infections, perinatal exposures, psychological stress, and occupational exposures are also linked to the development of asthma.[38,39] It is proposed that the lower SES contribute to the development of asthma through predisposing individuals to some of these environmental exposures.[8] However, the actual causal effects of SES on asthma may be too small to be detected by our study, considering that our study could only detect a rather large effect size according to the statistical power calculation. The GWAS summary data for asthma used in our study did not distinguish between childhood-onset asthma and adult-onset asthma, which means that the risk of asthma was evaluated during one's lifetime. However, the SES data were captured during one's adulthood in these GWAS studies. The criterion of time order was not met during the causal inference from SES to childhood-onset asthma. The SES → childhood-onset asthma causal inference could only make sense when we interpret the SES captured during

one's adulthood as a proxy of one's early life SES, i.e., the parents' SES. The residual bias caused by this proxy process may explain the negative results of SES → asthma MR to some extent.

It is believed that poor health status can lead to lower SES.[3] The IVW MR estimates supported the causal association between asthma and being socioeconomically disadvantaged, and this was further supported by the weighted median method, which has the advantage that only half the SNPs need to be valid instruments for the causal effect estimate to be unbiased.[31] However, the MR estimates returned by the MR-Egger method were statistically nonsignificant, which may be due to the reduced statistical power of the MR-Egger method and the existence of horizontal pleiotropy.

The intercepts of MR-Egger regression suggested no evidence for the existence of directional pleiotropy, which means that the MR estimates returned by the random effects IVW method were less likely to be biased. To further address the horizontal pleiotropy in sensitivity analyses, we excluded instrumental SNPs that are associated with phenotypes that may affect the SES, and we found only the asthma → low household income causation remained significant.

The mechanisms by which asthma causes lower SES are straightforward. In the childhood, poorly controlled asthma can undermine the cognitive function by sleep disruption, leading to the compromised educational performance.[9] Asthma can also result in poor school connectedness and school absenteeism, and hence cause poor education outcomes.[9] To minimize the adverse effects of asthma on education outcomes, a multifaceted approach to asthma control and prevention, in which schools can and must play a central role, is essential.[9] For example, schools can engage youth with asthma in asthma education and control programs; schools can also provide youth with asthma with tailored educational programs and social and emotional support. In adulthood, severe asthma, especially work-related asthma, can result in work restrictions, impaired work effectiveness, increased lost workdays, and unemployment, and lead to a substantial loss of income.[11] To minimize the adverse effects of asthma on work abilities and income, social supports, such as compensation and insurance schemes provided by the government, should play an important role.

As with any MR study, several limitations should be noted in our study. First, we only included individuals of European descent to minimize the bias from population stratification. Thus, whether our findings are generalizable to other populations still needs to be confirmed. Second, although we conducted sensitivity analyses to rule out horizontal pleiotropy, it is impossible to fully rule out pleiotropic mechanisms without detailed knowledge about the biological action of these instrumental SNPs. Finally, there are differences in etiology between the childhood-onset asthma and adult-onset asthma.[40] Cautions are needed when interpreting our results since our study did not distinguish childhood-onset asthma from adult-onset asthma.

CONCLUSION

Our bidirectional MR study provided evidence to suggest that genetically predicted asthma may play a causal role in lowering the household income, while its causal relationships with years of schooling and TDI were not robust. This finding reminds the policy makers to interrupt the causal pathway between asthma and lower SES by providing more social supports to those with asthma, which is an important measure to reduce the inequality in personal development. However, the causal role of lower SES in asthma development was not supported by our MR analyses, which may be due to the low statistical power of the current study. Considering the heterogeneity in the current study, additional MR studies are needed to validate the results in the future.

Abbreviations

SES, socioeconomic status; MR, Mendelian randomization; SNPs, single-nucleotide polymorphisms; IVs, instrumental variables; GWAS, genome-wide association study; TDI, Townsend deprivation index; MRC-IEU, Medical Research Council Integrative Epidemiology Unit; TAGC, Trans-National Asthma Genetic Consortium; LD, linkage disequilibrium; IVW, inverse variance weighted; OR, odds ratio; SD, standard deviation.

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Availability of data and materials
The datasets analyzed during the current study are available in the IEU OpenGWAS project (https://gwas.mrcieu.ac.uk/).

Authors' contributions
LP: Conceptualization; Data curation; Formal analysis; Investigation; Methodology; Resources; Software; Validation; Visualization; Writing - original draft.
W-PW: Conceptualization; Project administration; Supervision; Funding acquisition; Writing - review & editing.

Ethics statement
As the study was conducted using publicly available data, there was no requirement for informed consent or ethics committee approval.

Authors' consent for publication
All authors agreed to the publication of this work in the World Allergy Organization Journal.

Declaration of competing interest
The authors report no competing interests.

Submission declaration
Authors confirm that this manuscript is original, has not been published before, is not currently being considered for publication elsewhere, and has not been posted to a preprint server.

Appendix A. Supplementary data
Supplementary data to this article can be found online at https://doi.org/10.1016/j.waojou.2023.100790.

Author details
[a]Department of Otorhinolaryngology Head and Neck Surgery, The First Affiliated Hospital, Sun Yat-sen University, Guangzhou, Guangdong, China. [b]Institute of Otorhinolaryngology Head and Neck Surgery, Sun Yat-sen University, Guangzhou, Guangdong, China. [c]Department of Otorhinolaryngology, The Sixth Affiliated Hospital, Sun Yat-sen University, Guangzhou, Guangdong, China.

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