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Review Article

Air Pollution and Influenza: A Systematic Review and Meta-Analysis

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Abstract

Background: Influenza is the first infectious disease that implements global monitoring and is one of the major public health issues in the world. Air pollutants have become an important global public health issue, in recent years, and much epidemiological and clinical evidence has shown that air pollutants are associated with respiratory diseases.

Methods: We comprehensively searched articles published up to 15 November 2022 in PubMed, Web of Science, China National Knowledge Infrastructure (CNKI), Database of Chinese sci-tech periodicals, and Wanfang Database. The search strategies were based on keyword combinations related to influenza and air pollutants. The air pollutants included particulate matter ($PM_{2.5}$, PM_{10}), nitrogen dioxide (NO_2), sulfur dioxide (SO_2), carbon monoxide (CO), and ozone (O_3). Meta-analysis was performed using the R programming language (R4.2.1).

Results: A total of 2926 records were identified and 1220 duplicates were excluded. Finally, 19 studies were included in the meta-analysis according to inclusion and exclusion criteria. We observed a significant association between partial air pollutants ($PM_{2.5}$, NO_2, PM_{10} and SO_2) and the incidence risk of influenza. The RRs were 1.0221 (95% CI: 1.0093~1.0352), 1.0395 (95% CI: 1.0131~1.0666), 1.007 (95% CI: 1.0009~1.0132), and 1.0352 (95% CI. 1.0076~1.0635), respectively. However, there was no significant relationship between CO and O_3 exposure and influenza, and the RRs were 1.2272 (95% CI: 0.9253~1.6275) and 1.0045 (95% CI: 0.9930~1.0160), respectively.

Conclusion: Exposure to $PM_{2.5}$, NO_2, PM_{10}, and SO_2 was significantly associated with influenza, which may be risk factors for influenza. The association of CO and O_3 with influenza needs further investigation.

Keywords: Influenza-like illness; Air pollutants; Meta-analysis

Introduction

Influenza is an acute respiratory tract infectious disease caused by infecting influenza viruses, with high incidence, strong infectivity, and rapid transmission (1). Influenza-like illness (ILI) is a symptom monitoring case that reflects epidemic and flu trends, which is important for preventing and controlling flu (2). Influenza is the first infectious disease that implements global monitoring and is one of the major public health issues in the world (3). Due to its high infectivity and high incidence, influenza has a great negative influence on human health. It can lead to serious complications such as pneumonia, and may even cause respiratory death (4).

Air pollutants have become an important global public health issue, in recent years, and a large amount of epidemiological and clinical evidence has shown that air pollutants are associated with respiratory diseases, and their adverse health effects have been well documented (5). Both brief and prolonged exposure to air pollution raises the risk of morbidity and death from a range of systemic illnesses, which can result in the emergence and spread of influenza (6). Air pollution can increase the incidence risk of influenza, including diagnosis cases (7) and outpatient visits (8). In toxicology studies, there are three possible mechanisms that explain why air pollutants increase the incidence of influenza cases, including inflammatory responses, oxidative stress, and mechanical damage (6). Air pollutants can weaken the body's immunity, make infected people sick, and carry microorganisms directly to infect people (9).

Air pollutants have different relative risks at different lag times, with lag effects (10), and the impact on people of each age is different (11). A study (12) used a generalized additive model to demonstrate that influenza is more likely to occur in young children and the elderly. The occurrence of influenza depends on the season. In both the northern and southern hemispheres, influenza epidemics in temperate regions occur in winter, while seasonal influenza is also evident in tropical regions (13). In Warsaw, Poland, the flu in the temperate zone was more likely to occur in the cold season, especially in winter (4). Although many studies have investigated the relationship between air pollutants and influenza, the results have been inconsistent. In Ningbo, China exposure to O_3 and NO_2 increased the risk of influenza (14). However, Su et al. found a negative association between NO_2 exposure and the incidence risk of influenza and did not observe a significant association of NO_2 with influenza (15). $PM_{2.5}$ could increase cases of clinical Influenza-like illness, and PM_{10} is a protective factor for clinical Influenza-like illness (16). Increased $PM_{2.5}$ concentrations were associated with incident cases of influenza at lag days 2 and 3 (17), but there was no systematic analysis of the association of multiple air pollutants and influenza. Exposure to $PM_{2.5}$ and PM_{10} would increase the mortality and incidence of influenza and pneumonia (18). However, the authors only pooled the estimates of the two original pieces of literature and did not discuss the association of PM_{10} and CO with influenza.

