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Air pollution and risk of 32 health conditions: outcome-wide analyses in a population-based prospective cohort in Southwest China

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Abstract

Background Uncertainty remains about the long-term effects of air pollutants (AP) on multiple diseases, especially subtypes of cardiovascular disease (CVD). We aimed to assess the individual and joint associations of fine particulate matter ($PM_{2.5}$), along with its chemical components, nitrogen dioxide (NO_2) and ozone (O_3), with risks of 32 health conditions.

Methods A total of 17,566 participants in Sichuan Province, China, were included in 2018 and followed until 2022, with an average follow-up period of 4.2 years. The concentrations of AP were measured using a machine-learning approach. The Cox proportional hazards model and quantile g-computation were applied to assess the associations between AP and CVD.

Results Per interquartile range (IQR) increase in $PM_{2.5}$ mass, NO_2, O_3, nitrate, ammonium, organic matter (OM), black carbon (BC), chloride, and sulfate were significantly associated with increased risks of various conditions, with hazard ratios (HRs) ranging from 1.06 to 2.48. Exposure to multiple air pollutants was associated with total cardiovascular disease (HR 1.75, 95% confidence intervals (CIs) 1.62–1.89), hypertensive diseases (1.49, 1.38–1.62), cardiac arrests (1.52, 1.30–1.77), arrhythmia (1.76, 1.44–2.15), cerebrovascular diseases (1.86, 1.65–2.10), stroke (1.77, 1.54–2.03), ischemic stroke (1.85, 1.61–2.12), atherosclerosis (1.77, 1.57–1.99), diseases of veins, lymphatic vessels, and lymph nodes (1.32, 1.15–1.51), pneumonia (1.37, 1.16–1.61), inflammatory bowel diseases (1.34, 1.16–1.55), liver diseases (1.59, 1.43–1.77), type 2 diabetes (1.48, 1.26–1.73), lipoprotein metabolism disorders (2.20, 1.96–2.47), purine metabolism disorders (1.61, 1.38–1.88), anemia (1.29, 1.15–1.45), sleep disorders (1.54, 1.33–1.78), renal failure (1.44, 1.21–1.72), kidney stone (1.27, 1.13–1.43), osteoarthritis (2.18, 2.00–2.39), osteoporosis (1.36, 1.14–1.61). OM had max weights for joint effects of AP on many conditions.

Conclusions Long-term exposure to increased levels of multiple air pollutants was associated with risks of multiple health conditions. OM accounted for substantial weight for these increased risks, suggesting it may play an important role in these associations.

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Key messages

What was your research question? The associations between AP and multiple diseases remain unclear, especially $PM_{2.5}$ components and subtypes of CVD.

What did you find? Various AP were found to be associated with multiple diseases. OM may be the important component accounting for these associations.

Why is it important? Controlling specific constituents such as OM may be essential for preventing multiple diseases.

Keywords Air pollution, Fine particulate matter components, Prospective cohort study, Multiple exposure analysis, Outcome-wide analysis

Background

The World Health Organization has updated its air quality guidelines for pollutants, drawing from substantial evidence that air pollutants (AP) contribute heavily to the global burden of disease [1]. Currently, drawing upon extensive environmental health research, studies have turned to focus on fine particulate matter (particles ≤ 2.5 μm in diameter ($PM_{2.5}$)) and gas pollutants (nitrogen dioxide (NO_2) and ozone (O_3)) [2].

Existing evidence links AP to various organic systems, including the heart, lungs, and kidneys, among others [3]. However, the long-term effects of AP mainly focus on total cardiovascular diseases (CVD) [4, 5], diabetes mellitus [6], and chronic kidney disease (CKD) [7, 8]. There's limited evidence available on specific subtypes of diseases, such as cardiac arrests (CAR), as opposed to total CVD [9] or on other health conditions like osteoarthritis and osteoporosis [10].

On the other hand, $PM_{2.5}$ comprises various chemical components, including black carbon (BC), organic matter (OM), nitrate, chloride, sulfate, and ammonium [11]. The associations between $PM_{2.5}$ and morbidity risks differ widely between and within regions, probably explained by the differences in $PM_{2.5}$ composition [12, 13]. While recent studies have begun to assess the health effects of $PM_{2.5}$ chemical components rather than traditional $PM_{2.5}$ mass, they frequently use single-pollutant or two-pollutant models [4, 14]. This approach tends to ignore the real-world scenario of co-exposure, the correlations among the pollutants, and the joint effects of these pollutants. A deeper exploration into these joint effects can provide valuable insights into clarifying which pollutants, especially $PM_{2.5}$ chemical components, are the most significant contributors to adverse health outcomes [15].

Further, current studies examining exposure-outcome relationships one at a time may introduce "P-hacking" and outcome selection bias (i.e., only reporting outcomes that are positive and statistically significant [16–18]). Given that AP likely affects multiple diseases through various mechanisms, examining the associations with as many outcomes as possible within the same large cohort could unveil new perspectives for public health implications [19].

