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Large-scale genome-wide association studies reveal the genetic causal etiology between air pollutants and autoimmune diseases

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Abstract

Background Epidemiological evidence links a close correlation between long-term exposure to air pollutants and autoimmune diseases, while the causality remained unknown.

Methods Two-sample Mendelian randomization (TSMR) was used to investigate the role of PM₁₀, PM_{2.5}, NO₂, and NO_x (N=423,796–456,380) in 15 autoimmune diseases (N = 14,890–314,995) using data from large European GWASs including UKB, FINNGEN, IMSGC, and IPSCSG. Multivariable Mendelian randomization (MVMR) was conducted to investigate the direct effect of each air pollutant and the mediating role of common factors, including body mass index (BMI), alcohol consumption, smoking status, and household income. Transcriptome-wide association studies (TWAS), two-step MR, and colocalization analyses were performed to explore underlying mechanisms between air pollution and autoimmune diseases.

Results In TSMR, after correction of multiple testing, hypothyroidism was causally associated with higher exposure to NO₂ [odds ratio (OR): 1.37, $p=9.08 \times 10^{-4}$] and NO_x [OR: 1.34, $p=2.86 \times 10^{-3}$], ulcerative colitis (UC) was causally associated with higher exposure to NO_x [OR: 2.24, $p=1.23 \times 10^{-2}$] and PM_{2.5} [OR: 2.60, $p=5.96 \times 10^{-3}$], rheumatoid arthritis was causally associated with higher exposure to NO_x [OR: 1.72, $p=1.50 \times 10^{-2}$], systemic lupus erythematosus was causally associated with higher exposure to NO_x [OR: 4.92, $p=6.89 \times 10^{-3}$], celiac disease was causally associated with lower exposure to NO_x [OR: 0.14, $p=6.74 \times 10^{-4}$] and PM_{2.5} [OR: 0.17, $p=3.18 \times 10^{-3}$]. The risky effects of PM_{2.5} on UC remained significant in MVMR analyses after adjusting for other air pollutants. MVMR revealed several common mediators between air pollutants and autoimmune diseases. Transcriptional analysis identified specific gene transcripts and pathways interconnecting air pollutants and autoimmune diseases. Two-step MR revealed that POR, HSPA1B, and BRD2 might mediate from air pollutants to autoimmune diseases. POR pQTL (rs59882870, PPH4=1.00) strongly colocalized with autoimmune diseases.

Conclusion This research underscores the necessity of rigorous air pollutant surveillance within public health studies to curb the prevalence of autoimmune diseases.

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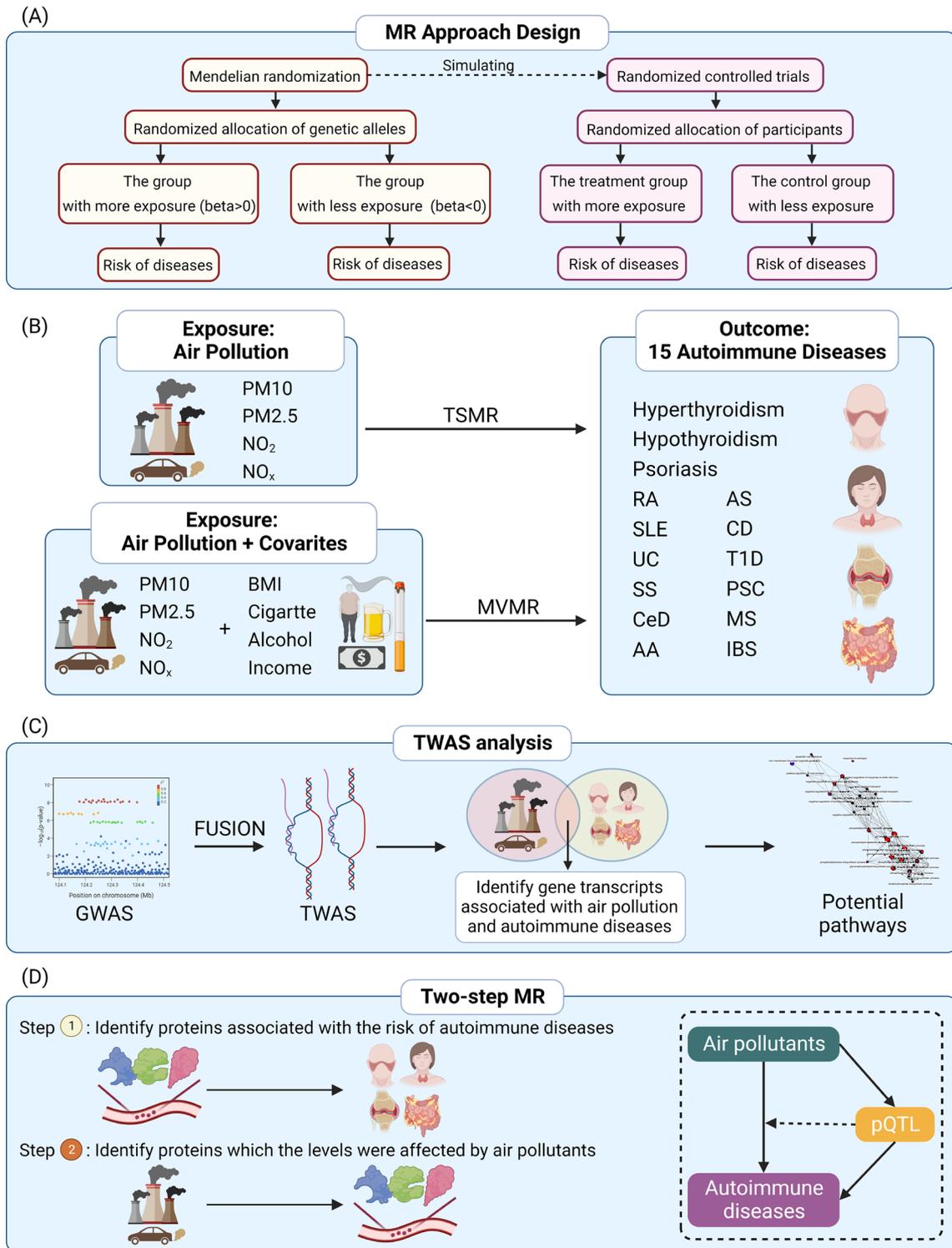
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Keywords Air pollutants, Autoimmune disease, Mendelian randomization, TWAS, Causal relationship

Graphical abstract (Built by the Biorender)



Introduction

Autoimmune diseases (ADs) are an intricate group of chronic inflammatory disorders characterized by an aberrant response to normal host tissues and rank third in global morbidity statistics, with an unknown etiology [1]. This significantly strains public health systems, further intensified by the critical shortage of effective intervention strategies. The pathogenesis of inflammatory autoimmune diseases exhibits a distinctive pattern: a stable or sudden metamorphosis from the existence of minimal or no pathogenic autoantigen-specific T and B cells to a pathogenic state, which consequently results in the discharge of copious amounts of IgG antibodies [2]. Despite noteworthy advances in animal-modeled autoimmune disease treatment, a significant temporal gap persists before such strategies can yield clinical breakthroughs [3]. Thus, the present-day therapeutic approaches remain anchored in treating patients with nonspecific immunosuppression, unfortunately culminating in heightened morbidity and mortality rates [4]. Importantly, a diverse range of factors—environmental, behavioral, and genetic—collectively contribute to the instigation and progression of autoimmune diseases. These encompass aspects such as dietary habits, infections, drug exposure, physical activity levels, smoking habits, microorganism interaction, and contact with various pollutants [5, 6]. It is essential to recognize and understand these influences in order to effectively combat the global autoimmune disease burden. Notably, with increased awareness of environmental protection, exposure to environmental pollutants, also known as particulate matter, is a key risk factor for susceptibility to autoimmune diseases, leading to growing concern. [7, 8].

