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ORIGINAL ARTICLE

Causal relationships between air pollutants and upper respiratory tract infections: A two-sample, Mendelian randomization study

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Abstract

Background: The issue of air pollution is a concern that affects the health of individuals globally. Air pollutants (APs) have been linked to upper respiratory tract infections (URTIs); however, the exact association between them remains unclear.

Methods: Two-sample Mendelian randomization (MR) was performed to examine the causal relationship between APs and URTIs. Data regarding APs and URTIs were obtained from genome-wide association studies. Single-nucleotide polymorphisms associated with each exposure were defined as instrumental variables. Inverse variance weighting is the primary method for analyzing causal effects. Quality control was performed using MR-Egger, weighted mode, simple mode, and weighted median. Heterogeneity was assessed using Cochran's Q. The MR-Egger test was used to evaluate pleiotropy. Sensitivity analysis was performed using the "leave-one-out" method.

Results: MR analysis revealed that airborne particulate matter with a diameter ≤10 micrometers (PM_{10}) had a notable impact on acute pharyngitis, whereas nitrogen dioxide had a significant impact on chronic rhinitis, chronic nasopharyngitis, and chronic pharyngitis. Pleiotropy and heterogeneity were not observed.

Conclusion: Higher PM_{10} levels were associated with a greater likelihood of developing acute pharyngitis. Increased nitrogen dioxide concentrations were associated with an increased risk for chronic rhinitis, nasopharyngitis, and pharyngitis. As such, controlling APs is crucial for preventing and treating URTIs.

Keywords: Air pollutants; Causal effect; Mendelian randomization; Upper respiratory tract infection

Lay Summary: Air pollution can affect personal health, especially respiratory diseases. After analyzing the relationship between common air pollutants and some common upper respiratory tract diseases, we found that an increase in the concentration of particulate matter and nitrogen dioxide is causally related to the occurrence of some upper respiratory tract diseases, such as acute pharyngitis, chronic rhinitis, chronic nasopharyngitis, and chronic pharyngitis.

1. INTRODUCTION

Infections of the upper respiratory system, such as rhinitis, sinusitis, pharyngitis, nasopharyngitis, laryngitis, tonsillitis, and epiglottitis, affect the function and structure of the nose, sinuses, throat, and larynx. Most upper respiratory tract infections (URTIs) are brief, mild, and resolve independently, although some may result in severe complications. Typically, 20% to 40% of outpatients and 12% to 35% of hospital inpatients are diagnosed with acute UTRIs.[1] Adults usually experience approximately two to four episodes of acute URTIs per year, and preschool children experience approximately six to 10.[2] In addition to affecting health, URTIs negatively affect the quality of life, study, and work of affected individuals.[3–6] Due to their high incidence and associated economic losses, URTIs have become a public health issue that cannot be ignored.

Air pollution is a major environmental and health issue requiring serious attention. It has been established that widespread and long-term industrial production, vehicles using gasoline or diesel fuel, and questionable behaviors in the activities of daily living produce large amounts of air pollutants (APs). Prevalent APs include airborne particulate matter with diameters ≤2.5, 2.5 to 10, and 10 μm ($PM_{2.5}$, $PM_{2.5\text{-}10}$, PM_{10}, respectively), nitrogen dioxide (NO_2), sulfur dioxide (SO_2), nitrogen oxides (NO, NO_2, and N_2O), carbon monoxide (CO), and ozone (O_3).[7] The World Health Organization reports that >4 million early deaths worldwide are attributed to outdoor air pollution, with an additional 3.8 million attributed to indoor air pollution among individuals and countries with lower incomes.[8]

Air pollution has been linked to human health—particularly URTIs—in several studies.[9–11] Li et al[12] reported a positive association between APs and the occurrence of rhinitis, noting that local economic status and geographical surroundings could influence this relationship. Zhang et al[13] reported that the prevalence of chronic sinusitis was significantly increased among patients exposed to $PM_{2.5}$ over prolonged periods, while Han et al[13,14] reported that chronic sinusitis was independent of AP

