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Mendelian randomization study reveals the effects of air pollution on the risk of male and female infertility

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Abstract

Recent observational studies have reported the links between particulate air pollutants and infertility, but the causal links still remain uncertain. This study was designed to determine the link between 5 types of air pollutants (NOx, PM2.5, PM2.5–10, PM10, and NO_2) and risk of infertility via Mendelian randomization (MR) analysis. Genetically predicted air pollutants (NOx, PM2.5, PM2.5–10, PM10, and NO_2) and outcomes (male and female infertility) were obtained from UKbiobank and Finngen, respectively. Instrumental variables were strictly selected based on the 3 assumptions. Four mainstream MR analysis methods and sensitivity analyses were performed to provide a satisfactory level of causal evidence between 5 types of air pollutants (NOx, PM2.5, PM2.5–10, PM10, and NO_2) and female and male infertility. Genetically predicted PM2.5 was correlated with the increased risk of male infertility ($P = .04$), but this correlation became indicative after Bonferroni test. No support was found for the causal associations between exposure to NOx, PM2.5–10, PM10, NO_2, and male infertility. However, no evidence of causal associations was observed between 5 types of air pollutants (NOx, PM2.5, PM2.5–10, PM10, and NO_2) and female infertility. Moreover, neither heterogeneity nor pleiotropy was found in any causal relationship. The present MR study suggests that PM2.5 might have a detrimental effect on male infertility, which indicates that PM2.5 contributes to the occurrence of male infertility. This study highlights the importance of improving air quality to reduce male infertility.

Abbreviations: CI = confidence interval, GWAS = genome-wide association studies, IVW = inverse-variance weighted, MR = Mendelian randomization, OR = odds ratio, SNPs = single nucleotide polymorphisms.

Keywords: air pollution, infertility, Mendelian randomization, PM2.5, reproductive health

1. Introduction

Fertility is declining year by year, with rates below the replacement level in most countries and territories. Fertility rates will continue to decrease worldwide and still remain low even under successful implementation of pro-natal policies in the near future.[1] Infertility is a major global health concern,[2] and the overall prevalence of infertility all over the world is about 50 to 70 million couples.[3] Infertility will cause heavy psychosocial burden to the couples and finally cause family breakdown. Unfortunately, infertility is also associated with decreased quality of life and overall health status in both men and women. The most common causes of infertility in couples are tubal diseases, ovulatory dysfunction, and male factor infertility.[4] Recently, some research has demonstrated that exposure to environmental factors plays a significant role in infertility, especially air pollution.[5]

Against the backdrop of rapid urbanization and industrialization, the reproductive health hazards posed by environmental contaminants have attracted escalating attention. Expanded fossil fuel combustion has elevated global levels of gaseous and particulate air pollutants, with ambient air concentrations regularly surpassing World Health Organization safety guidelines.[6] Air pollution is linked to quite a few diseases. These pollutants act through several mechanisms that can affect numerous physiological functions.[7] Air pollution was reported to be linked to immune dysfunction and a variety of autoimmune diseases.[8] Seli et al[9] thought that air pollution may have a negative impact on female and male

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The authors have no conflicts of interest to declare.

The datasets generated during and/or analyzed during the current study are available from the corresponding author on reasonable request.

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reproductive function. A recent meta-analysis revealed that exposure to outdoor environmental pollutants may reduce human fecundability.[10] A study on nationwide prospective cohort reported that exposure to PM2.5 was associated with a higher risk of infertility in men but not in women.[11] Hence, whether exposure to air pollution could definitely lead to infertility is still unclear.

Air pollutants constitute a complex cocktail of particulate and gaseous components, including fine particulate matter (PM2.5), inhalable coarse particulate matter (PM10), ozone, sulfur dioxide, and nitrogen oxides. To date, the causal relationships between air pollutant exposure and male and female infertility remain insufficiently characterized. This Mendelian randomization (MR) study was therefore performed to systematically evaluate the causal associations of 5 representative air pollutants (NOx, PM2.5, PM2.5–10, PM10, and NO_2) with infertility risks in males and females. Findings from this work may inform targeted environmental governance policies to mitigate pollution-related fertility impairment.

