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Article

Composition-Specific Effects of PM_{2.5} on Influenza-Like Illness: Independent Roles of Chemical Components and Mixture Profiles in a Multi-City Study

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Abstract

Background Short-term exposure to PM_{2.5} has been associated with respiratory infections, yet evidence on the health effects of its chemical components remains limited. Moreover, as PM_{2.5} components coexist as complex mixtures, it is unclear whether differences in compositional profiles contribute additional influenza-like illness (ILI) risk beyond the independent effects of individual components. **Methods** We analyzed weekly ILI surveillance data from 111 sentinel hospitals in 17 cities of Hubei, China (2021-2024), together with weekly PM_{2.5} concentrations and chemical components (sulfate, nitrate, ammonium, organic matter, and black carbon) from the TAP dataset and meteorological variables from ERA5-Land. To evaluate the associations of individual PM_{2.5} components and overall compositional profiles with ILI, we applied K-means clustering to identify distinct PM_{2.5} profiles and fitted city-specific quasi-Poisson models, which were then pooled using DerSimonian-Laird method. **Results** Among 2,804,416 ILI cases, PM_{2.5} mass was positively associated with weekly ILI, with a pooled RR of 1.041 (95% CI: 1.028-1.054) per 10 µg/m³ increase. Positive associations were also observed for sulfate, nitrate, ammonium, OM, and BC. Three compositional profiles were identified (SID: secondary inorganic-dominated, MOD: mixed organic-dominated; ORM: Other-rich mixed). After adjustment for PM_{2.5} and its component concentrations, exposure to ORM was associated with an extra 19.6% higher ILI risk than SID (RR = 1.196, 95% CI: 1.096-1.305), while exposure to the MOD was associated with an 8.9% higher ILI risk (RR = 1.089, 95% CI: 1.008-1.176). **Conclusions** These findings suggest that PM_{2.5} related ILI risk may depend not only on overall mass concentration and individual components, but also on compositional profiles. Incorporating PM_{2.5} mixture heterogeneity may improve assessment of air pollution related respiratory health risks.

Keywords: fine particulate matter; chemical component; air pollution; influenza

Introduction

Rapid industrialization and urbanization in China have heightened concerns about air quality, particularly regarding health risks from fine particulate matter (PM_{2.5}), ozone (O₃), and other pollutants [1]. As air pollution continues to worsen, it has increasingly severe impacts on respiratory health [2]. Numerous studies have demonstrated strong associations between air pollution and both

the incidence and mortality of respiratory diseases, including chronic obstructive pulmonary disease (COPD), asthma, and lung cancer [3–6]. Among major air pollutants, PM_{2.5} is recognized as a critical factor, contributing to chronic respiratory conditions while also to infectious respiratory diseases [1,2].

Although pathogenic agents have traditionally been considered the primary cause of respiratory infections, growing evidence indicates that PM_{2.5} significantly increases infection risks [7–9]. PM_{2.5} exposure may enhance respiratory infection risk by impairing airway defenses, increasing host vulnerability, and facilitating viral persistence in the environment [10,11]. Several studies from China and Europe have reported positive associations between PM_{2.5} exposure and the incidence of acute respiratory infections [7–9,12–15]. Nevertheless, findings across regions remain inconsistent. For example, significant positive associations have been consistently observed in many northern Chinese cities, whereas studies conducted in southern regions have often reported weak or non-significant associations between PM_{2.5} concentrations and respiratory infections [7,16,17].

These discrepancies may be explained by local climatic conditions and demographic characteristics. Climatic conditions can modify the effects of PM_{2.5}, as lower temperatures and higher humidity have been reported to strengthen the association between air pollution and respiratory infection risk [7,18]. In northern China, more frequent cold spells during winter may further amplify these effects. Additionally, regional differences in heating practices and ventilation patterns may influence exposure, as enclosed or poorly ventilated indoor environments (always in northern China) can increase pollutant accumulation and potential contact with airborne pathogens.