Accordingly, we aimed to explore the association of air pollutants ($PM_{2.5}$, PM_{10}, NO_2, SO_2, CO, and O_3) with influenza or ILI.

Materials and Methods

The protocol for this review was submitted to the international prospective register of systematic reviews (PROSPERO) under the trial registration number CRD42023384355. We followed the reporting protocol for systematic reviews of Observational studies: Meta-analysis of Observational Studies in Epidemiology (MOOSE guidelines).

Search strategy

We hand-searched PubMed, Web of Science, China National Knowledge Infrastructure (CNKI), Database of Chinese sci-tech periodicals, and Wanfang Database. To find the literature on the association of air pollutants with influenza or influenza-like illness up to November 15, 2022. The search terms were "influenza", "influenza-like disease", "air pollutant", "air quality", "air pollution", "particulate matter", "fine particulate", "nitrogen dioxide", "ozone", "sulfur dioxide", "carbon monoxide". The search strategy for each database is shown in the Supplementary Table.

Literature screening
Inclusion criteria
1) The original literature explored the association between air pollutants and the incidence of influenza or influenza-like illness.
2) The studies included were original studies published in peer-reviewed journals.
3) Studies report at least one relative or cumulative relative risk of air pollutants and influenza with a 95% confidence interval (sufficient data to pool the estimates).
4) The original study reported a lag day for the effect of air pollutants on influenza.

Exclusion criteria
1) Excluded reviews, commentaries, case reports, or editorials.
2) Excluded duplicate publications, duplicate inclusion, or low-quality literature.
3) Excluded animal experiments.
4) Excluded literature that did not report sample size.

Data extraction and quality evaluation
Two investigators extracted the following data from each included study independently: lead author, publication year, study areas, research period, sample size, gender, age, climatic zone, research methods, increase in air pollutant concentration, air pollutant type, study results, and lag days. RR and 95% CI were used to measure the association between air pollutants and influenza. All the estimates were pooled for an increase in air pollutant concentration. The results of the single-pollutant model were included first, if there were no single-pollutant mode results, the results of the two-pollutant models were included. We first included risk estimates with the single lag day otherwise, we included estimates of an average lag day (19). The quality of the included studies was evaluated concerning The Newcastle-Ottawa Quality Assessment Form. For each study, two investigators independently extracted the information. If there were any conflicts, they were adjudicated through discussion or consultation with a third investigator.

Statistical methods
The meta-analysis was performed using R4.2.1 to pool the estimates (RR and 95% CI) for associations between air pollution and the incidence of influenza in 19 studies included. A chi square-based Q test and I^2 test were used to assess the heterogeneity of included studies. Unless otherwise noted, all *p*-values less than 0.05 was considered statistically significant. If there was little heterogeneity among studies ($I^2 \leq 50\%$, $P \geq 0.05$), the fixed-effect model was adopted. If there was statistically significant ($I^2 > 50\%$, $P<0.05$), the random effects model was applied. If the heterogeneity is too large, subgroup analysis and sensitivity analysis should be performed to determine the robustness. Sensitivity analysis was used to determine the robustness and reliability of the outcome of statistical analysis (20). Publication bias was assessed using Egger's test (21). If there is publication bias, trim scores and fill methods are used to correct the asymmetry.
In the included studies, if the estimate was attributable risk percent (AR%) or excess risk (ER), the estimate was converted to relative risk (RR). Conversion formula:
AR%=（RR-1）×100% (22)
ER =（RR-1）×100% (23)

Results

Features of the included literature
The flow of literature retrieval is shown in Fig. 1. A total of 2926 records, including 617 Chinese databases, 2,309 English databases, 1220 repetitions, 134 full-text readings, and finally 19 studies for meta-analysis.