Air contamination remains a cardinal health concern, encompassing a complex amalgamation of gases and particulate matter, inclusive but not exhaustive of carbon monoxide, nitrates, sulfur dioxide, ozone, lead, and tobacco-linked by-products [9]. Nitrogen oxide (NO_x), a molecule composed of nitrogen and oxygen, is particularly relevant to ambient air pollutants and is an environmental pollutant in the public health policies of many industrial countries. Respirable particulate matter (PM) itself can be classified into PM₁₀, PM_{2.5}, and ultrafine particulate matter (UFP) based on particle size. In general, particles larger than 10 μm are mostly filtered by the nose and upper respiratory tract and are unlikely to reach the lower respiratory tract. In contrast, particles smaller than 10 μm will reach the lower airways, penetrate, and deposit in deeper airways such as the terminal bronchi and alveoli. Inhaling such pollutants has been associated with generating oxidative stress and subsequent inflammation, causing acute and extended systemic inflammation and autoimmunity [10]. Though the

correlation between continuous exposure to atmospheric contaminants and autoimmune diseases has been under investigation, the evidence supporting this claim remains inconclusive. Limited studies have indicated that when air pollutant molecules enter the respiratory tract or skin mucosa, they can trigger the activation of macrophages, inflammatory neutrophils, dendritic cells, and lymphocytes, leading to an imbalance in the immune system [11]. This state of immune dysregulation may contribute to the development of autoimmune diseases.

A recent large observational study involving 12 million individuals showed that for every one-decile increase in industrial air pollutant emissions, including fine particulate matter (PM_{2.5}), nitrogen dioxide (NO_2), and sulfur dioxide (SO_2), the adjusted hazard ratio was 1.018 [95% confidence interval (CI)=1.013–1.022] [12]. The study found that industrial PM_{2.5} was the most significant contributor to systemic autoimmune rheumatic diseases (SARDs). Meanwhile, mice spontaneously susceptible to systemic lupus erythematosus (SLE) exhibited a number of negative health effects after daily exposure to 600 $\mu\text{g}/\text{m}^3$ of inhaled concentrated PM_{2.5}. The mice showed decreased survival, increased circulating neutrophil counts, early onset of proteinuria, increased kidney weight, and enlarged kidney cortex as compared to mice that were exposed to filtered air [13]. Chronic air pollution exposure can cause lung inflammation through mechanisms such as inducing oxidative stress, damaging airway mucosa, and inducing a localized inflammatory response, and maybe the point of initiation of inflammatory responses in autoimmune diseases. Air pollutants can not only affect T and B cells, producing large numbers of antibodies and auto-reactive T lymphocytes, but can also potentially cause epigenetic changes. Given the limitations of observational studies, this paper employs Mendelian randomization grounded in Mendel's law to probe into the causative relationship between air pollutants and autoimmune diseases. This approach allows to establish new perspectives on the environmental determinants of these diseases, offering a broader understanding and potential interventions for autoimmune conditions.

Mendelian randomization (MR) is an instrumental approach employed in genetic epidemiology, utilizing genetic variants to analyze the causal associations between a particular exposure (here air pollutants) and an outcome (here ADs) [14]. Rooted firmly in Mendel's principles of inheritance, MR posits that the allocation of genetic variants from parents to offspring is an arbitrary process [15]. Thus, by juxtaposing genetic variants related to exposure within a population against the prevalence of a disease, researchers can discern whether the exposure under investigation is causally

linked to the concerned disease [16]. Mendelian randomization works by exploiting the random allocation of genetic variants that affect the exposure of interest (such as air pollutants) and using these as genetic instrumental variables in statistical analysis, which mimics the design of randomized controlled trials. This genetic variation is fixed at conception and thus not subject to the confounding factors that affect the exposure-disease relationship in traditional observational studies [17]. Therefore, Mendelian randomization can help to establish causality between exposure and disease outcome. Nevertheless, it is paramount to recognize the limitations of the Mendelian randomization approach, including the potential for pleiotropic effects scenarios in which one genetic variant influences multiple traits of population stratification, which could potentially integrate bias into the conducted analyses. Comprehensive and careful study design and the precise selection of genetic variants are vital to uphold the reliability of the deduced results [18]. Additionally, the execution of critical sensitivity analyses, including weighted median, MR-Egger, and leave-out-one analysis, can facilitate the identification of pleiotropic and heterogeneous effects, thus boosting the credibility of the results [19].

Importantly, transcriptome-wide association studies (TWAS) are a genetic approach to study the role of gene expression in the development of specific traits and diseases by prioritizing the identification of candidate causal genes in analyses following genome-wide association studies [20]. The UK Biobank database of air pollution data is one of the most commonly used and largest publicly available databases and contains data on PM₁₀, PM_{2.5}, NO_x, and NO₂ measured in 2010 [21, 22]. This paper has hence pinpointed genetic variants correlated with exposure to four air pollutants using summary statistics from expansive genetic studies on European populations. By incorporating these as instruments in a Mendelian randomization approach, we aim to estimate the causal impacts of air pollutants on various autoimmune diseases, including type 1 diabetes (T1D), Crohn's disease (CD), celiac disease (CeD), asthma and allergy (AA), multiple sclerosis (MS), ulcerative colitis (UC), systemic lupus erythematosus (SLE), rheumatoid arthritis (RA), psoriasis, primary sclerosing cholangitis (PSC), irritable bowel syndrome (IBS), sicca syndrome (SS), ankylosing spondylitis (AS), hypothyroidism, and hyperthyroidism. Moreover, TWAS was utilized to identify hub genes that play key roles in air pollution-genetic-autoimmune disease interactions to explore the possible pathological mechanisms of air pollution-induced autoimmune diseases.