Moreover, PM_{2.5} exposure characteristics vary substantially across regions because PM_{2.5} is not a homogeneous pollutant but a chemically complex mixture shaped by local emission sources and atmospheric transformation processes. In northern China, PM_{2.5} is strongly influenced by residential coal combustion, industrial emissions, and biomass burning during the heating season, resulting in elevated levels of elemental carbon, SO₂, and NO_x, which further contribute to the formation of secondary inorganic aerosols such as sulfate, nitrate, and ammonium [19]. These components have been linked to enhanced oxidative stress, airway inflammation, and impaired immune defense, thereby increasing susceptibility to respiratory infections. In contrast, PM_{2.5} in southern regions is more frequently associated with secondary aerosol formation and industrial emissions, often exhibiting distinct chemical profiles and source mixtures. Such regional heterogeneity suggests that equal PM_{2.5} mass concentrations may not necessarily correspond to equal biological toxicity.

However, most previous epidemiological studies have primarily focused on the overall effects of PM_{2.5} mass concentration, while relatively few have evaluated the associations between PM_{2.5} components and ILI. More importantly, PM_{2.5} components coexist within complex mixtures rather than acting independently. Different compositional structures may alter the overall toxicity of PM_{2.5} even at similar component concentrations, potentially leading to synergistic or interactive effects beyond the independent effects of individual components alone [20,21]. Nevertheless, whether variations in PM_{2.5} compositional profiles can further modify the association between PM_{2.5} exposure and ILI risk remains largely unclear.

Hubei Province, located in central China, has a population of nearly 60 million and spans over 180,000 km². Its low-lying terrain and monsoon-influenced climate, combined with frequent autumn and winter temperature inversions, favor the accumulation of PM_{2.5}. Moreover, situated at the transition between northern and southern China, Hubei exhibits substantial spatial heterogeneity in PM_{2.5} sources and pollution characteristics, including industrial emissions, vehicle exhaust, and biomass burning. Thus, investigating the chemical composition and health impacts of PM_{2.5} is crucial for source apportionment and for accurately assessing regional pollution-related health risks.

Therefore, using data from the Influenza Surveillance Sentinel System in Hubei Province, this study aimed to investigate the associations between PM_{2.5} chemical components and ILI incidence, and to determine whether the association between PM_{2.5} exposure and ILI varies across different PM_{2.5} compositional profiles beyond individual component concentrations. We further examined whether these associations remained stable under different meteorological conditions.

Methods

Data Sources and Study Population

Data were obtained from the Influenza Surveillance Sentinel System of the Hubei Provincial Center for Disease Control and Prevention, from January, 2021 to December, 2024. The system covers 88 administrative districts and counties and includes 117 healthcare institutions. The number of weekly ILI cases was extracted from the medical information systems of participating institutions by the surveillance system. All cases were clinically confirmed by physicians and met the standard case definition for influenza-like illness (ILI), defined as a body temperature $\geq 38^\circ\text{C}$ accompanied by cough or sore throat [8]. Finally, 111 sentinel hospitals in 86 districts/counties were included in this study, covering all 17 cities in Hubei (**Figure 1**).