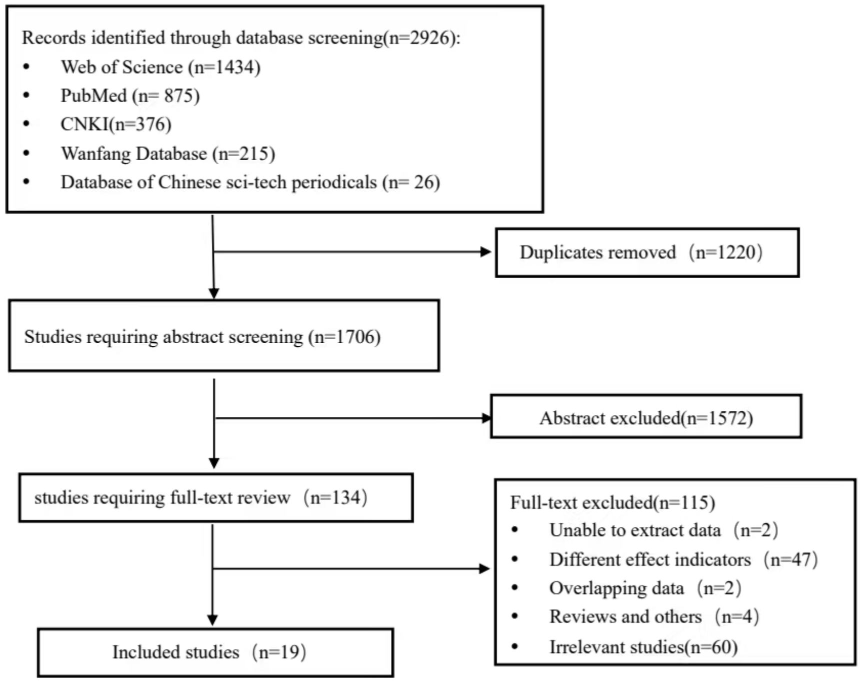

Fig. 1: Literature Screening Flow Chart

The publication year of the included studies was 2017 to 2022, from China, Singapore, and Poland, involving 17 regions (Table 1). The included studies had different sample sizes and subject characteristics. The average daily number of cases in Fan et al. 's (3) study was only 0.3, compared with 704 in a study from Hefei, China (16). The generalized additive model method was used in 9 studies (3,4,7,8,9,15,16,27,28), the distributed lag non-linear model method was used in 7 studies (10,11,14,22,23,25,26). The remaining three studies each used a Bayesian spatiotemporal hierarchical model (24), multivariable fractional polynomials model (5), and generalize linear model (1). Eleven regions were sub-tropical, seven were temperate, and one study was from the tropics. Almost all studies that report seasons indicate that the influenza season is in the winter. The air pollutants included were $PM_{2.5}$, PM_{10}, NO_2, SO_2, CO, O_3. Details of the six air pollutants are shown in the Supplementary Table.

Meta-analysis of air pollution exposure and influenza

The between-study heterogeneity I^2 values of $PM_{2.5}$, PM_{10}, NO_2, SO_2, CO, and O_3 exposure were 98.1%, 95.8%, 94.3%, 95.4%, 99.2%, and 85.1%, respectively, all of which were significant heterogeneity, and the Cochran's Q of each air pollutant was larger, so a random-effects model was used to pool the estimates (Table 2). The pooled RRs of influenza incidence for $PM_{2.5}$, PM_{10}, NO_2 and SO_2 were 1.0221 (95% CI: 1.0093~1.0352), 1.0070 (95% CI: 1.0009~1.0132), 1.0395 (95% CI: 1.0131~1.0666), 1.0332 (95% CI: 1.0076~1.0635), all the statistically significant results ($P<0.05$). There was no significant association of exposure to CO and O_3 with influenza incidence (Table 2). Forest plots of the association between air pollutants and influenza are shown in Fig. 2.