2. Methods

2.1. Study design

The present study is a strict MR analysis under the principle of the Strengthening the Reporting of Observational Studies in Epidemiology using Mendelian randomization guidelines. This study was designed to determine the causal correlation between 5 air pollutants (NOx, PM2.5, PM2.5–10, PM10, and NO_2) and male and female infertility via MR analysis, which is based on the following 3 assumptions (Fig. 1). First, instrumental variables (IVs) are directly correlated with the exposures (air contaminants). Second, IVs have no correlation with the outcome (infertility) via confounders. Finally, IVs could not directly affect the outcomes.

2.2. Data sources

The dataset containing information on air pollutants was acquired from the UK Biobank. Five types of air contaminants (NOx, PM2.5, PM2.5–10, PM10, and NO_2) were selected for further analyses: nitrogen oxides (NOx), particulate matter with diameter <2.5 μm (PM2.5), particulate matter with diameter of 2.5 to 10 μm (PM2.5–10), particulate matter with diameter of <10 μm (PM10), and nitrogen dioxide (NO_2). Genetic associations for infertility were gained from the Finngen study, which is the latest summary-level genetic data among European populations. All MR analyses in the present study relied on publicly released summary statistics from published GWAS cohorts, so additional ethical clearance was waived.

2.3. Selection of genetic instruments

For each type of air pollutant, a strict quality control procedure was followed to select eligible IVs. First, we selected single nucleotide polymorphisms (SNPs) associated with NOx, PM2.5, PM2.5–10, PM10, and NO_2 at a liberal genome-wide significance ($P < 5e^{-5}$) as potential IVs. Then, the linkage disequilibrium (LD)-based clumping was applied to remove SNPs in strong LD ($r^2 = 0.1$, window size = 10 Mb), which could ensure the IVs for type of air contaminants are independent. Proxy SNPs with LD $r^2 > 0.8$ were assigned for genetic variants absent from the outcome GWAS summary data. *F*-statistics was calculated to assess the strength of IVs, and *F*-statistics > 10 indicated a low possibility of weak IV.

2.4. Statistical analysis

The summary statistics (β coefficients and odds ratios) were utilized to estimate the causal correlations between 5 types of air pollutants (NOx, PM2.5, PM2.5–10, PM10, and NO_2) and infertility separately using 4 MR methods, which were

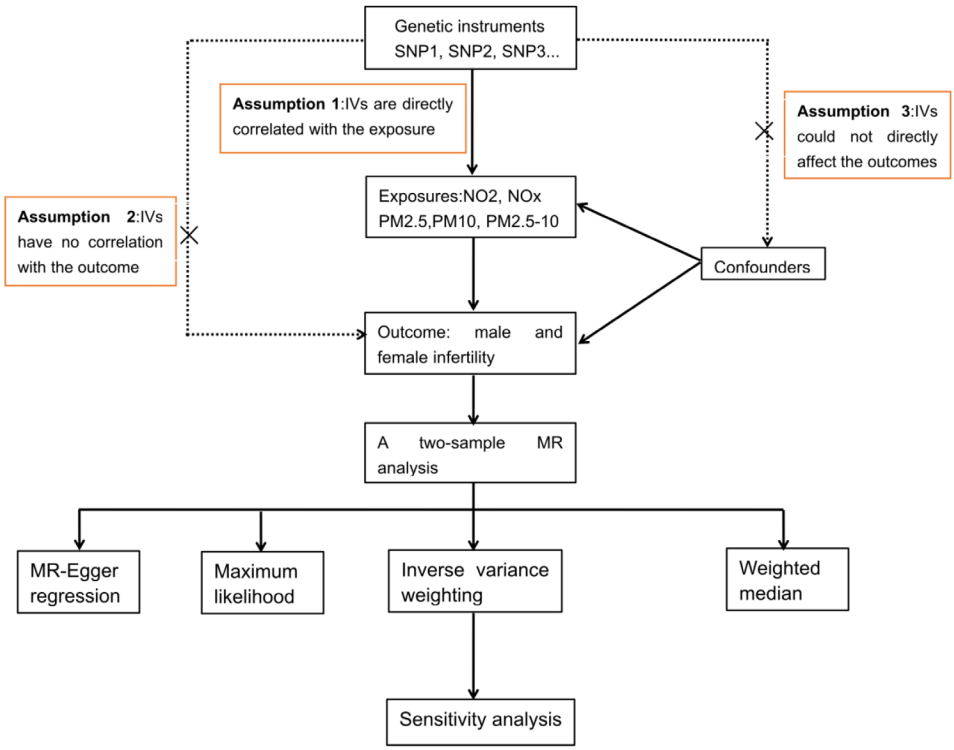

Figure 1. Study design of this 2-sample Mendelian randomization.