Methods

Study design and data sources

The flow chart of our study design is shown in the Graphical abstract (Built by the Biorender). The summary-level Genome-wide association studies (GWAS) data we used in this study were all collected from publicly available databases of European cohorts. Briefly, the GWAS data of participants living in the area with different air pollutants were derived from UK Biobank, which was obtained from MRC IEU [23–26]. As part of the European Cohort Study on the Effects of Air Pollution (ESCAPE) (<http://www.escapeproject.eu/>), the estimated Annual Average of Air Pollution in 2010 was derived from Land Use Regression (LUR) modeling to measure particulate matter within a 400 km radius of the monitoring site [21, 22]. Annual averages of PM_{2.5}, PM₁₀, NO₂, and NO_x exposures were estimated by modeling the x–y coordinates of each UK Biobank participant's baseline residential area. PM_{2.5} ranged from 8.17 to 21.31 micro-g/m³ with a mean value of 9.99 ± 1.06 micro-g/m³; PM₁₀ ranged from 11.78 to 31.39 micro-g/m³ with a mean value of 16.24 ± 1.90 micro-g/m³; NO₂ ranged from 12.93 to 108.49 micro-g/m³ with a mean value of 26.71 ± 7.58 micro-g/m³; NO_x ranged from 19.74–265.94 micro-g/m³ with a mean value of 44.11 ± 15.53 micro-g/m³. The sample sizes for the datasets of PM₁₀, PM_{2.5}, NO₂, and NO_x were 423,796, 423,796, 456,380, and 456,380, respectively.

The GWAS data for the potential mediators (BMI, alcohol intake frequency, number of cigarettes previously smoked daily, and income) were obtained from Locke et al. GWAS meta-analysis [26], GWAS and Sequencing Consortium of Alcohol and Nicotine use (GSCAN) Consortium, within family GWAS consortium, and UK biobank.

The GWAS data for 15 autoimmune diseases were obtained from three large-scale GWAS sources [27, 28], International Inflammatory Bowel Disease Genetics Consortium (IBDGC), International Multiple Sclerosis Genetics Consortium (IMSGC), International PSC Study Group (IPSCSG), and FINNGEN Consortium. Independent GWAS for hypothyroidism [29], UC [30], RA [31], CeD [30], and SLE [29] was selected for TSMR meta-analyses.

All participants in these studies were of European ancestry. All data used for analysis in our paper are from publicly available GWAS datasets and, therefore, do not require ethical approval or informed consent.

The details for the number of cases and controls for each included GWAS data were shown in Additional file 1: Methods and Additional file 2: Table S1.

Selection of instrumental variants

As there are few SNPs associated with air pollutants under p of 5×10^{-8} for genome-wide correlation, we set 5×10^{-6} to select sufficiently strong instrumental variants (IVs) as previous study [15, 32]. The further selection involved conducting linkage disequilibrium analyses with $r^2 < 0.001$ and distance < 10 MB. Using the formula $(R^2/K)/[(1-R^2)(N-K-1)]$, where K represents the number of SNPs and N is the sample size, F statistics were calculated for each instrument in the exposures. The variance explained by SNPs was calculated by $2 * EAF(1 - EAF) * (\text{Beta}/SE)^2$. IVs with $F < 10$ were excluded to remove weak IVs. IVs strongly associated with the outcome were excluded to ensure that IVs only act on the outcome via the exposure. Manhattan plots was visualized by the 'qqman' package [33] in R (version 4.2.2).

Statistical analysis

Analyses and visualization were conducted using the combination of 'TwoSampleMR' [23], 'meta' [34], 'ggplot2', 'clusterProfiler' [35], 'enrichplot', 'DOSE' [36], and Coloc [37] in R (version 4.2.2) and FUSION software [38].

Two-sample Mendelian randomization

We applied three distinct techniques [random-effect inverse-variance weighted (IVW), weighted median, MR egger] in our two-sample Mendelian randomization (TSMR) analysis. IVW was designated as the primary measure, wherein we conducted a weighted regression of SNP-outcome effects and SNP-exposure effects while constraining the intercept at zero. Although IVW demonstrated the most advantageous statistical power, it relies on the assumption that all instruments are valid and free from pleiotropy [39]. Additional file outcomes were obtained using weighted median and MR egger, which present more substantial estimates in more diverse contexts, albeit being less efficient [40, 41]. A false discovery rate ($FDR < 0.05$) was performed to correct for multiple independent tests. Results with $FDR < 0.05$ were regarded as significant, meanwhile, those $p < 0.05$ with $FDR > 0.05$ were regarded as suggestive [42, 43]. To examine horizontal pleiotropy, we performed MR egger intercept analysis and leave-one-out analysis [41]. Cochran's Q evaluation was employed to assess heterogeneity [44]. Statistical power for each significant TSMR result was calculated.

For the outcome that exhibited a significant correlation with exposure in TSMR, we performed another TSMR for another independent GWAS. Then, meta-analysis across different GWAS cohorts was performed

using fixed-effects analysis, under the assumption that 1 true effect size applied across all GWAS considered, as in previous studies [45].

Multivariable Mendelian randomization

Multivariable Mendelian randomization (MVMR) enabled us to evaluate the impact of multiple exposures on a given outcome. The exposures analyzed may include mediating or colliding factors [46]. Additionally, MVMR proved useful for controlling the effects of pleiotropic variants [47]. In this study, our implementation of MVMR focused on determining the direct effects of air pollutants on autoimmune diseases. We included all four air pollutants in MVMR to identify the most robust causal relationship between air pollutants and ADs. Exposures with collinearity were excluded by `mv_lasso_feature_selection`. We also accounted for mediators in MVMR, including BMI, alcoholic drinks per week, smoking behavior (ever smoked), and income. A difference between the total causal effects (by TSMR) and the direct causal effects (by MVMR) would indicate a mediating role of common factors on the pathway from air pollutants to ADs [48].

Transcriptome-wide association study

For the transcriptome-wide association study (TWAS), we employed the FUSION method to convert GWAS into TWAS [38]. In FUSION, an expression quantitative trait loci (eQTL)-based linear model was utilized to predict gene expression using RNA-seq reference panels. Our reference panels included European whole blood samples of RNA-seq from Genotype-Tissue Expression version 8 (GTEx v8) ($N=558$) [49]. The TWAS results identified genes significantly associated with air pollutants and autoimmune diseases in the same direction. To further understand the biological mechanisms underlying these associations, we performed a biological pathway enrichment analysis of these genes. P for air pollutants and autoimmune diseases were combined using Fisher's Combined p -value (FCP) method.

Two-step Mendelian randomization

Two-step MR was performed to investigate the potential mediators, from air pollutants to autoimmune diseases, with potential causality. Summarized GWAS for the plasma proteome was collected from 35,559 Icelanders and it included 4907 protein information [50]. We separate protein quantitative trait loci (pQTL) into cis-pQTL (within ± 1 MB window of the gene encoding the corresponding protein) and trans-pQTL (outside ± 1 MB window).