Table 1: Basic information of the included study

Study ID	*Location*	*No.*	*Method*	*Climatic zone*	*Epidemic season*	*Time*[a]	*Effect indicators*
Lindner-Cendrowska K (4)	Warsaw, Poland	19	GAM	Temperate zone	Winter	Jan,2013~Dec,2018	RR
Zhang R (24)	Guangzhou, China	75	BSTHM	Subtropics	NA	Jan,2013~Dec,2019	RR
Meng Y (9)	Wuhan, China	10	GAM	Subtropics	Winter	2015~2017	RR
Toczylowski k (25)	Bialystok, Poland	135	DLNM	Temperate zone	Winter	Jan,2013~Dec,2019	RR
Su W (15)	Jinan, China	111	GAM	Temperate zone	Winter	Jan,2016~Dec,2017	RR
Liu XX (16)	Hefei, China	704	GAM	Subtropics	NA	Dec,2013 ~Dec,2015	RR
Seah A (5)	Singapore	1.8	MFPM	Tropics	NA	2009~2019	RR
Cao MH (23)	Hefei, China	101	DLNM	Subtropics	Winter	Jan,2014~Dec,2017	ER
Chen Q (7)	Shanghai, China	1.6	GAM	Subtropics	NA	2014 ~2018	AR
Zeng YM (1)	Dongguan, China	306	GLM	Subtropics	NA	Jul,2016 ~Jul,2017	ER
Zeng W (26)	Chongqing, China	8	DLNM	Subtropics	Winter and spring	2013 ~2017	RR
Liao Q (11)	Yichang, China	31	DLNM	Subtropics	NA	Jan,2014~ Dec ,2016	ER
Wang SJ (22)	Ningbo, China	23	DLNM	Subtropics	Winter,spring and summer	Jan,2014~ Dec ,2016	AR
Fan CY (3)	Weicheng	0.3	GAM	Temperate zone	Winter and spring	Jan,2015~ Dec ,2020	RR
Li P (10)	Jining, China	1.4	DLNM	Temperate zone	Winter	Jan,2014~ Dec ,2017	RR
Li X (8)	Beijing, China	31	GAM	Temperate zone	NA	Jan,2015~Mar,2018	RR
Zhao X (27)	Lianyungang, China	166	GAM	Temperate zone	NA	2014~2016	RR
Huang ZF (28)	Shenzhen, China	346	GAM	Subtropics	NA	Jan,2013~ Dec ,2014	RR
Zhang R (14)	Ningbo, China	10	DLNM	Subtropics	Winter and summer	Jan,2014~ Dec ,2017	RR

No. Average daily number of cases, GAM Generalized additive model, DLNM Distributed lag non-linear model, BSTHM Bayesian spatiotemporal hierarchical model, MFPM Multivariable fractional polynomials model, GLM Generalize linear model, RR Relative risk, ER Excess risk， AR Attributable risk， NA Not available, a Time of onset.

Table 2: Forest plots results of the association between air pollutants and influenza

Air pollutants	*No.*	*I^2 (%)*	*Cochran's Q*	*Effects model*	*Pooled RR*	*95%CI*	*Z-value*	*P-value*
$PM_{2.5}$	19	98.1	948.00	Random	1.0221	1.0093~1.0352	3.39	0.0007[a]
PM_{10}	15	95.8	330.44	Random	1.0070	1.0009~1.0132	2.23	0.0255[a]
NO_2	10	94.3	157.11	Random	1.0395	1.0131~1.0666	2.95	0.0031[a]
SO_2	8	95.4	152.56	Random	1.0352	1.0076~1.0635	2.51	0.0119[a]
CO	6	99.2	599.74	Random	1.2272	0.9253~1.6275	1.42	0.1554
O_3	7	85.1	40.38	Random	1.0045	0.9930~1.0160	0.76	0.4449

No. The number of studies.