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(PM, NO_2, SO_2, O_3) concentration. A previous study examined the immediate impact of six APs ($PM_{2.5}$, PM_{10}, SO_2, NO_2, CO, and O_3) on 62 823 individuals with chronic inflammation of the pharynx. Results indicated that those <15 years of age exhibited an increased vulnerability to APs, except O_3.[15] A study involving 9468 individuals over a 2-year period in 10 different areas across four cities in Guangdong Province, China, revealed that exposure to elevated levels of $PM_{2.5}$ for both short and prolonged periods increased the likelihood of developing acute nasopharyngitis.[16] A study from Korea reported a direct correlation between prolonged exposure to PM_{10} and the likelihood of developing chronic laryngitis.[17] However, observational studies may have methodological problems, and the results obtained may not be completely reliable and may not necessarily prove causation. However, conducting randomized controlled trials (RCTs) on APs and URTIs involves many ethical issues and are more time-consuming. To avoid methodological and ethical problems, and to determine a more reliable causal relationship, the present study used Mendelian randomization (MR) to determine whether APs and URTIs are causally related.

MR is a new method used to determine the cause-and-effect relationship between exposure (a possible risk factor) and outcome (illness).[18,19] By identifying single-nucleotide polymorphisms (SNPs) associated with exposure as instrumental variables, we aimed to investigate the correlation between exposure and outcome. To the best of our knowledge, no previous studies have explored the causal relationship between APs and URTIs using MR methods, which were used in the present study to explore such a relationship.

2. METHODS

2.1. Study design

MR analysis is based on three assumptions, as follows: instrumental variables are related to exposure factors; instrumental variables can only impact outcomes when exposure factors are present; and instrumental variables do not interact with other potential confounding factors.

Five methods are used to evaluate causal effects, with inverse-weighted variance (IVW) the most important. MR-Egger, weighted median, simple mode, and weighted mode analyses are the remaining four tools.

Cochran's Q tests were used to assess the heterogeneity of SNPs using the IVW and MR-Egger approaches, while funnel plots were used to estimate heterogeneity. MR-Egger regression was used to confirm the presence of horizontal pleiotropy in SNPs. The overall impact was reassessed by excluding individual SNPs one-at-a-time using the "leave-one-out" method. Additionally, a forest plot was constructed to estimate overall impact.

2.2. Data sources

Researchers collected information from genome-wide association studies (GWAS) involving individuals of European descent. The present study examined exposure variables for APs, including $PM_{2.5}$, $PM_{2.5-10}$, PM_{10}, NO_2, and N_xO_y (a mixture of NO, NO_2, and N_2O). Acute and chronic URTIs were included as outcome factors. Details regarding data sources for all exposures and outcomes are summarized in Tables 1 and 2. The primary researcher obtained ethics approval for this study and informed consent from all participants.

2.3. Selection of instrumental variables (genetic variants)

Genome-wide significance was defined as a p value $<5 \times 10^{-8}$. SNPs exhibiting palindromic structure and linkage disequilibrium ($r^2 > 0.001$ and <10 000 kb) were excluded.

2.4. Statistical analysis

Odds ratio (OR) and corresponding 95% CI were used to express the impact of exposure on the outcomes. Differences with $p < 0.05$ were considered to be statistically significant. R version 4.2.3 (R Core Team [2020]. R Foundation for Statistical Computing, Vienna, Austria, https://www.R-project.org/) was used to extract, analyze, and visualize the data, while TwoSampleMR version 0.5.6 was implemented in the R package.

3. RESULTS

3.1. MR analysis

MR analysis was performed using different APs as exposures and various URTIs as outcomes. MR analysis revealed that PM_{10} had a notable impact on acute pharyngitis, whereas NO_2 had a significant impact on chronic rhinitis, chronic nasopharyngitis, and chronic pharyngitis.