In the first step of two-step MR, proteome-wide MR was performed by using cis-pQTL ($p < 1 \times 10^{-5}$,

clump_kb=10,000 and $r^2=0.001$) (as exposure) to identify the potential proteins causally associated with the risk of autoimmune diseases (as outcome). The proteins with $FDR < 0.05$ were deemed as risk proteins for autoimmune disease. In the second step, the effects of air pollutants (as exposure) on these risk proteins (as outcome) were assessed by MR. The mediating effect of risk proteins was calculated by β_1 (effects of pQTL on autoimmune diseases) * β_2 (effects of air pollutants on pQTL). Standard errors were estimated by delta method [47].

Colocalization analysis

To investigate shared causal variants between the mediating proteins and autoimmune diseases, colocalization analyses were performed by R Coloc [37]. IVs for cis-pQTL were identified as lead SNPs. All SNPs within 1 MB around the lead SNPs for pQTL and autoimmune diseases GWAS were extracted and calculated the posterior for H4 (PPH4, the probability of shared causal variant for both traits). A locus was deemed as colocalized if $PPH4 > 0.8$. The shared variants between pQTL and autoimmune diseases could reinforce the causal effects of plasma proteins on autoimmune diseases [51, 52].

More detailed information for methods was described in Additional file 1: Methods.

Results

Identification of instrumental variables

Under the threshold of $p < 5 \times 10^{-8}$, there were only 8 IVs for NO_2 , NO_x , PM2.5, and none for PM10. Under the threshold of $p < 5 \times 10^{-6}$, a series of IVs ($NO_2=84$, $NO_x=75$, $PM2.5=58$, $PM10=29$) that were strongly (F -statistic > 10) associated with air pollutants and independent ($kb=10,000$ and $r^2=0.001$) were selected after multi-step quality control (Additional file 2: Tables S2–S5). The F -statistics of IVs ranged between 20.20 and 66.68, indicating the absence of weak instrumental bias.

Causal effects of air pollutants on autoimmune disease

First, by TSMR, we found that these air pollutants were strongly associated with the risks of several autoimmune diseases, and there were significant causal relationships (Fig. 1; Table 1). Details are shown in Additional file 2: Table S6. Specifically, after correction of multiple tests, the risks of four ADs significantly associated with higher exposure to air pollutants, including hypothyroidism, UC, RA, and SLE ($OR > 1$, $FDR < 0.05$). SLE owned the highest correlation, with NO_x ($OR: 4.92$, $95\%CI: 1.55-15.62$, $p=6.89 \times 10^{-3}$, $FDR < 0.05$). Oppositely, the risk of CeD was significantly correlated with lower exposure to NO_x and PM2.5. The statistical power for these significant TSMR

results were all above 0.93 (Additional file 2: Table S7). The risks of SS and AA were found to be suggestively correlated with higher exposure to NO_x and PM2.5, respectively ($p < 0.05$, $FDR > 0.05$). However, hyperthyroidism, MS, CD, T1D, AS, IBS, psoriasis, and PSC showed no correlation with exposure to any of the air pollutants in TSMR ($p > 0.05$).

Sensitivity analyses were performed for TSMR, including pleiotropy and heterogeneity testing (Additional file 2: Tables S8–S15). None of the significant or suggestive TSMR results showed pleiotropy. Leave-one-out plots also showed no peculiar IVs (Fig. S1). These results showed the robustness of our results.

Then, to further validate our results, we performed TSMR meta-analysis for these significant outcomes across different GWAS cohorts. All these ADs were still significantly correlated with corresponding air pollutants in meta-analysis results (Additional file 1: Fig. S2). The results for the validated TSMR and sensitivity analyses are shown in Additional file 2: Tables S16–S18.

As air pollutants are a complex class of mixtures, different types of pollutants might affect each other. Thus, we performed MVMR to identify the most correlated air pollutants with ADs. PM2.5 exerting risky effects on UC was the only significant result after correcting for other air pollutants ($OR: 2.50$, $95\%CI: 1.27-4.91$, $p=7.80 \times 10^{-3}$), suggesting the strong direct causality between this pair (Additional file 2: Table S19).

Next, potential mediators (BMI, smoking, alcohol, and income) were included in MVMR with air pollutants (Fig. 2). We found that there are still several strong associations between air pollutants and ADs in MVMR (Table 2). Meanwhile, several mediating effects from air pollutants to ADs were also revealed, such as alcohol and income in NO_2/NO_x to hypothyroidism (Fig. 2). The detailed results for MVMR were shown in Additional file 2: Table S19.

Identification of common enrichment pathways for air pollutants and autoimmune diseases

To explore the underlying molecular mechanisms, we used the TWAS approach to identify a series of genes that are commonly expressed in air pollutants and autoimmune diseases. A total of 71, 68, 70, and 40 common genes were found to be expressed in both autoimmune diseases and NO_2 , NO_x , PM2.5, and PM10 in the same direction, respectively. Based on these shared genes, a total of 162, 143, 72, 117 biological pathways were enriched between ADs and NO_2 , NO_x , PM2.5, PM10 respectively, mainly in metabolic processes, immune activities, epigenetic and transcriptomic regulations (Fig. 3A–D). Especially, we identified a total of 11 common hub genes expressed both in air pollutants and

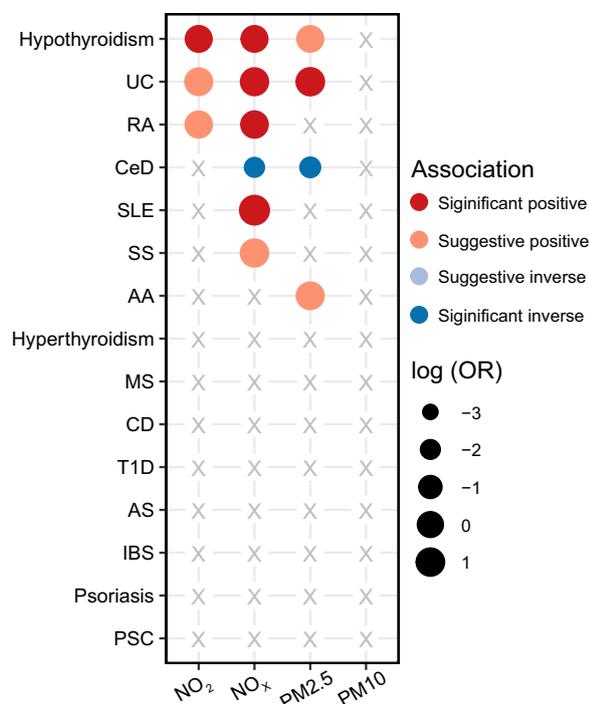


Fig. 1 Results of Inverse-variance weighted analysis of air pollution and autoimmune diseases.

autoimmune diseases, including BEND3, PPA2, PSMG2, RNF40, ZMYM1, ZNF780A, SFR1, NDST2, SLC35A1, OLIG1, and PI4KB (Table 3 and Additional file 1: Fig. S3), which will provide a reliable theoretical basis for exploring the pathological mechanisms of air pollutants molecules in the occurrence and development of autoimmune diseases.