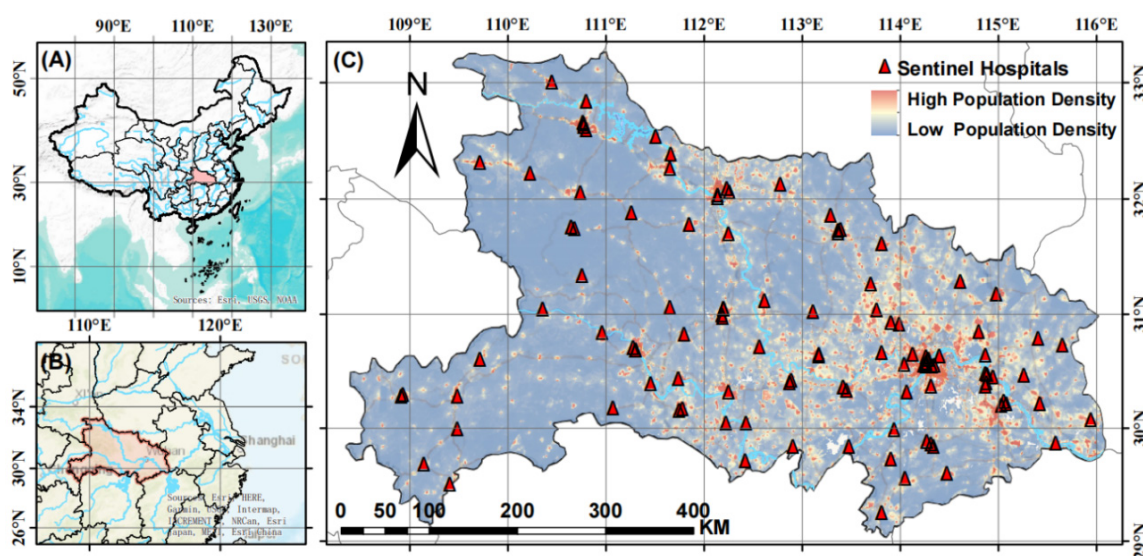


Figure 1. Location of Hubei province in China and distribution of sentinel hospitals and population density in Hubei. Panel (A) and (B) shows the location of Hubei province within China. Panel (C) displays the distribution of 111 sentinel hospitals.

Daily concentrations of $\text{PM}_{2.5}$ and its constituents, including sulfate (SO_4^{2-}), nitrate (NO_3^-), ammonium (NH_4^+), organic matter (OM), and black carbon (BC) were obtained from Tracking Air Pollution (TAP, <http://tapdata.org.cn/>), a dataset developed by integrating multi-source monitoring data and applying standardized quality control processes to ensure reliability [22,23]. Daily relative humidity and temperature was derived from the land component of the 5th generation of the European reanalysis (ERA5-Land) dataset [24]. Subsequently, weekly average concentrations of $\text{PM}_{2.5}$ and its chemical components, as well as weekly average meteorological variables, were calculated to characterize short-term exposure levels.

This study was approved by the Ethics Committee of Wuhan Children's Hospital (IRB No.: 2025R086-E01). Retrospective surveillance data from the healthcare system were used for the analysis, and the requirement for informed consent from individual patients was waived in accordance with this ethical approval.

Statistical Analysis

To examine the short-term associations between ambient $\text{PM}_{2.5}$ exposure, its chemical components, $\text{PM}_{2.5}$ compositional profiles, and ILI risk, we applied a two-stage time-series analytical framework. In the first stage, city-specific quasi-Poisson regression models were fitted to estimate the relative risks (RRs) of weekly ILI counts associated with $\text{PM}_{2.5}$, individual chemical components, and $\text{PM}_{2.5}$ compositional profiles. The general model was specified as follows:

$$Y_{c,w} \sim \text{QuasiPoisson}(\mu_{c,w})$$

$$\log(\mu_{c,w}) = \alpha_c + \beta_1 X_{c,w} + ns(\text{Meteo}_{c,w,v}, 3) + ns(\text{Time}_w, 16)$$

where $Y_{c,w}$ denotes the daily number of ILI cases in city c on week w , $X_{c,w}$ represents the average exposure to PM_{2.5} or its chemical component during the week w , $ns(\text{Meteo}_{c,w,v}, 3)$ denotes natural cubic spline functions of weekly average meteorological variables v , including air temperature, relative humidity, vapour pressure, and wind speed. $ns(\text{Time}_w, 16)$ represents a natural cubic spline function of calendar time, which was used to control for long-term trends and seasonality. In the second stage, RRs were pooled using DerSimonian-Laird random-effects meta-analysis. Heterogeneity across cities was quantified using I^2 and τ^2 statistics, with I^2 values all below 1%, indicating low between-city variability (**Supplementary Figures S3**).