The likelihood of developing acute pharyngitis increased as PM_{10} levels increased (IVW, OR = 3.83 [95% CI, 1.04-14.15]; $p < 0.05$) (Table 3). The correlation between PM_{10} and the likelihood of developing acute pharyngitis is illustrated in Fig. 1A. Using the IVW method, forest plot results revealed that PM_{10} increased the risk for acute pharyngitis (Supplementary Fig. S1, https://links.lww.com/JCMA/A330). The likelihood of developing chronic rhinitis, chronic nasopharyngitis, and chronic pharyngitis increased as NO_2 levels increased (IVW, OR = 12.13 [95% CI, 1.49-98.67]; $p < 0.05$) (Table 3). The correlation between NO_2 and the likelihood of developing chronic rhinitis, chronic nasopharyngitis, and chronic pharyngitis is illustrated in Fig. 1B. Using the IVW method, forest plot revealed that NO_2 increased the risks for chronic rhinitis, chronic nasopharyngitis, and chronic pharyngitis (Supplementary Fig. S2, https://links.lww.com/JCMA/A330).

3.2. Analysis of pleiotropy and heterogeneity

No evidence of horizontal pleiotropy in the causal impact of PM_{10} on acute pharyngitis was found (Egger-intercept –0.04;

Table 1

The details of the data sources of exposures

Exposures	GWAS ID	Year	Consortium	Number of samples	Number of SNPs
PM					
$PM_{2.5}$	ukb-b-10817	2018	MRC-IEU	423 796	9 851 867
$PM_{2.5-10}$	ukb-b-12963	2018	MRC-IEU	423 796	9 851 867
PM_{10}	ukb-b-589	2018	MRC-IEU	455 314	9 851 867
Nitrogen dioxide	ukb-b-2618	2018	MRC-IEU	456 380	9 851 867
Nitrogen oxides	ukb-b-12417	2018	MRC-IEU	456 380	9 851 867

GWAS = genome-wide association studies; SNPs = single-nucleotide polymorphisms; MRC-IEU = the Medical Research Council Integrative Epidemiology Unit; PM = particulate matter.

Table 2

The details of the data sources of outcomes

Outcomes	GWAS ID	Year	Consortium	Number of samples	Number of SNPs
Acute sinusitis	finn-b-J10_SINUSITIS	2021	NA	193 861	16 380 415
Acute nasopharyngitis (acute rhinitis, common cold)	finn-b-J10_COLD	2021	NA	185 198	16 380 347
Acute pharyngitis	finn-b-J10_PHARYNGITIS	2021	NA	185 225	16 380 351
Acute epiglottitis	finn-b-J10_EPIGLOTTITIS	2021	NA	183 144	16 380 351
Acute laryngitis and tracheitis	finn-b-J10_LARYNGITIS	2021	NA	185 139	16 380 355
Chronic sinusitis	finn-b-J10_CHRONSINUSITIS	2021	NA	176 373	16 380 288
Chronic rhinitis, nasopharyngitis, pharyngitis	finn-b-J10_CHRONRHINITIS	2021	NA	173 204	16 380 284
Chronic laryngitis and tracheitis	finn-b-J10_CHRONLARYNGITIS	2021	NA	169 987	16 380 258
Tonsillitis	ebi-a-GCST90018930	2021	NA	458 829	24 187 447

GWAS = genome-wide association study; NA = data not available; SNPs = single-nucleotide polymorphisms.

Table 3

Causal effects of air pollutants on upper respiratory tract infections

Exposure	Outcome	Number of SNPs	Method	*p*	OR (95% CI)
PM_{10}	AP	22	MR Egger	0.05	33.66 (1.22-931.67)
			WM1	0.04	5.62 (1.12-28.17)
			IVW	0.04	3.83 (1.04-14.15)
			SM	0.12	9.87 (0.61-158.63)
			WM2	0.11	9.45 (0.68-131.26)
NO_2	CR/CNP/CP	5	MR Egger	0.10	NA
			WM1	0.12	4.82 (0.44-52.33)
			IVW	0.02	12.13 (1.49-98.67)
			SM	0.52	3.07 (0.13-70.58)
			WM2	0.51	3.07 (0.14-66.08)