Identification of the proteins mediating from air pollutants to autoimmune disease and colocalization analyses

In the first step of MR, we finally identified 22 risk proteins for autoimmune diseases from a total of 1825 actionable proteins (FDR<0.05) (Fig. 4A), in which 9 increased the risk and 13 decreased the risk. In the second step MR, the levels of 4 risky proteins were affected by air pollutants (Fig. 4B). Then, we performed mediation analyses, which showed that POR, HSPA1B, SHANK3, and BRD2 might exert mediating effects from air pollutants to increased risk of autoimmune diseases (Fig. 4C, Additional file 2: Table S20).

Then we performed colocalization analyses to determine whether the variants within proteins GWAS drive the associations between proteins and autoimmune diseases. POR had strong evidence for colocalization with autoimmune diseases at rs59882870 (PP.H4=1.00), which reinforced the causal effect of POR on autoimmune diseases (Fig. 4D, Additional file 2: Table S21). The rest of the mediating proteins showed no colocalized SNPs (Additional file 2: Tables S22–S24).

Discussion

To the best of our knowledge, this study performed a two-sample and multivariable MR for the first time to explore the causal relationship between air pollutants and multiple autoimmune diseases and investigate the potential mediators between them. Combining observational evidence from previous studies and genetic evidence from this MR analysis, we suggested that air pollutants were causally related to higher risks of hypothyroidism, SLE, RA, and UC and a lower risk of CeD.

Table 1 Significant and suggestive TSMR results (IVW) for effects of air pollutants on autoimmune disorders

Exposure	Outcome	OR	LCI	UCI	P	FDR
NO ₂	Hypothyroidism	1.37	1.14	1.66	9.08 × 10 ⁻⁴	1.36 × 10⁻²
	RA	1.55	1.08	2.23	1.76 × 10 ⁻²	1.32 × 10 ⁻¹
	UC	1.96	1.02	3.78	4.47 × 10 ⁻²	2.23 × 10 ⁻¹
NO _x	CeD	0.14	0.04	0.43	6.74 × 10 ⁻⁴	1.01 × 10⁻²
	Hypothyroidism	1.34	1.10	1.62	2.86 × 10 ⁻³	2.14 × 10⁻²
	SLE	4.92	1.55	15.62	6.89 × 10 ⁻³	3.45 × 10⁻²
	UC	2.24	1.19	4.22	1.23 × 10 ⁻²	4.49 × 10⁻²
	RA	1.72	1.11	2.66	1.50 × 10 ⁻²	4.49 × 10⁻²
	SS	2.42	1.04	5.63	4.12 × 10 ⁻²	1.03 × 10 ⁻¹
PM _{2.5}	CeD	0.17	0.05	0.55	3.18 × 10 ⁻³	4.47 × 10⁻²
	UC	2.60	1.32	5.15	5.96 × 10 ⁻³	4.47 × 10⁻²
	Hypothyroidism	1.31	1.03	1.66	2.94 × 10 ⁻²	1.47 × 10 ⁻¹
	AA	1.97	1.02	3.80	4.20 × 10 ⁻²	1.58 × 10 ⁻¹

Annotation: FDR < 0.05 were bolded

Table 2 Significant MVMR results for air pollution and autoimmune diseases

Exposure	Model	Outcome	OR	LCI	UCI	P
NO ₂	NO ₂ + Smoking	Hypothyroidism	1.30	1.02	1.65	1.27 × 10 ⁻²
	NO ₂ + Alcohol	Hypothyroidism	1.32	1.04	1.68	7.96 × 10 ⁻⁵
	NO ₂ + Income	Hypothyroidism	1.32	1.03	1.68	4.90 × 10 ⁻²
NO _x	NO _x + Income	SS	2.91	1.08	7.86	2.44 × 10 ⁻²
	NO _x + Smoking	CD	0.46	0.25	0.85	1.51 × 10 ⁻²
	NO _x + Smoking	CeD	0.12	0.04	0.35	3.51 × 10 ⁻²
	NO _x + Alcohol	Hypothyroidism	1.27	1.00	1.62	2.43 × 10 ⁻²
	NO _x + Income	Hypothyroidism	1.31	1.04	1.67	2.55 × 10 ⁻²
PM2.5	PM2.5 + Alcohol	AA	4.81	1.35	17.05	3.52 × 10 ⁻²
	PM2.5 + Smoking	AA	2.67	1.24	5.72	2.66 × 10 ⁻²
	PM2.5 + Smoking	CeD	0.15	0.05	0.42	3.15 × 10 ⁻²
	PM2.5 + Alcohol	Hypothyroidism	1.41	1.09	1.83	1.18 × 10 ⁻²
	PM2.5 + Income	SS	4.06	1.12	14.78	3.11 × 10 ⁻⁴
PM10	PM10 + Alcohol	UC	2.54	1.14	5.66	1.00 × 10 ⁻²
	PM10 + Smoking	CeD	0.04	0.00	0.69	3.36 × 10 ⁻²
	PM10 + BMI	SLE	41.72	1.39	1249.68	2.26 × 10 ⁻²

The integrity of a dynamic, balanced immune system is pivotal for facilitating optimal health. Current findings depicting a putative association between airborne pollutants and autoimmune diseases generate a spectrum of perspectives, underscoring the necessity for more precise analyses, including the exploration of genetic susceptibility's pivotal role in moderating this relationship. Limited

studies have shown that air pollutants contribute to the development of autoimmune diseases mainly by modulating the immune response of different cell types, such as macrophages, inflammatory neutrophils, dendritic cells, and lymphocytes, which produce pro-inflammatory factors [11]. Cellular experiments have confirmed that air pollutant components activate inflammatory