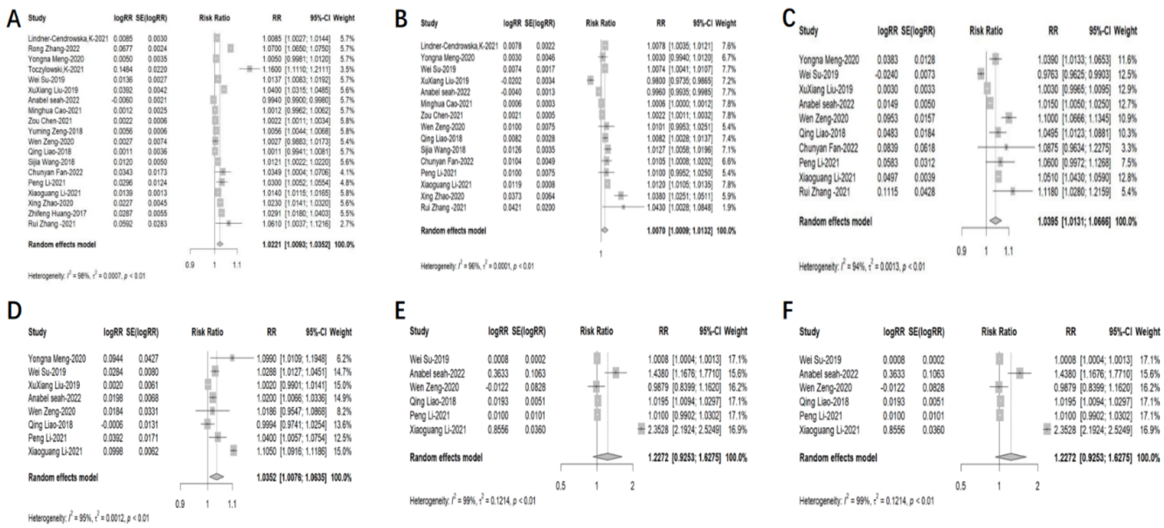

Fig. 2: Forest plots of the association between air pollutants and influenza. A, $PM_{2.5}$. B, PM_{10}. C, NO_2. D, SO_2. E, CO. F, O_3

Subgroup analysis

According to the research methods of the included studies, the age and gender of the research objects, the climatic zone of the study location, increase in air pollutant concentration, and the subgroup was compared to explore the heterogeneity of between-study. The age of research objects were categorized into 0 ~ 4 years old (infants and toddlers), 5 ~ 14 years old (school-age children), 15 ~ 24 years old (adolescents), 25 ~ 59 years old (adults), and ＞60 years old (elderly) subgroups. Because almost all the included studies discussed the association of every 10 ug/m^3 increase in $PM_{2.5}$, PM_{10}, NO_2, SO_2, and O_3 with influenza, this study would focus on the relationship between the concentration change of CO and influenza. Different research methods may lead to between-study heterogeneity. There are five different research methods in the included studies. Three methods, namely the Bayesian spatiotemporal hierarchical model, multivariable fractional polynomials model, and generalized linear model were used in only one included study for each research method, so their heterogeneity cannot be obtained. Therefore, based on the research methods, we categorized them into two subgroups (the generalized additive model and distributed hysterical nonlinear model subgroups).

Categorized into subgroups by age

The results are shown in Supplementary Table 4a. The heterogeneity of exposure to NO_2 and SO_2 was significantly decreased in the 5-14 years subgroups (I^2=0.0%). The pooled RRs for NO_2 and SO_2 were 1.0053 (95% CI: 0.9737~1.0379) and 1.1135 (95% CI: 1.0478~1.1833), respectively, both with statistical differences. In the 15-24 years subgroups, the between-study heterogeneity of O_3 exposure was significantly decreased (I^2=0.0%), and the pooled RR was 1.0033 (95%CI: 0.9943~1.1379). In the 25-59 years subgroups, the pooled RR of influenza incidence was 1.0552 (95% CI: 1.0463~1.0641, P<0.05) for NO_2 and the between-study heterogeneity was significantly decreased (I^2=0.0%). The pooled RR of influenza incidence was 1.0071 (95% CI: 1.0045 ~1.0097, P<0.05) for $PM_{2.5}$ in the >60 years subgroups and the between-study heterogeneity was significantly decreased (I^2=0.0%). The heterogeneity and relative risks of exposure to CO and PM_{10} were not significantly different between age subgroups and non-groups.

Categorized into subgroups by gender

The heterogeneity of $PM_{2.5}$ and PM_{10} exposure was significantly decreased in the female gender subgroup, and the pooled RRs were 1.0055 (95% CI: 1.0024 ~1.0087) and 1.0047 (95% CI: 1.0020 ~1.0075), respectively, using a fixed-effects model, all of which were statistically difference (Supplementary Table 4b). The included studies did not estimate the effects of other air pollutants（NO_2、SO_2、CO and O_3）by gender.