AP = acute pharyngitis; CR/CNP/CP = chronic rhinitis/chronic nasopharyngitis/chronic pharyngitis; IVW = inverse-variance weighted; MR = Mendelian randomization; NA = data not available; NO_2 = nitrogen dioxide; OR = odds ratio; PM_{10} = particulate matter 10; SM = simple mode; SNP = single-nucleotide polymorphism; WM1 = weighted median; WM2 = weighted mode.

p = 0.18) (Table 4). Furthermore, neither IVW nor MR-Egger analysis revealed signs of heterogeneity in the causal effect of PM_{10} on acute pharyngitis (IVW, Q = 30.32, Q_degrees of freedom [df] = 21, p = 0.09; MR-Egger, Q = 27.65, Q_df = 20, p = 0.12) revealed no heterogeneity in the funnel plot (Supplementary Fig. S3A, https://links.lww.com/JCMA/A330).

There was no evidence of horizontal pleiotropy in the causal impact of NO_2 on chronic rhinitis, chronic nasopharyngitis, and chronic pharyngitis (Egger-intercept = –0.11; p = 0.18) (Table 4). Furthermore, neither IVW nor MR-Egger analysis revealed any indication of heterogeneity in the causal effect of NO_2 on chronic rhinitis, nasopharyngitis, or pharyngitis (IVW, Q = 5.57, Q_df = 4, p = 0.23; MR-Egger, Q = 2.51, Q_df = 3, p = 0.47). Heterogeneity reflected by a funnel plot is illustrated in Supplementary Fig. S3 (https://links.lww.com/JCMA/A330).

3.3. Sensitivity analysis

Sensitivity analysis was performed using the "leave-one-out" method and revealed that the causal effect of PM_{10} on acute pharyngitis was not significantly influenced by any single SNP (Supplementary Fig. S4, https://links.lww.com/JCMA/A330). The same was true for NO_2 on chronic rhinitis, chronic nasopharyngitis, and chronic pharyngitis (Supplementary Fig. S5, https://links.lww.com/JCMA/A330).

4. DISCUSSION

Several studies have linked APs to URTIs[9–11]; however, it remains unclear whether these two factors are causally related. There are methodological issues with previous studies that have examined the relationship between APs and the URTIs. First, there are limitations due to constraints imposed by study design. For example, cross-sectional studies may not establish causality because they do not provide temporal sequence information. Additionally, cohort studies require long-term follow-up, which can lead to participant attrition and recall bias. Second, there is the issue of exposure assessment errors, with some studies relying on outdoor air pollution monitoring station data to estimate individual exposure levels, which may not accurately reflect the actual extent of individual contact with APs, particularly those generated by indoor and personal activities. Third, selecting the appropriate biomarkers to reflect the health status of the upper respiratory system remains a challenge. Fourth, factors such as climate, cultural background, population characteristics, and lifestyle in different regions, can affect exposure to APs and health outcomes. MR research methods have several advantages. First, MR studies are typically faster and more cost-effective because they can leverage existing GWAS data for their design. Second, MR analysis can reveal potential causal relationships between specific exposures and diseases, whereas RCTs often require large sample sizes and long-term follow-up to observe a sufficient number of endpoint events. Third, based on ethical considerations, some RCTs are not ethically permissible. Fourth, because genetic variations are fixed at conception, MR results reflect the potential lifelong impact of risk factors. Fifth, MR studies use genetic data to reduce the influence of confounding factors. These advantages make MR a valuable research tool that can overcome some of the limitations and issues inherent in traditional observational studies and RCTs. Nevertheless, the MR design has its own assumptions and considerations and should be approached with caution. As such, we used MR analysis to determine the causal