inverse-variance weighting (IVW), MR-Egger regression, maximum likelihood, and weighted median. IVW method is the core statistical model for MR analysis, with 3 supplementary methods implemented to detect the consistency of the results. The fixed-effects IVW method was performed to estimate the causal correlations between 5 types of air pollutants (NOx, PM2.5, PM2.5–10, PM10, and NO_2) and infertility. The random-effects IVW method will be utilized for the presence of significant heterogeneity ($P < .05$). Multiple testing was corrected via the Bonferroni method in the present study. With a total of 5 exposure factors and 2 outcomes incorporated into the analysis, the corrected significance threshold was set at 0.01 (calculated as 0.05/10). Specifically, associations with $P < .005$ were identified as robust evidence supporting causal effects, whereas associations with $.005 \leq P < .05$ were deemed suggestive evidence of causal relevance.

Cochran's *Q* statistics was used to assess the heterogeneity among genetic instruments from the IVW method, and *P* value > .05 indicated no significant heterogeneity. MR-Egger intercept test combined with the Mendelian Randomization Pleiotropy RESidual Sum and Outlier (MR-PRESSO) test were utilized to examine the effects of directional pleiotropy. Finally, we evaluated the bias due to individual SNP effects on outcomes (infertility) using a leave-one-out analysis. All statistical analyses were 2-sided in the present study. R software (version 3.3.0; The R Foundation for Statistical Computing, Vienna, Austria, https://cran.r-project.org/) along with the MR-PRESSO and TwoSampleMR packages were used for the present Mendelian randomization analysis.

3. Results

3.1. Causal correlations between 5 types of air pollutants and male infertility

The comprehensive study design of the MR research is shown in Figure 1. Genetic liability to PM2.5 was closely correlated with an increased risk of male infertility (odds ratio [OR] = 1.48, 95% confidence interval [CI]: 1.05–2.62, *P* = .04) using IVW method (Fig. 2). This correlation became indicative after Bonferroni test. Our results showed no support for the causal associations between exposure to NOx (OR = 1.09, 95% CI: 0.57–2.07, *P* = .798), PM2.5–10 (OR = 0.94, 95% CI: 0.36–2.44, *P* = .90), PM10 (OR = 0.61, 95% CI: 0.21–1.74, *P* = .351), and NO_2 (OR = 1.03, 95% CI: 0.51–2.06, *P* = .94), and male infertility (Fig. 2).

To validate the causal associations from the IVW method, 3 additional MR methods (MR-Egger regression, maximum likelihood, and weighted median) were performed. The positive correlation between PM2.5 exposure and male infertility was confirmed by weighted median method (OR = 3.45, 95% CI: 1.09–11, *P* = .0359), while other 3 MR methods also showed no support for the causal associations between exposure to NOx, PM2.5–10, PM10, and NO_2, and male infertility (Fig. 2). The scatter plots using all genetic SNPs revealed the consistent β directions using the 4 MR methods (Fig. 3). In brief, exposure to PM2.5 might increase the risk of male infertility, while exposure to NOx, PM2.5–10, PM10, and NO_2 did not increase the risk of male infertility.

3.2. Causal correlations between 5 types of air pollutants and female infertility

No evidence of causal relationship between exposure to PM2.5 (OR = 1.02, 95% CI: 0.82–1.26, *P* = .885), NOx (OR = 0.99, 95% CI: 0.78–1.24, *P* = .906), PM2.5–10 (OR = 0.82, 95% CI: 0.58–1.17, *P* = .275), PM10 (OR = 1.19, 95% CI: 0.84–1.67, *P* = .322), NO_2 (OR = 0.88, 95% CI: 0.70–1.11, *P* = .279) and female infertility using the IVW method (Fig. S1, Supplemental Digital Content 1). When validated with the other 3 MR methods (MR-Egger regression, maximum likelihood, and weighted median), no causal relationship was confirmed between the exposure to PM2.5, NOx, PM2.5–10, PM10, and NO_2, and female infertility (Fig. S1, Supplemental Digital Content 1). The scatter plots using all genetic SNPs revealed consistent β directions using the 4 MR methods (Fig. S2, Supplemental Digital Content 2). Hence, we deemed that exposure to the 5 types of air pollutants did not increase the risk of female infertility.