Categorized into subgroups by the climatic zone of the study area

The heterogeneity of exposure to SO_2 was significantly decreased in the subtropical region (I^2=38.8%), and the pooled RR was 1.0035 (P<0.05). The pooled RR of influenza incidence was 1.0194 (95%CI: 1.0094~1.0295), P<0.05) for CO in the subtropical region, and the between-study heterogeneity was significantly decreased (I^2=0.0%). The remaining air pollutants showed no significant decrease in heterogeneity in temperate and subtropical regions. The results are shown in Supplementary Table 4c.

Categorized into subgroups by research methods

The heterogeneity of exposure to NO_2, SO_2, CO, and O_3 was significantly decreased in the DLNM subgroup. And the pooled RRs of influenza incidence were 1.0786, 1.0146, 1.0175, and 1.0155, respectively, all of which were statistically different. The heterogeneity and relative risks of exposure to $PM_{2.5}$ and PM_{10} showed no significant difference (Supplementary Table 4d).

Categorized into subgroups by the change in pollutant concentration

We did not find the between-study heterogeneity for every 0.1 mg/m^3 increase in CO (I^2=0.0%) and the RR of influenza incidence for CO was 1.0176 (95% CI: 1.0086~1.0266, P<0.05) (Supplementary Table 4e). The subgroup analysis of other air pollutants is shown in Supplementary Table 4f.

Sensitivity Analysis and Publication bias

Sensitivity analysis using the leave-one-out method was performed to estimate the stability of results, with one study excluded in turn and pooling the estimates for the remaining study (n-1). The sensitivity analyses showed that the pooled estimates were generally robust, except for the associations between SO_2 and influenza.

Egger's test was used to examine publication bias. The results of Egger's test showed that there was little evidence of significant publication bias for all the meta-analyses (Table 3).

Table 3: Egger's test results

Air pollutants	*t-value*	*P-value*
$PM_{2.5}$	1.91	0.0736
PM_{10}	1.27	0.2261
NO_2	0.89	0.3989
SO_2	-0.15	0.8879
CO	1.44	0.2234
O_3	0.33	0.7573

Discussion

This study found that an increase of 10 ug/m^3 in $PM_{2.5}$, NO_2 and SO_2 could increase the risk of influenza by 2.17%, 3.14% and 4.12%, respectively. And an increase of 0.1mg/m^3 in CO could increase the risk of influenza by 1.76%. Although PM_{10} per 10 ug/m^3 increased the number of influenza cases, it did not reach the statistical threshold. Nor did we see a significant correlation between O_3 and influenza. The sensitivity analysis revealed that the pooled estimates were generally robust except for the associations between SO_2 and influenza.

Several studies have shown that PM_{10} is associated with the risk of developing influenza. $PM_{2.5}$ was significantly associated with the risk of ILI (29). This is consistent with our research. With the expression of antibacterial peptides (AMPs), this may inhibit respiratory antibacterial activity, damage to respiratory pathogenic immune defense, and ultimately promote pathogen intrusion and increase the susceptibility to respiratory infection (30). We found that exposure to $PM_{2.5}$ has the most significant effect in the 0-14 years subgroup. Huang et al. (28) showed a significant association between influenza-like cases and $PM_{2.5}$ exposure in those under 15 years of age. This may be because children tend to spend more time playing outdoors (12).

SO_2 and NO_2 are other air pollutants associated with the risk of influenza. Li et al. (8) observed a significant association of every 0.1ug/m^3 increase of $PM_{2.5}$ at 0-day lag and SO_2 and NO_2 at 1-day lag with the increased outpatient visiting rate of influenza-like diseases, which was consistent with the results of our study. NO_2 may increase the susceptibility of exposure to NO_2 respiratory virus, so these groups are more likely to be infected than those who breathe clean air (31). Due to its high solubility, SO_2 is mostly absorbed in the upper respiratory tract, thus reducing human immunity (32). A study on the effects of air pollutants on occurrences of influenza-like illness and laboratory-confirmed influenza showed that exposure to SO_2 and NO_2 is not significantly associated with the incidence risk of influenza-like diseases (16). People of different ages have different sensitivities to each air pollutant (11). The results of our study showed that NO_2 was significantly associated with the incidence of influenza in the 25-59 years subgroup. This may be because the 25-59 age group is the dominant working population and they spend more time outdoors than younger and older people, thus increasing the incidence of exposure to air pollutants (15). Exposure to SO_2 has the statistical significance for the effect of influenza in the population aged 5-14 years, but not in other age groups. This result is in general accord with the findings of Liao with her research team who found that exposure to SO_2 was associated with the incidence of influenza in the age group of 5 to 14 years in an age-stratified analysis (11). The reason for this may be that adolescents aged 5 to 14, who do not have heavy schoolwork and spend more time outdoors, are more susceptible to atmospheric pollutants. They are more likely to be exposed to influenza viruses, so transmit them.