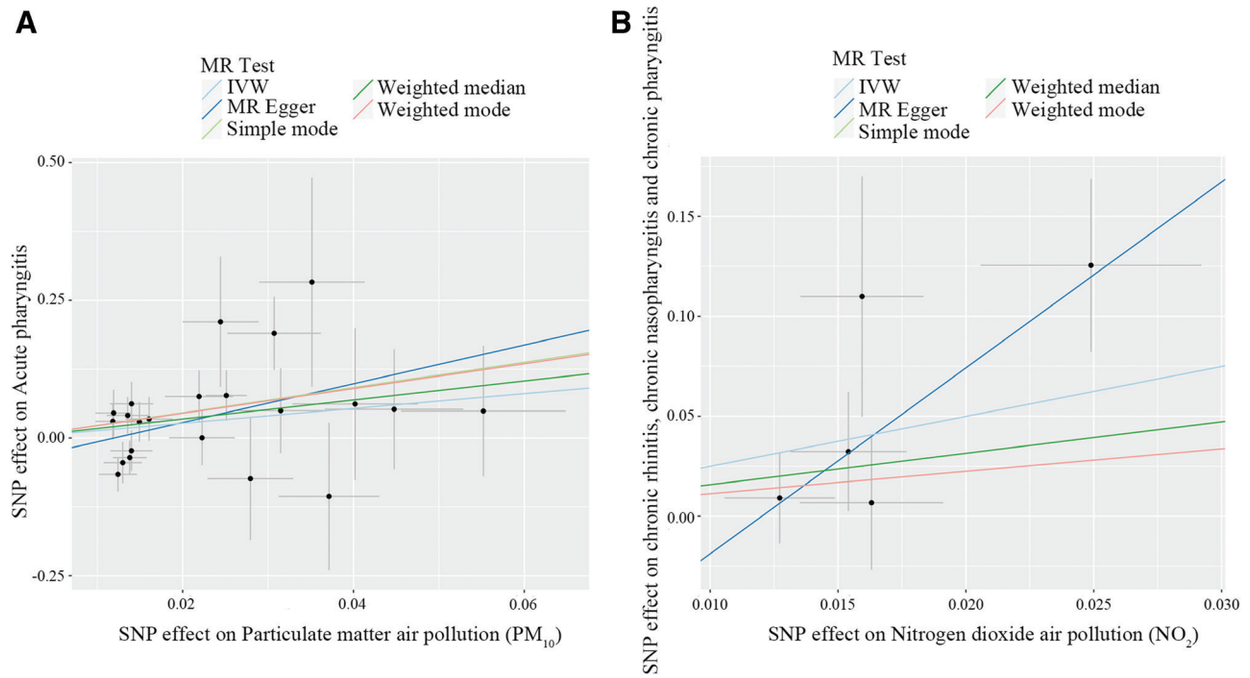

Fig. 1 Assessments regarding the impact of air pollutants on upper respiratory tract infections. A, The horizontal axis displays the impact of the SNP and SE on every PM_{10}. The vertical axis displays the impact of the SNP and SE on acute pharyngitis. B, The horizontal axis displays the impact of the SNP and SE on each NO_2. Chronic rhinitis, chronic nasopharyngitis, and chronic pharyngitis are displayed on the vertical axis, indicating the SNP effect and SE. IVW = inverse-variance weighted; MR = Mendelian randomization; NO_2 = nitrogen dioxide; PM_{10} = particulate matter 10; SNP = single-nucleotide polymorphism.

Table 4

Testing for pleiotropy and heterogeneity of air pollutants genetic instrumental variables in GWAS for upper respiratory tract infections

Air pollutants	Testing for pleiotropy			Testing for heterogeneity					
	MR-egger			MR-egger			Inverse variance weighted		
	Intercept	SE	*p*	*Q*	*Q*_df	*p*	*Q*	*Q*_df	*p*
PM_{10}	−0.04	0.03	0.18	27.65	20	0.12	30.32	21	0.09
NO_2	−0.11	0.06	0.18	2.51	3	0.47	5.57	4	0.23

A *p* value of ≥0.05 indicates no significant pleiotropy or heterogeneity.
GWAS = genome-wide association study; MR = Mendelian randomization; NO_2 = nitrogen dioxide; PM_{10} = particulate matter 10.