3.3. Sensitivity analysis

Cochran's *Q* statistics detected no significant heterogeneity between exposure to air contaminants and male infertility (Table 1) and female infertility (Table S1, Supplemental Digital Content 3). Moreover, funnel plots derived from IVW and MR-Egger regression showed a roughly symmetrical distribution of IVs, further indicating the absence of directional pleiotropy both in the male (Fig. 4) and female population (Fig. S3, Supplemental Digital Content 4). Finally, leave-one-out analysis sequentially excluded individual SNPs to examine the influence

Exposure	Methods	nSNP	P value	FDR	OR(95%CI)	Q	Q_Pval	Egger_intercept	Pleiotropy_pval
PM2.5	Inverse variance weighted	96	4.18e-02	9.4e-01	1.48(1.05-2.62)	112.43	1.07e-01	-0.00	9.35e-01
	MR Egger	96	6.55e-01		1.33 (0.38-4.65)	112.42	9.47e-02		
	Maximum likelihood	96	4.62e-01		1.29 (0.65-2.54)				
	Weighted median	96	3.59e-02		3.45 (1.09-11.00)				
N0x	Inverse variance weighted	117	7.98e-01	9.4e-01	1.09 (0.57-2.07)	106.58	7.23e-01	-0.00	7.62e-01
	MR Egger	117	6.94e-01		1.27 (0.39-4.13)	106.48	7.03e-01		
	Maximum likelihood	117	7.95e-01		1.09 (0.56-2.11)				
	Weighted median	117	2.06e-01		2.07 (0.67-6.38)				
PM2.5-10	Inverse variance weighted	39	9.00e-01	9.4e-01	0.94 (0.36-2.44)	35.52	5.85e-01	0.01	6.20e-01
	MR Egger	39	6.49e-01		0.71 (0.17-3.05)	35.27	5.50e-01		
	Maximum likelihood	39	8.99e-01		0.94 (0.36-2.47)				
	Weighted median	39	6.25e-01		0.70 (0.17-2.91)				
PM2.5	Inverse variance weighted	57	3.51e-01	9.4e-01	0.61 (0.21-1.74)	57.46	4.21e-01	-0.02	2.76e-01
	MR Egger	57	5.92e-01		1.86 (0.19-17.83)	56.23	4.29e-01		
	Maximum likelihood	57	3.52e-01		0.60 (0.21-1.75)				
	Weighted median	57	2.81e-01		0.44 (0.10-1.97)				
N02	Inverse variance weighted	109	9.40e-01	9.4e-01	1.03 (0.51-2.06)	116.79	2.65e-01	-0.01	5.47e-01
	MR Egger	109	5.81e-01		1.46 (0.38-5.55)	116.40	2.52e-01		
	Maximum likelihood	109	9.38e-01		1.03 (0.52-2.05)				
	Weighted median	109	1.86e-01		2.23 (0.68-7.29)				

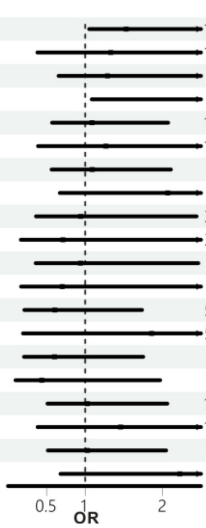

Figure 2. Forest plot of MR analyses for exploring the causal associations between 5 air pollutants and male infertility. MR = Mendelian randomization.