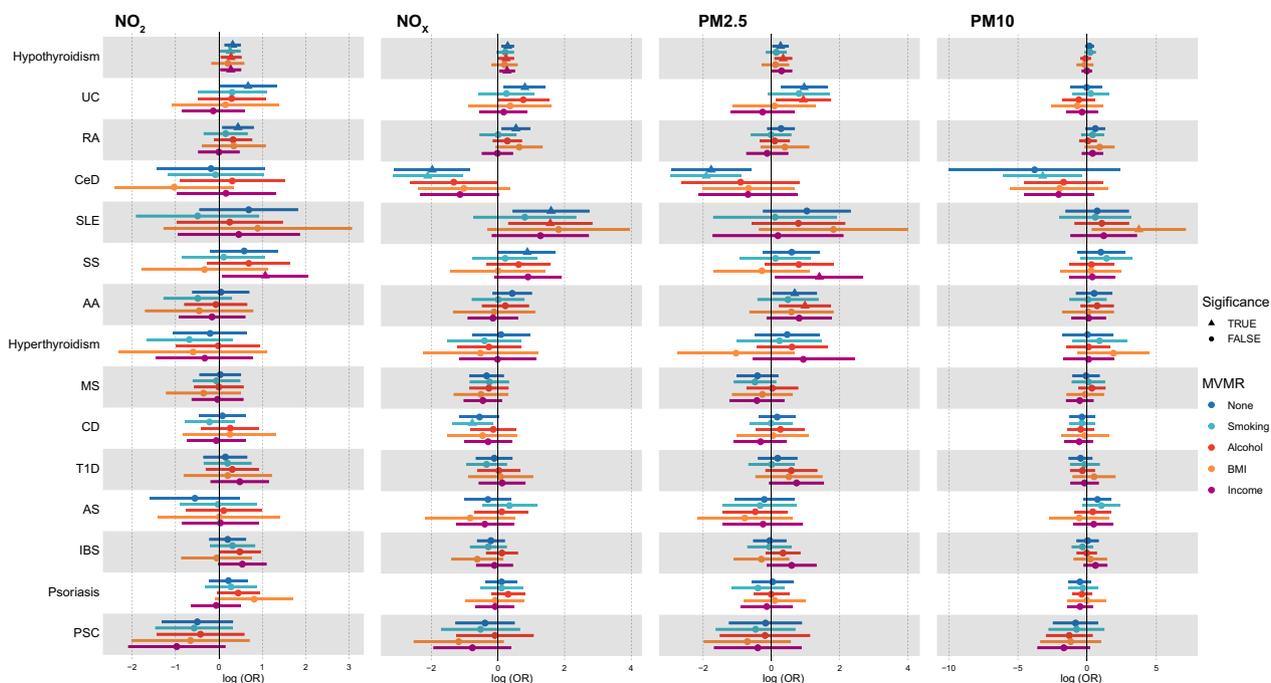


Fig. 2 The role of possible mediators (smoking, Alcohol, BMI and income) between air pollution and autoimmune diseases

Table 3 Common genes between air pollution and autoimmune diseases in TWAS analysis

ID	Autoimmune diseases			NO _x			PM _{2.5}			PM ₁₀			FCPAI		Rank
	TWAS.P	NO ₂	Rank	TWAS.P	Rank	FCP	TWAS.P	Rank	FCP	TWAS.P	Rank	FCP	Rank	FCP	
BEND3	3.35 × 10 ⁻⁵	2.82 × 10 ⁻²	1	1.39 × 10 ⁻²	1	7.25 × 10 ⁻²	2.15 × 10 ⁻²	1	1.09 × 10 ⁻⁵	9.78 × 10 ⁻³	1	5.22 × 10 ⁻³	1	1.04 × 10 ⁻¹⁶	1
PPA2	1.78 × 10 ⁻²	3.80 × 10 ⁻⁴	2	1.97 × 10 ⁻³	7	3.96 × 10 ⁻⁴	3.35 × 10 ⁻³	7	6.41 × 10 ⁻⁴	2.87 × 10 ⁻³	3	5.58 × 10 ⁻⁴	4	7.44 × 10 ⁻¹¹	2
PSMG2	3.91 × 10 ⁻³	1.26 × 10 ⁻²	4	2.85 × 10 ⁻³	2	1.38 × 10 ⁻⁴	5.45 × 10 ⁻³	2	2.50 × 10 ⁻⁴	2.00 × 10 ⁻²	2	8.19 × 10 ⁻⁴	5	8.98 × 10 ⁻¹¹	3
RNF40	3.62 × 10 ⁻³	3.23 × 10 ⁻³	3	8.85 × 10 ⁻³	3	3.63 × 10 ⁻⁴	4.33 × 10 ⁻²	6	1.53 × 10 ⁻³	4.38 × 10 ⁻³	7	1.91 × 10 ⁻⁴	3	9.04 × 10 ⁻¹¹	4
ZMYM1	5.37 × 10 ⁻³	1.14 × 10 ⁻²	5	4.10 × 10 ⁻³	3	2.58 × 10 ⁻⁴	1.34 × 10 ⁻²	3	7.58 × 10 ⁻⁴	3.72 × 10 ⁻²	4	1.90 × 10 ⁻³	8	1.11 × 10 ⁻⁹	5
ZNF780A	2.42 × 10 ⁻³	3.76 × 10 ⁻²	7	1.09 × 10 ⁻²	4	3.04 × 10 ⁻⁴	3.47 × 10 ⁻²	4	8.72 × 10 ⁻⁴	4.12 × 10 ⁻²	5	1.02 × 10 ⁻³	6	1.15 × 10 ⁻⁹	6
SFR1	1.55 × 10 ⁻²	5.67 × 10 ⁻³	6	1.89 × 10 ⁻³	6	3.35 × 10 ⁻⁴	1.48 × 10 ⁻²	5	2.15 × 10 ⁻³	2.57 × 10 ⁻²	8	3.52 × 10 ⁻³	9	8.29 × 10 ⁻⁹	7
NDST2	1.82 × 10 ⁻²	1.17 × 10 ⁻²	9	7.19 × 10 ⁻³	8	1.30 × 10 ⁻³	7.46 × 10 ⁻³	8	1.34 × 10 ⁻³	7.17 × 10 ⁻³	6	1.30 × 10 ⁻³	7	1.52 × 10 ⁻⁸	8
SLC35A1	2.63 × 10 ⁻²	3.54 × 10 ⁻²	11	1.64 × 10 ⁻²	10	3.77 × 10 ⁻³	9.90 × 10 ⁻³	10	2.41 × 10 ⁻³	2.41 × 10 ⁻⁴	9	8.22 × 10 ⁻⁵	2	1.81 × 10 ⁻⁸	9
OLIG1	2.39 × 10 ⁻²	5.06 × 10 ⁻³	8	1.24 × 10 ⁻²	9	2.69 × 10 ⁻³	1.63 × 10 ⁻²	9	3.45 × 10 ⁻³	1.86 × 10 ⁻²	10	3.88 × 10 ⁻³	10	1.12 × 10 ⁻⁷	10
PI4KB	3.53 × 10 ⁻²	2.13 × 10 ⁻²	10	3.77 × 10 ⁻²	11	1.01 × 10 ⁻²	2.17 × 10 ⁻²	11	6.26 × 10 ⁻³	4.19 × 10 ⁻²	11	1.11 × 10 ⁻²	11	6.07 × 10 ⁻⁶	11