To characterize PM_{2.5} compositional profiles, we performed cluster analysis. The relative abundance of each component was calculated by dividing the component concentration by total PM_{2.5}. Because relative abundances are compositional data constrained to sum to 1, we applied a centered log-ratio (CLR) transformation prior to clustering. K-means clustering was performed on the transformed data with 10 random starts, and the optimal number of clusters ($k=3$) was selected based on the elbow and silhouette methods (**Supplementary Figures S1 and S2**). The optimal number of clusters was evaluated using the elbow method and silhouette scores. Based on this assessment, three clusters were selected as optimal. Based on this combined assessment, three clusters were selected as optimal. Detailed clustering procedures are provided in the Supplementary Materials.

To evaluate whether distinct PM_{2.5} compositional profiles were associated with additional ILI risk beyond overall PM_{2.5} mass concentration and component variation, profile indicators were further included in the models. Because major PM_{2.5} components were highly correlated, PCA was applied to reduce multicollinearity. We retained the first two principal components, which together explained over 90% of the total variance, along with total PM_{2.5} concentration, as covariates in the profile models. The general model was specified as follows:

$$\log(\mu_{c,w}) = \alpha_c + \beta_2 \text{Profile}_{c,w} + ns(\text{Meteo}_{c,w,v}, 3) + \gamma_2 PC_{d,c,w} + \gamma_3 PM2.5_{c,w} + ns(\text{Time}_w, 16)$$

where $\text{Profile}_{c,w}$ represents the PM_{2.5} compositional profile, $PM2.5_{c,w}$ represents the weekly PM_{2.5} concentration, and $PC_{d,c,w}$ denotes the retained principal components derived from PM_{2.5} component concentrations using PCA.

We further conducted stratified analyses to examine whether meteorological conditions modified the associations between PM_{2.5} components, compositional profiles, and ILI risk. Weekly average temperature, relative humidity, vapour pressure, and wind speed were each divided into tertiles and categorized as low, moderate, and high levels. The profile models were then repeated within each stratum, while adjusting for the remaining meteorological variables. All statistical analyses were conducted using R software. Statistical significance was assessed using two-sided tests, with a P value <0.05 considered statistically significant.

Results

A total of 2,804,416 ILI cases were included, of which 1,009,629 (36.0%) were aged 0-4 years, 812,959 (29.0%) were aged 5-14 years, and 981,828 (35.0%) were aged ≥ 15 years. Geographically, 790,338 cases (28.2%) were from western Hubei, 573,671 (20.5%) from central Hubei, and 1,440,407 (51.4%) from eastern Hubei. By year, 458,816 (16.4%) cases occurred in 2021, 641,741 (22.9%) in 2022, 857,813 (30.6%) in 2023, and 846,046 (30.2%) in 2024. Seasonally, 761,028 (27.1%) cases occurred in spring, 676,720 (24.1%) in summer, 508,441 (18.1%) in fall, and 858,227 (30.6%) in winter. (**Table 1**)

Figure 2 shows the pooled associations of PM_{2.5}, its chemical components, and PM_{2.5} compositional profiles with weekly ILI counts. PM_{2.5} mass concentration was positively associated with ILI, with a pooled RR of 1.041 (95% CI: 1.028-1.054) per 10 $\mu\text{g}/\text{m}^3$ increase. Positive associations were also observed for all examined PM_{2.5} components, with pooled RRs of 1.195 (95% CI: 1.122-1.273)

for SO_4^{2-} , 1.110 (95% CI: 1.059-1.164) for NO_3^- , 1.178 (95% CI: 1.100-1.262) for NH_4^+ , 1.155 (95% CI: 1.086-1.229) for OM, and 1.090 (95% CI: 1.057-1.123) for BC.