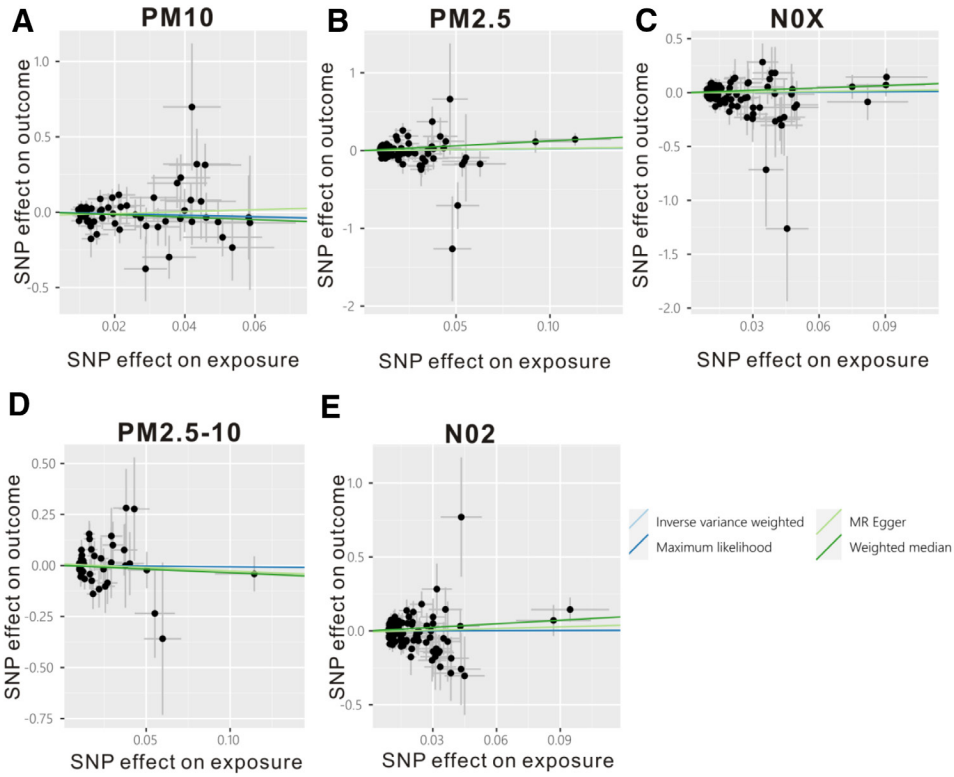

Figure 3. Scatter plots of MR analyses for estimating the causal associations between 5 air pollutants and male infertility. (A) PM10, (B) PM2.5, (C) NOx, (D) PM2.5–10, (E) NO_2. MR = Mendelian randomization.

Table 1

Detailed information on data sources and sensitivity analysis of causal effects of 5 air pollutants on male infertility.

Exposure	Exposure	Method	nSNP	OR	*P* value	*Q*	Q_*p* value	Egger_intercept	Pleiotropy_pval
PM2.5	ukb-b-10817	Inverse-variance weighted	96	1.4828	0.0418	112.4	0.107082	−0.000892	0.934755068
	ukb-b-10817	MR Egger	96	1.3316	0.6547	112.4	0.094673		
	ukb-b-10817	Maximum likelihood	96	1.2889	0.4624				
	ukb-b-10817	Weighted median	96	3.4546	0.0358				
NOx	ukb-b-12417	Inverse-variance weighted	117	1.0879	0.7978	106.5	0.723121	−0.002914	0.761854558
	ukb-b-12417	MR Egger	117	1.2682	0.6940	106.4	0.702534		
	ukb-b-12417	Maximum likelihood	117	1.0912	0.7951				
	ukb-b-12417	Weighted median	117	2.0693	0.2056				
PM2.5–10	ukb-b-12963	Inverse-variance weighted	39	0.9408	0.9003	35.52	0.584564	0.0077069	0.620313184
	ukb-b-12963	MR Egger	39	0.7112	0.6487	35.27	0.550151		
	ukb-b-12963	Maximum likelihood	39	0.9393	0.8988				
	ukb-b-12963	Weighted median	39	0.7016	0.6251				
PM10	ukb-b-18469	Inverse-variance weighted	57	0.6057	0.3506	57.46	0.420732	−0.021209	0.276441626
	ukb-b-18469	MR Egger	57	1.8607	0.5923	56.22	0.428675		
	ukb-b-18469	Maximum likelihood	57	0.6020	0.3517				
	ukb-b-18469	Weighted median	57	0.4369	0.2813				
NO_2	ukb-b-9942	Inverse-variance weighted	109	1.0270	0.9402	116.7	0.265041	−0.006530	0.54671484
	ukb-b-9942	MR Egger	109	1.4587	0.5806	116.3	0.251541		
	ukb-b-9942	Maximum likelihood	109	1.0278	0.9377				
	ukb-b-9942	Weighted median	109	2.2264	0.1857				