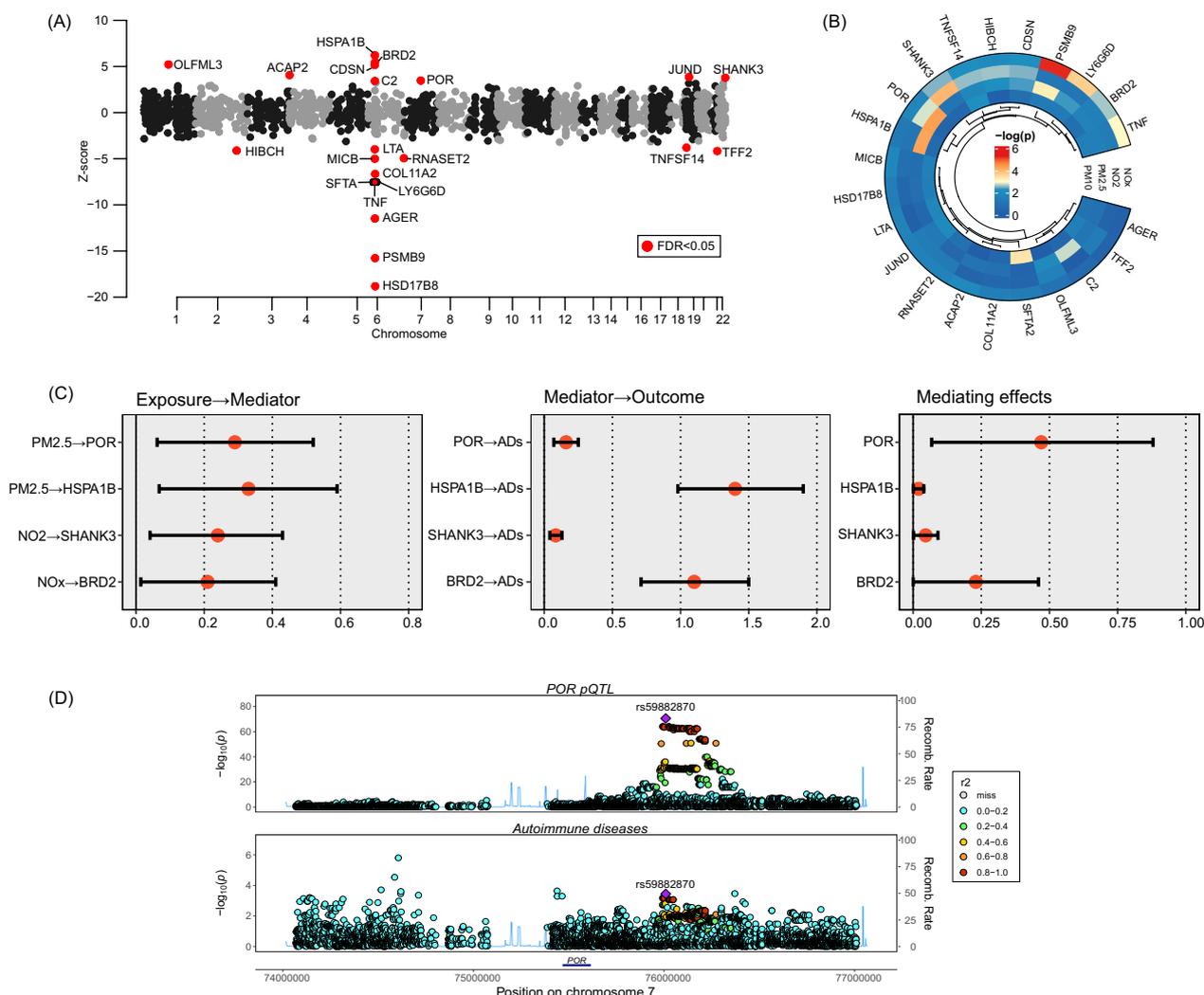


Fig. 4 Two-step MR to reveal mediating proteins in the pathway from air pollutants to autoimmune diseases. **A** Protein-wide MR to reveal proteins associated with the risk of autoimmune diseases. **B** Causal effects of air pollutants on protein levels in plasma. **C** Mediation analysis to estimate the mediating effects of the proteins passing two-step MR. **D** Colocalization analysis of POR pQTL and autoimmune diseases

PM2.5 (18–46 $\mu\text{g}/\text{m}^3$) was associated with an increased risk of SLE, and SLE was positively associated with a 10.2 $\mu\text{g}/\text{m}^3$ increase in exposure to fine particles (PM2.5) (HR=1.12, 95% CI: 1.02–1.23) [54]. A time-series study found that chronic exposure to particulate matter (PM2.5 and PM10) was significantly associated with readmission rates for rheumatoid arthritis and was more pronounced in women and older patients [58].

Interestingly, this paper identified a lot of key genes and enriched signaling pathways that are involved in air pollutants and autoimmune diseases that not been discovered out before. For example, the BEN structural domain-containing protein 3 (BEND3), localized in the cytoplasm, is involved in chromatin function and transcription. It has been shown that BEND3 is expressed

in both CD4⁺ and CD8⁺ T cells in peripheral blood and can lead to the production of various cytokines via the TCR/CD3 complex [59]. Protein phosphatase 2A (PP2A) is a serine-threonine phosphatase that plays an important role in regulating the activation, differentiation, and function of T cells [60]. RNF20, encoding the E3 ubiquitin-protein ligase BRE1A, thereby mediates monoubiquitination of histone H2B at lysine 120 and has been shown to play a background-dependent role in the development of inflammatory bowel disease [61]. C–C chemokine receptor type 9 (CCR9) is a heptameric transmembrane protein that maps to the chemokine receptor gene cluster region. Studies have shown that CCR9 and its ligands can play important roles in a variety of inflammation-related diseases by targeting inflammatory cells and promoting

inflammatory responses [62]. Recent studies have demonstrated the important role of AMP-dependent transcription factor 7 (ATF7) in innate immune memory. ATF7 enhances protection against re-infection by inhibiting the expression of a group of genes encoding factors involved in innate immunity in macrophages [63].

In addition, we found that most of these enrichment pathways are related to cellular metabolism, immune regulation, amino acid, and gene modification pathways. For example, ubiquitination is a highly specific and tightly regulated ATP-dependent biological process that proceeds through a complex enzymatic cascade. It has been shown that ubiquitin-related genes play an important role in a variety of autoimmune diseases [64]. Many lipid metabolism-related pathways have been found to be enriched in both NO₂ and autoimmune diseases. Studies have shown that many biologically active lipids are involved in various stages of the inflammatory process as well as in the pathophysiology of different chronic autoimmune diseases, such as RA, MS, T1D, and SLE [65]. Human metabolism is closely linked to ongoing inflammatory and immune responses, and alterations in the metabolic structure of immune cells can lead to dysregulation of immune responses and are characteristic of autoimmunity [66]. When faced with various dynamically changing and challenging environmental conditions, immune cells need to display dynamic metabolic adaptation processes. Inflammation-stimulated immune cells urgently need to produce more energy and biomolecules to support the growth, proliferation, and production of pro-inflammatory molecules. Metabolic reorganization affects the effector phase of inflammation and the resolution of inflammation by regulating the fate and function of immune cells. Increasing research suggests that exploring the immunometabolic pathways that control the fate of cells of the innate and adaptive immune system at all stages of activation, proliferation, differentiation, and effector response is critical to the development of new targets for the treatment of autoimmune diseases. Furthermore, intermediate analyses revealed that air pollutants increased the risk of autoimmune diseases by modulating the expression of POR, HSPA1B, SHANK3, and BRD2. Cytochrome P450 reductase (POR) is a membrane-bound enzyme that mediates electron transfer between NADPH, cytochrome P450, and heme proteins in the endoplasmic reticulum of eukaryotic cells [67]. Studies have shown that POR plays an important role in energy metabolism, inflammatory immunity, and tumor development [68]. P450 (CYP) regulates the conversion of fatty acids to pro- or anti-inflammatory mediators, including interleukin (IL)-1 β , IL-6, and tumor necrosis factor- α (TNF- α) [69]. Bromodomain-containing protein 2 (BRD2), belongs to a novel protein kinase with a role in

the transcription of cell cycle responses in autoimmune and cancer diseases [70]. BRD2 coordinates various extracellular or intracellular danger signals through PRRs expressed in immune and non-immune cells in a variety of diseases and has emerged as a promising therapeutic target [71].