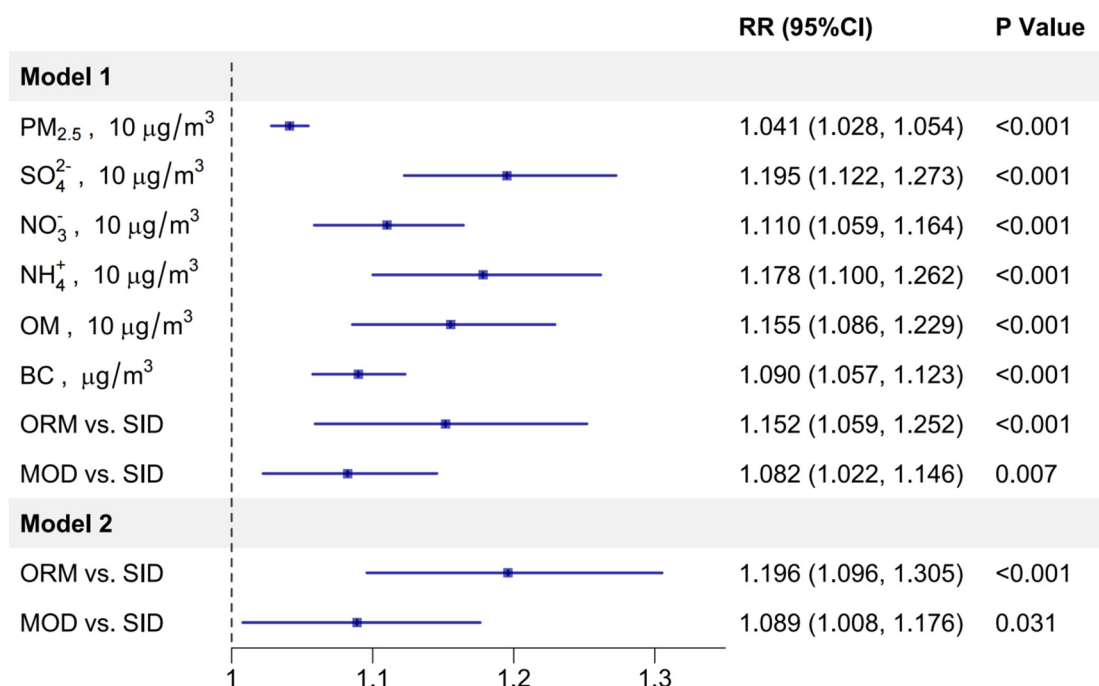


Figure 2. Relative risks (RRs) and 95% confidence intervals (CIs) for influenza-like illness (ILI) associated with PM_{2.5}, its major chemical components, and PM_{2.5} compositional profiles. Model 1 represents single-pollutant models for PM_{2.5}, individual components, and compositional profiles. Model 2 evaluated the additional effects of PM_{2.5} compositional profiles after adjustment for total PM_{2.5} concentration and PCA-derived component variation. SID was used as the reference compositional profile. ORM, other rich mixture; MOD, mixed organic-dominant mixture; SID, secondary inorganic-dominant mixture.

Table 1. Distribution of reported influenza like illness cases during 2021-2024 by age group, region, time in Hubei, China.