OR = odds ratio, SNPs = single nucleotide polymorphisms.

of any single variant on the causal estimate, suggesting that no single SNP disproportionately drove the causal links between air pollutants and male infertility (Fig. 5) or female infertility (Fig. S4, Supplemental Digital Content 5).

4. Discussion

From the UK Biobank, we systematically evaluated the causal effects of 5 key air pollutants (PM2.5, NOx, PM2.5–10, PM10, and NO_2) on infertility risk in males and females. Within this genetics-driven causal inquiry into the etiological contribution of air pollution to human reproductive health across sexes, we identified a possible genetic association between PM2.5 exposure and elevated male infertility risk, whereas no robust causal signals were detected for the remaining 4 air pollutants in either male or female infertility analyses. To our knowledge, this study represents the first Mendelian randomization analysis to comprehensively dissect the causal links between these 5 ambient

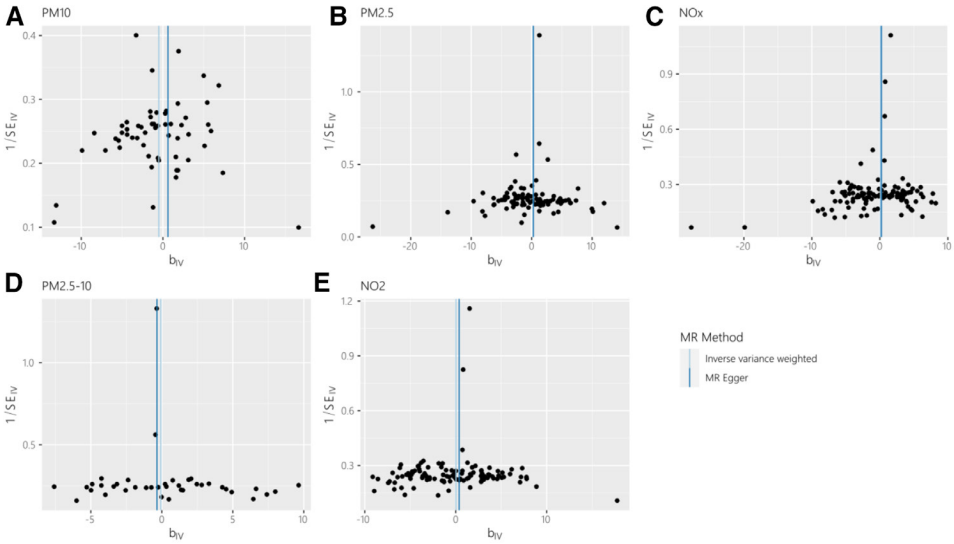

Figure 4. Funnel plots for 5 air pollutants on male infertility. (A) PM10, (B) PM2.5, (C) NOx, (D) PM2.5–10, (E) NO_2.

pollutants and infertility risk stratified by sex. Collectively, our findings underscore the public health value of targeted air quality governance as a potential strategy to mitigate pollution-related male infertility burden.

MR analysis is a highly efficient statistical method using summary GWAS data to explore the connections between exposure and outcomes.[12] The core strength of MR analysis lies in reducing the effects of confounding bias and reverse causality via natural random assignment of genetics, which is similar to randomization in randomized controlled trials. MR analysis is based on GWAS, without obtaining exposure or outcomes, which could save research funds and time. Importantly, as the effects of genetic variants are carried out throughout life, MR analysis could evaluate the cumulative effect of exposure factors on the outcome.[13] In brief, genetic variation is a lifetime constant, independent of confounding effects of the environment. In this MR study, we found that exposure to PM2.5 might increase the risk of male infertility. Although these MR results are based on rigorous analysis, they still need more prospective cohort studies with a large sample size to validate in the future.