connection between APs and URTIs. According to the MR theory, human genetic variation is distributed randomly, and these variations must satisfy certain conditions that are not influenced by other factors. This study examined a variety of APs and URTIs, with APs consisting of $PM_{2.5}$, $PM_{2.5\text{-}10}$, PM_{10}, NO_2, and nitrogen oxides (a mixture of NO, NO_2, and N_2O), while URTIs included both acute (acute nasopharyngitis, acute sinusitis, acute pharyngitis, acute laryngitis, tonsillitis, acute epiglottitis) and chronic (chronic sinusitis, chronic laryngitis, chronic rhinitis, nasopharyngitis, pharyngitis) cases. A literature search revealed that researchers have been more inclined to study the relationship between APs and allergic rhinitis or sinusitis and the relationship between other URTIs, such as acute/chronic rhinitis, nasopharyngitis, pharyngitis, laryngitis, tonsillitis, epiglottitis, and APs are relatively less studied. For the first time, in this study, MR analysis was used to investigate the causal connection between APs and URTIs. Two main results were obtained through the analysis. First, PM_{10} and acute pharyngitis exhibited a causal relationship. Second, NO_2 was causally related to chronic rhinitis, chronic nasopharyngitis, and chronic pharyngitis.

We found that the incidence of acute pharyngitis increased with increasing PM_{10} concentration. Previous studies have reported that specific APs may be correlated with the occurrence of acute pharyngitis and secretory otitis media[20]; however, the exact composition of functional contaminants is unclear. Exposure to particulate and gasoline APs can temporarily increase the likelihood of acute URTIs (eg, acute pharyngitis, acute tonsillitis, acute obstructive laryngitis, and epiglottitis) and lower respiratory tract infections.[21] However, there has been no proven causal connection between other APs ($PM_{2.5}$, PM_{10}, NO_2, and N_xO_y) and acute URTIs, or between PM_{10} and chronic URTIs.

Additionally, our research indicated that higher NO_2 levels were closely linked to a greater likelihood of developing chronic rhinitis, chronic nasopharyngitis, and chronic pharyngitis. A study using logistic regression and a general linear model found that the risks for chronic rhinitis, chronic pharyngitis, and throat pain were associated with vehicle exhaust emissions; however, the specific components of exhaust emissions were not described.[22] Studies have shown that exposure to APs ($PM_{2.5}$, PM_{10}, NO_2, N_xO_y, and O_3) may contribute to the pathogenesis of chronic sinusitis.[23,24] However, we did not obtain similar

results in this study. A time series analysis examined the immediate impacts of six atmospheric pollutants ($PM_{2.5}$, PM_{10}, SO_2, NO_2, CO, and O_3) on 62 823 individuals with chronic inflammation of the pharynx. The findings indicated that higher levels of PM_{10}, SO_2, NO_2, and CO were associated with varying degrees of increased outpatient cases with chronic pharyngitis, with males appearing to be more vulnerable.[15] Furthermore, there is no evidence of a direct link between NO_2 exposure and acute URTIs.

For the first time, this study revealed a link between APs and URTIs using MR analysis. However, the present study had a few noteworthy limitations. First, although we analyzed the relationship between various APs and URTIs, the number of patients in some projects was relatively insufficient. Larger datasets yield more persuasive findings when examining causality. Furthermore, this study had a limited scope, and additional long-term studies are necessary to investigate the cause-and-effect relationship between antipsychotics and URTIs. Third, because no GWAS data for O_3, SO_2, CO, or other APs were found, more comprehensive results were not obtained through the analysis. Additionally, this study did not delve deeper into the relationship between APs and URTIs. Finally, the data used for this study pertain exclusively to the European population, which may limit the generalizability of the findings due to the absence of data from other populations and races.

In conclusion, the present study found an exact causal relationship between APs and URTIs; as such, the prevention and control of specific APs may help reduce the occurrence and aggravation of some upper airway diseases.

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APPENDIX A. SUPPLEMENTARY DATA

Supplementary data related to this article can be found at https://links.lww.com/JCMA/A330.

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