	Total	Age 0-4	Age 5-14	Age 15-24	Age 25-59	Age 60+
Total	2,804,416	1,009,629 (36.00%)	812,959 (28.99%)	247,892 (8.84%)	506,414 (18.06%)	227,522 (8.11%)
Area						
West	790,338	335,673 (42.47%)	240,581 (30.44%)	61,935 (7.84%)	108,083 (13.68%)	44,066 (5.58%)
Middle	573,671	193,734 (33.77%)	163,128 (28.44%)	58,067 (10.12%)	100,117 (17.45%)	58,625 (10.22%)
East	1,440,407	480,222 (33.34%)	409,250 (28.41%)	127,890 (8.88%)	298,214 (20.70%)	124,831 (8.67%)
Year						
2021	458,816	216,652 (47.22%)	110,750 (24.14%)	34,431 (7.50%)	73,091 (15.93%)	23,892 (5.21%)
2022	641,741	224,637 (35.00%)	151,292 (23.58%)	60,488 (9.43%)	144,588 (22.53%)	60,736 (9.46%)
2023	857,813	274,193 (31.96%)	283,854 (33.09%)	93,575 (10.91%)	137,656 (16.05%)	68,535 (7.99%)
2024	846,046	294,147 (34.77%)	267,063 (31.57%)	59,398 (7.02%)	151,079 (17.86%)	74,359 (8.79%)
Season						
Spring	761,028	282,204 (37.08%)	225,669 (29.65%)	70,511 (9.27%)	120,503 (15.83%)	62,141 (8.17%)
Summer	676,720	285,940 (42.25%)	173,571 (25.65%)	41,440 (6.12%)	119,179 (17.61%)	56,590 (8.36%)
Fall	508,441	201,268 (39.59%)	151,361 (29.77%)	42,641 (8.39%)	76,546 (15.06%)	36,625 (7.20%)
Winter	858,227	240,217 (27.99%)	262,358 (30.57%)	93,300 (10.87%)	190,186 (22.16%)	72,166 (8.41%)

Note: The sum of proportions may not equal 100% due to the use of rounding-off method.

Based on the relative abundances of PM_{2.5} chemical components, K-means clustering identified three distinct PM_{2.5} compositional profiles characterized by different chemical component patterns (**Supple. Figure S1 and S2**). The first profile was dominated by secondary inorganic aerosols, including SO₄²⁻, NO₃⁻, and NH₄⁺, and was classified as the secondary inorganic-dominant (SID) profile. The second profile exhibited relatively high contributions from residual (“Other”) components, representing a chemically mixed pattern, and was classified as the other-rich mixed (ORM) profile. The third profile showed the highest proportion of OM along with mixed contributions from BC and other components and was classified as the mixed organic-dominated (MOD) profile.

In model 1, when PM_{2.5} compositional profiles were examined without additional adjustment for PM_{2.5} concentration or principal components, both ORM and MOD profiles were associated with higher ILI risk compared with the SID profile. The pooled RR was 1.152 (95% CI: 1.059-1.252) for ORM versus SID and 1.082 (95% CI: 1.022-1.146) for MOD versus SID. In model 2, after further adjustment for total PM_{2.5} and its components concentration concentrations, the associations remained statistically significant. Compared with the SID profile, the ORM profile was associated with a 19.6% higher ILI risk (RR: 1.196, 95% CI: 1.096-1.305), while the MOD profile was associated with an 8.9% higher ILI risk (RR: 1.089, 95% CI: 1.008-1.176).

Figure 3 presents the stratified associations between PM_{2.5} compositional profiles and weekly ILI counts under different meteorological conditions. For ORM v.s. SID, stronger positive associations were observed in the low-temperature stratum (RR: 1.342, 95% CI: 1.160-1.552), low-humidity stratum (RR: 1.471, 95% CI: 1.183-1.828), low-vapour-pressure stratum (RR: 1.304, 95% CI: 1.138-1.495), and high-wind-speed stratum (RR: 1.462, 95% CI: 1.274-1.678). By contrast, the corresponding associations were not statistically significant in the medium or high strata of temperature and vapour pressure.