Air pollution is a research focus due to its adverse effects on human health, including on infertility. Whether exposure to air pollution positively affected the fertility is still under debate. Gaskins et al[14] hold the view that frequent exposure to air pollution was associated with inflammation response and oxidative stress, which may mediate the occurrence of infertility. A recent study[15] indicated that individuals exposed to air pollution are 8.62% less likely to bear more than 1 child, highlighting the importance of environmental protection among the public. Wdowiak et al[16]. observed a significant negative association($R = -0.8311$, $P = .040$) between the levels of air ozone and the percentage of sperm with normal morphology. Another observational study from south Taiwan also reported a negative association between levels of NO_2 and SO_2 and semen motility.[17] However, the results from a North American cohort study showed that exposure to NO_2, O3, and PM2.5 was not correlated with reduced fecundability among pregnancy planners.[18] Thampy et al[19] held the view that exposure to PM2.5 prior to conception was positively correlated with fertility treatment. In the present study, exposure to PM2.5 was significantly associated with increased risk of male infertility, while no evidence was found between exposure to NO_2 and infertility. Toxicology studies should be performed to investigate the underlying pathogenesis of infertility under air pollutant exposure among male and female populations.

Although several factors involved in the development of infertility have been uncovered, the precise etiology and pathogenesis of infertility remain obscure. The potential mechanism underlying the side effects of environmental pollution on fertility might involve the following aspects. First, air pollutants can increase the production of reactive oxygen species, which could cause oxidative stress and lipid peroxidation.[20] Then, excessive oxidative stress and persistent lipid peroxidation could cause DNA strand breaks.[21] For instance, a Polish study reported that exposure to air pollutants (PM2.5 and PM10) increased the percentage of cells with immature chromatin, indicating DNA damage, in male population.[22] Moreover, air pollution has also been linked to the sperm aneuploidy in human.[23] Importantly, air pollutants could mimic the impact of estrogens in female body. These endocrine-disrupting properties caused by air pollutants could exert their effect by interacting with nuclear receptors, leading to the activation of the Ras/Erk pathway.[24] Although the detailed mechanism underlying infertility effects is not well-understood, urgent action is needed to minimize these impacts through reducing air pollution and taking necessary steps to reduce exposure.

Mendelian randomization revealed that genetically predicted PM2.5 exposure was associated with increased male infertility risk ($P = .04$). After Bonferroni correction, this fell into the suggestive range, indicating a potential association requiring validation in larger or independent samples. The other 4 pollutants (NOx, PM2.5–10, PM10, and NO_2) showed no significant association with male infertility even at the uncorrected level (all $P \geq .05$), so correction did not alter their negative interpretation. For female infertility, none of the 5 pollutants reached raw $P < .05$, and all remained nonsignificant after correction, confirming no detectable causal link. No heterogeneity or horizontal pleiotropy was detected across analyses, ruling out SNP-related biases and supporting the reliability of the correction. Thus, Bonferroni correction effectively controlled Type I error inflation from simultaneous testing. The originally nominal PM2.5–male infertility association was downgraded from robust to suggestive, underscoring the need for stringent multiple-testing control in multi-exposure MR studies. All negative findings remained unchanged post-correction, strengthening their credibility.