However, there are still several unavoidable limitations in our study. First, the participants included in our data were all European populations and without other ethnic groups. The current observational studies of air pollutants and autoimmune diseases cover data from various populations and countries, leading to possible incompleteness and partial bias in our conclusions. Second, air pollutant intake changes over time as people's lifestyles and regional environmental protection measures change. In this paper, we used GWAS data on air pollution measured by participants in the UK in 2010. The causal relationship between air pollution and autoimmune disease may need to be reassessed in the future as sample size increases. Third, based on the paucity of current basic research on air pollutants in autoimmune diseases, we have not explored these possible molecular mechanisms in depth, although we have identified many key genes and pathways using TWAS and enrichment pathway analysis. Fourth, in the selection of covariates, we chose those modifiable lifestyles that were closely related to air pollution and autoimmune diseases based on previous studies. This leads us to inevitably overlook some other important variables. Fifth, in designing this study, we had to choose 5×10^{-6} instead of 5×10^{-8} in order to obtain sufficient instrumental variables. MR was based on three key assumptions: (1) IVs are strongly associated with the exposure; (2) no shared cause with the outcome; (3) IVs only affect the outcome through the exposure. Thus, compared with the threshold of 5×10^{-8} , 5×10^{-6} might bring less strong IVs and potential pleiotropy, although we made several analyses to test these potential biases. Additionally, the validated GWAS of the SLE, CeD, and hypothyroidism we employed had partial sample overlapping with the exposure from the UK biobank, although the overlap might not bias the results as previously thought when IVs are strong enough [72]. The current study included only four air pollution molecules as exposures and did not include other molecules such as nitrous oxide and sulfide, most notably due to the lack of appropriate GWAS data. Last but not least, many other mediating factors, such as family/genetic background, physical/mental health status, and type of work, were not included in the study analysis.

In summary, using single nucleotide polymorphisms obtained from the latest large-scale GWAS in this paper, robust evidence suggests a causal relationship between air pollutants and autoimmune disease. Our findings

might shed light on the development of air pollutants-based interventions for autoimmune diseases in the future.

Abbreviations

AS	Ankylosing spondylitis
ARE	Antioxidant response element
AhR	Aryl hydrocarbon receptor
AA	Asthma and allergy
ADs	Autoimmune diseases
BEND3	BEN structural domain-containing protein 3
CeD	Celiac disease
CI	Confidence interval
CD	Crohn's disease
eQTL	Expression quantitative trait loci
FCP	Fisher's Combined P-value
GWAS	Genome-wide association studies
GTEX v8	Genotype-Tissue Expression version 8
GSCAN	GWAS and Sequencing Consortium of Alcohol and Nicotine use
IVs	Instrumental variables
IIBDGC	International Inflammatory Bowel Disease Genetics Consortium
IMSGC	International Multiple Sclerosis Genetics Consortium
IPSCSG	International PSC Study Group
IWV	Inverse-variance weighted
IBS	Irritable bowel syndrome
MR	Mendelian randomization
MS	Multiple sclerosis
MVMR	Multivariate Mendelian randomization
NO ₂	Nitrogen dioxide
NO _x	Nitrogen oxides
AIHA	Other autoimmune hemolytic anemias
PM	Particulate matter
PAH	Polycyclic aromatic hydrocarbon
PP2A	Protein phosphatase 2A
PSC	Primary sclerosing cholangitis
ROS	Reactive oxygen species
RA	Rheumatoid arthritis
SS	Sicca syndrome
SO ₂	Sulfur dioxide
SLE	Systemic lupus erythematosus
TLRs	Toll-Like Receptors
TWAS	Transcriptome-wide association study
TSMR	Two-sample Mendelian randomization
T1D	Type 1 diabetes
UC	Ulcerative colitis

Supplementary Information

The online version contains supplementary material available at <https://doi.org/10.1186/s12967-024-04928-y>.

Additional file 1: Supplementary methods and figures. Figure S1.

The leave-out-one plot for air pollution and autoimmune diseases. **Figure S2.** TSMR meta-analysis between air pollution and autoimmune diseases. **Figure S3.** Hub gene transcripts analysis associated with air pollution and autoimmune diseases.

Additional file 2: Supplementary tables. Table S1. Summary of each genome-wide association study. **Table S2.** Instrument SNPs for NO₂. **Table S3.** Instrument SNPs for NO_x. **Table S4.** Instrument SNPs for PM_{2.5}. **Table S5.** Instrument SNPs for PM₁₀. **Table S6.** Results for TSMRs. **Table S7.** Statistical power for significant TSMR results. **Table S8.** Heterogeneity analyses for NO₂. **Table S9.** Pleiotropy analyses for NO₂. **Table S10.** Heterogeneity analyses for NO_x. **Table S11.** Pleiotropy analyses for NO_x. **Table S12.** Heterogeneity analyses for PM_{2.5}. **Table S13.** Pleiotropy analyses for PM_{2.5}. **Table S14.** Heterogeneity analyses for PM₁₀. **Table S15.** Pleiotropy analyses for PM₁₀ MRs. **Table S16.** Results for validated TSMRs. **Table S17.** Heterogeneity analyses for validated MRs. **Table S18.** Pleiotropy analyses for validated. **Table S19.** Results for MVMR.

Table S20. Mediating effects of pQTL by two-step MR. **Table S21.** Results of colocalization analysis for each SNPs in POR pQTL. **Table S22.** Results of colocalization analysis for each SNPs in HSPA1B pQTL. **Table S23.** Results of colocalization analysis for each SNPs in SHANK3 pQTL. **Table S24.** Results of colocalization analysis for each SNPs in BRD2 pQTL.

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Author contributions

Writing—original draft, methodology, statistical analysis, validation and revision: JW-Z and JW. Data collection, statistical analysis, validation and revision: HZ, NZ, YJ-D, and RY-L. Conceptualization, methodology, supervision, revision, project administration and funding acquisition: QC, HL, and PL. All authors contributed to the article and approved the submitted version.

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Availability of data and materials

All data used in this study were available in the original researches. Data generated in this study were included in the main text and Additional files.

Declarations

Ethics approval and consent to participate

All data used by this study were publicly available from participant studies with approval of ethical standards committee related to human experimentation. No additional ethical approval was required in this study.

Consent for publication

All authors consented to the submission and publication of this study.

Competing interests

All authors have no interest in conflict to be declared.

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