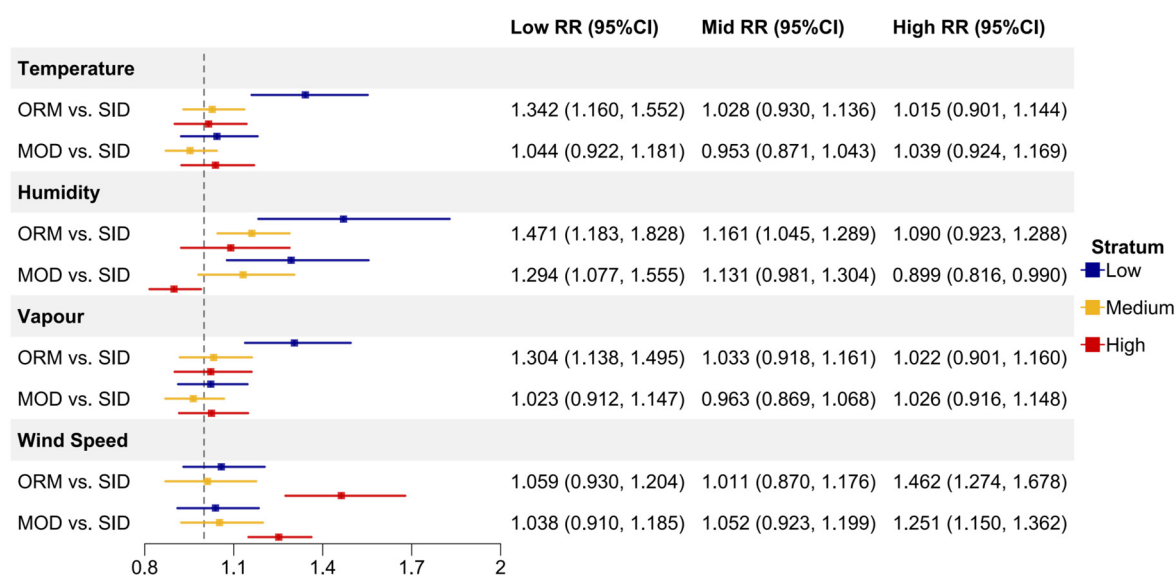


Figure 3. Relative risks (RRs) and 95% confidence intervals (CIs) for influenza-like illness (ILI) associated with PM_{2.5} compositional profiles across tertiles of temperature, humidity, vapour pressure, and wind speed. Estimates were derived from Model 2. SID was used as the reference compositional profile. ORM, other rich mixture; MOD, mixed organic-dominant mixture; SID, secondary inorganic-dominant mixture.

The stratified associations for MOD were less consistent. A positive association was observed in the low-humidity stratum (RR: 1.294, 95% CI: 1.077-1.555) and the high-wind-speed stratum (RR: 1.251, 95% CI: 1.150-1.362). Under high humidity, however, the MOD profile was associated with a lower ILI risk relative to the SID profile (RR: 0.899, 95% CI: 0.816-0.990). No statistically significant associations were observed across temperature strata or vapour-pressure strata for MOD.

Discussions

In this large-scale study in Hubei province, we confirmed that PM_{2.5} exposure was positively associated with ILI risk. Beyond total mass, individual chemical components also contributed to increased risk. Importantly, even after accounting for total PM_{2.5} and major component concentrations, specific PM_{2.5} compositional profiles exerted additional, independent effects. The ORM and MOD profiles were associated with higher ILI incidence compared to the SID profile, with ORM showing the strongest effect. These associations were further amplified under low temperature, low humidity, and high wind conditions, highlighting that the overall chemical composition of PM_{2.5} influences health risk beyond total concentration or individual components.

This study found that PM_{2.5} was significantly associated with an increased risk of ILI, with each 10 µg/m³ increase in PM_{2.5} corresponding to an 4.1% elevation in ILI risk. A multi-city study by Yu et al. involving 82 cities across China also reported a positive association between PM_{2.5} and influenza incidence; specifically, each 10 µg/m³ increase in the 7-day average PM_{2.5} concentration was associated with a 2.4% increase in influenza risk (95% CI: 1.5-3.3%) [7]. These findings suggest that PM_{2.5} may play a role in the occurrence of respiratory infections. Mechanistically, PM_{2.5} not only damages the respiratory system but also significantly affects the lung and immune system [25]. Exposure to PM_{2.5} has been shown to impair antiviral immunity against influenza viruses by inhibiting NLRP3 inflammasome activation and interferon-β expression, thereby weakening innate immune responses and increasing susceptibility to infection [25]. On the other hand, viral droplets could attach to PM_{2.5} mass and stay in the air longer, increasing the chance of being inhaled by humans [26]. In addition, associations were observed between ILI occurrence and major chemical components of PM_{2.5}, with black carbon (BC) exhibiting relatively stronger effect estimates, which was consistent with the findings reported by Liu et al. [26]. Several studies have reported that BC was more harmful than PM_{2.5} [26–28]. One possible explanation is that its ultra fine particle size and porous structure facilitate blood penetration and toxic substance adsorption, inducing sustained oxidative stress and chronic inflammation with irreversible damage [29].