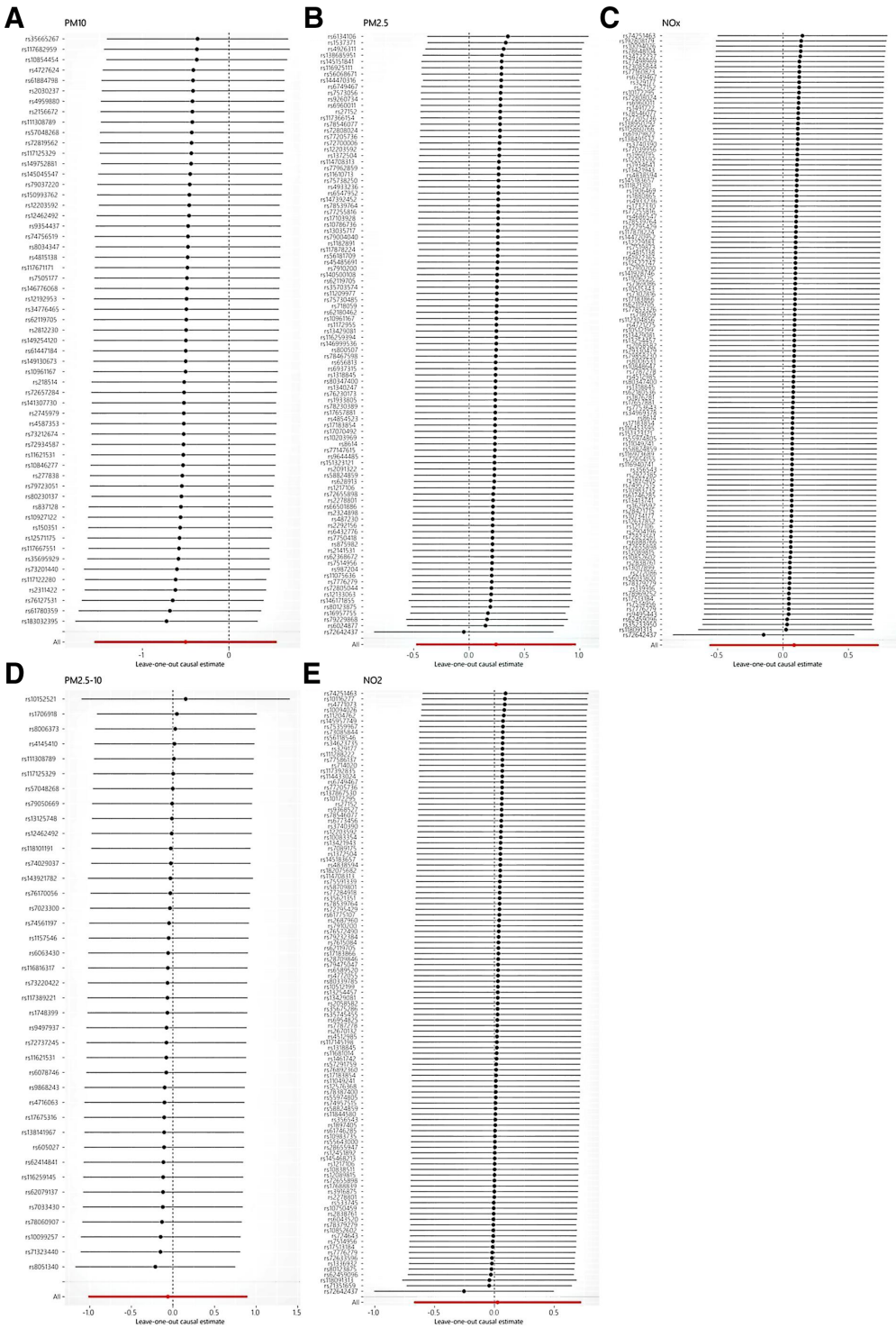

Figure 5. Leave-one-out analysis plots for 5 air pollutants on male infertility. (A) PM10, (B) PM2.5, (C) NOx, (D) PM2.5–10, (E) NO_2.

Three obvious limitations exist in this research. First, all GWAS summary datasets for air pollutants and infertility outcomes were exclusively derived from participants of European descent, and our causal estimates cannot be directly extrapolated to East Asian, African, Latin American, or other non-European populations. Then, we only analyzed circulating genetic proxies of long-term air pollutant exposure, without capturing short-term acute exposure or regional exposure variability. Finally, we could not account for complex environmental confounding factors (e.g., smoking, occupational toxicants) that may interact with air pollution to modify infertility risk. Hence, we need to further validate the association between air pollution exposure and infertility in cross-ethnic populations in the future.

5. Conclusion

The present MR study first identified the possible association between exposure to PM2.5 and male infertility, while no causal association was found between exposure to PM2.5 and female

infertility. Our study may provide essential public health implications in terms of improving air quality to reduce the incidence of infertility.

Author contributions

Conceptualization: Yan Huang, Xiulan Peng, Qunru Jiao.
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Formal analysis: Rui Zhang, Xing Li, Zhen Cai.
Methodology: Xing Li, Zhen Cai.
Supervision: Xing Li, Zhen Cai.
Resources: Qunru Jiao.
Writing – original draft: Yan Huang.
Writing – review & editing: Rui Zhang, Xing Li, Zhen Cai, Xiulan Peng, Qunru Jiao.

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