This study showed that every 0.1mg/m^3 of CO increased the risk of influenza by 1.76%. A study conducted in Yi Chang, China has shown that every 0.1mg/m^3 increase in CO was significantly associated with an increased incidence of influenza (11), which was in general agreement with our study. However, Li et al. (10) did not observe a significant relationship between every 0.1 ug/m^3 increment of CO and influenza, which might be related to regional differences and population specificity. When CO enters the human respiratory tract, CO will form a competitive relationship with O_2, which will prevent the delivery of oxygen in the body, thus reducing the resistance to influenza virus (6). However, when we pooled the results of all included original studies and did not stratify by the change in pollutant concentration, the significant association between CO and influenza risk disappeared. Therefore, the association between CO and influenza risk should be interpreted with caution.

Our study showed that air pollutants were significantly associated with increased influenza cases in the female population. A study of the burden of air pollution on years of life also confirmed that air pollution has a higher effect on women than men (33). Women's lungs and airway diameters are small, so these may increase airway reactivity and exacerbate the deposition of particulate matter (34). The male population is more sensitive to $PM_{2.5}$ and PM_{10}, but there was no statistical difference in sensitivity for influenza between the genders (14). There was no significant difference between air pollutants and the incidence risk of influenza in gender stratification analysis (3). In temperate regions, influenza is more likely to occur in winter. The incidence of influenza-like illness was highest in winter in Warsaw, Poland (4). The impact of air pollution on influenza is greater in the cold season than in the warm season, and the peak of the influenza incidence is more obvious in winter (9). Low temperatures increased the incidence of influenza-like disease (35), which might be due to the cold season improving the survival rate of influenza viruses in the environment and increasing the sensitivity of the host (36). Our study found that the heterogeneity of air pollutants and influenza incidence was significantly decreased in the distributed lag non-linear model subgroup.

The relationship between air pollutants and influenza incidence is nonlinear and has a lag effect (22, 26). Therefore, the distributed lag non-linear model is more advantageous than other models to analyze the association between air pollutants and the influence of influenza. Linear analysis is inadequate in describing the complex relationships between weather, air pollution, and respiratory infections (25). If the generalized additive model is used to simulate environmental exposure, although it can fit the potential non-linear relationships between environmental factors and the incidence of influenza (37), the lag effect is not taken into account. While the distributed lag non-linear model series can represent not only the nonlinear expose-response dependence but also the modeling framework of the delay effect (38).

To sum up, the existence of air pollutants will directly or indirectly affect the respiratory tract, reduce human immunity, and then aggravate lung diseases including influenza.

Conclusion

Influenza is still a serious problem in our society and presents a serious risk to human health and life to human life and health. By combining inconsistent results from several original studies, this study reveals an association between air pollutants and influenza, particularly $PM_{2.5}$, NO_2, and SO_2. The above-mentioned related findings suggest that air pollutants may be an important risk factor in influenza incidence. It is recommended that the relevant departments should strengthen local atmospheric pollutant concentration and influenza monitoring when formulating influenza prevention and control measures.

Journalism Ethics considerations

Ethical issues (Including plagiarism, informed consent, misconduct, data fabrication and/or falsification, double publication and/or submission, redundancy, etc.) have been completely observed by the authors.

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Conflicts of interest

The authors declare that they have no conflicts of interest.

Data availability

No supplementary materials in this paper were published. Respected readers may contact the corresponding authors for accessing, if needed.

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