In addition to the associations with total PM_{2.5} and individual constituents, our results show that distinct PM_{2.5} compositional profiles identified through clustering exert independent effects on ILI risk. Even after adjusting for total PM_{2.5} mass and major component concentrations, the ORM and MOD profiles were associated with higher ILI incidence compared to the SID profile. This indicates that compositional characteristics of PM_{2.5} contribute additional risk beyond what can be explained by overall concentration or individual chemical components. The observed excess risk may reflect synergistic or interactive effects among components within these profiles. For instance, ORM and MOD profiles contain higher proportions of organic matter and black carbon, which have been linked to enhanced oxidative stress, airway inflammation, and impaired antiviral immunity [30,31]. These species may also facilitate viral persistence or transport in the air, increasing exposure risk. Notably, the effect of ORM was further amplified under low temperature, low humidity, and high wind speed, consistent with previous findings that meteorological conditions can modulate the toxicity and health impact of PM_{2.5} mixtures [30].

To our knowledge, this study is the first to examine the impact of the relative composition of PM_{2.5} components on health effects. These findings underscore the critical importance of considering not only the total mass of PM_{2.5} but also its chemical composition in evaluating health risks. Moreover, the modulation of component-specific effects by the relative composition of PM_{2.5} highlights the potential for synergistic interactions within particle mixtures, implying that reductions in high-risk components or specific combinations may be more effective than interventions targeting overall PM_{2.5} mass.

This study has some limitations. ILI cases were collected from Influenza Surveillance Sentinel System where only sentinel hospitals were counted. This may affect the reflection of the truest impacts of PM_{2.5} and its major constituents on ILI. Second, the weekly aggregation of exposures and ILI counts may not capture shorter-term effects, finer temporal resolution could provide additional insights. Besides, although we adjusted for PM_{2.5} mass and major component variation using

principal components, the independence of the compositional profile effects cannot be fully guaranteed due to potential residual confounding among individual components.

Supplementary Materials: The following supporting information can be downloaded at the website of this paper posted on Preprints.org.

Author Contributions: Mingzhao Huang, Ying Deng and Xiaolu Zhang contributed to conceptualization, data curation, formal analysis, visualization, writing original draft, writing-review & editing and served as the equally contributing first authors of the manuscript. Yin Li and Yi Yan contributed to methodology, investigation and review & editing. Luli Xu, Xiya Qin, Kai Chen, Xiaoxuan Fan and Xiaofeng Mu contributed to data curation, resources, formal analysis and methodology. Lianting Hu, Wanjun Luo and Xiong Chao contributed to supervision, administration, funding acquisition and review & editing. Xiaoxia Lu contributed to supervision, administration, funding acquisition, resources and review & editing. All authors read and approved the final manuscript.

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Ethic approval and consent to participate: This study did not involve any human subjects, human data, or human materials. Retrospective surveillance data from the healthcare system were used for the analysis; this study was approved by the Ethics Committee of Wuhan Children's Hospital (IRB No.: 2025R086-E01), and the requirement for informed consent from patients was waived in accordance with the ethical approval.

Consent for publication: Not applicable.

Availability of data and materials: The datasets used and analyzed during the current study are available from the corresponding author on reasonable request.

Acknowledgments: Not Applicable.

Competing interests: The authors declare that they have no competing interests.

Generative AI: This paper utilizes Chat-GPT-5-mini exclusively for language refinement, without involvement in any other aspects of content creation.

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