To address the above research gaps, this study uses an outcome-wide framework in a population-based prospective cohort from Southwest China to (1) evaluate the individual associations of AP with risk of 32 health conditions identified as the leading diseases in the cohort and (2) explore the joint effect of these pollutants and identify which pollutant contributes most to the adverse effects.

Methods

Study design and participants

We used data from a sub-cohort of the China Multi-Ethnic Cohort (CMEC) in Sichuan, China. Sichuan is a representative province in Southwest China with a permanent population of approximately 83.7 million. In brief, a multistage stratified cluster sampling method was applied to ensure representation, and 21,592 adults of Han ethnicity aged 30–79 in 2018 were included. Participants in the study completed a baseline survey, including face-to-face interviews with electronic questionnaires, medical examinations, and clinical laboratory tests. They also provided informed consent to monitor their health through electronic medical records. Further, the baseline survey was carried out by a team of well-trained researchers and medical technicians, and the medical records during the follow-up period from 2018 to 2022 (average of 4.2 years) were provided by the Health Information Center of Sichuan Province. Detailed information about CMEC can be found in Additional file 1: Supplementary methods or a reference [20]. Ethical approval for the study was granted by the Sichuan University Medical Ethical Review Board (K2016038 and K2020022).

Moreover, to ensure the integrity and validity of the study, we excluded (1) participants who have lived in their current residence for less than 3 years; (2) participants who were diagnosed as having cancer prior to the baseline survey; and (3) participants with missing information on exposure data, medical examinations, clinical

laboratory tests, and covariate data. Detailed information on covariates was presented in Additional file 1: Supplementary methods [21, 22]. Finally, 17,566 participants were included in the study (Additional file 1: Fig. S1). Further, to minimize the risk of reverse causality, we excluded participants with a diagnosis of a relevant condition prior to recruitment, ascertained through the baseline survey and medical records for each condition. Detailed information on the exclusion criteria of each condition and sample size for each condition are presented in Additional file 1: Table S1. The timeline of our study assessment is shown in Additional file 1: Fig. S2.

Outcomes

The outcomes of interest in this study were the incident cases of 32 health conditions. These outcomes were selected based on systems or conditions that may have previously been shown to be related to $PM_{2.5}$, NO_2, or O_3 in other studies [3]. All diseases were diagnosed and recorded by local physicians based on the International Classification of Diseases 10th revision (ICD-10) codes. Further, we did not include some conditions (i.e., Parkinson's disease) because the incident cases were rare during the follow-up periods. Detailed information on the definition and associated ICD-10 codes for these outcomes can be found in Additional file 1: Table S1.

Exposure

We sourced air pollution data from the ChinaHighAirPollutants database (https://weijing-rs.github.io/product.html). Specifically, annual surface $PM_{2.5}$ and its chemical components (including BC, OM, nitrate, chloride, sulfate, and ammonium) were predicted at a high spatial resolution of $0.01^\circ \times 0.01^\circ$ ($\approx 1\ km^2$), while NO_2 and O_3 were predicted at a 10 km × 10 km spatial resolution. The concentrations of $PM_{2.5}$ mass [23, 24], NO_2 [25], and O_3 [26] were derived from big data, including ground-based measurements, meteorology reanalysis, land use information, pollution emissions, and other spatial and temporal predictors. These predictions were estimated using a space–time extremely randomized trees model. Furthermore, $PM_{2.5}$ chemical components were apportioned from the $PM_{2.5}$ data using the four-dimensional spatiotemporal deep forest (4D-STDF) model [27]. The 4D-STDF model utilized ground-based measurements of $PM_{2.5}$ chemical components and satellite-retrieved $PM_{2.5}$ as main inputs, with auxiliary factors including Modern-Era Retrospective Analysis for Research and Applications, Version 2 and Goddard Earth Observing System—Forward Processing simulations of $PM_{2.5}$ components, Copernicus Atmosphere Monitoring Service emission inventories, and other variables for training [23, 25, 28, 29]. The models were validated using the tenfold cross-validation approach, demonstrating high data quality with R^2 values of 0.87–0.95 and root mean squared error of 0.5–17.1 $\mu g/m^3$ on an annual basis. Using the geocoded residential addresses, the 3-year average concentrations of $PM_{2.5}$ and its chemical constituents, NO_2, and O_3 prior to the baseline survey were computed. These were then assigned to each participant as the exposure surrogates.

Statistical analysis

All analyses were conducted using R (version 4.1.2). The Spearman correlation coefficient was applied to measure correlativity for $PM_{2.5}$ chemical constituents, NO_2, and O_3. Cox proportional hazards regression models were used to assess associations between AP and risk for incident cases separately for each condition. In Model 1, the initial models were adjusted for age and sex. Model 2 additionally adjusted for education, annual household income, urbanicity, and body mass index (BMI). Model 3 further adjusted for smoke, second-hand smoke, alcohol, indoor air pollution, physical activity, and alternative Mediterranean diet (aMED) index. Model 4 additionally adjusted for hypertension and diabetes. Further, Bonferroni correction was applied for multiple testing (for 32 outcomes, $P < 1.56 \times 10^{-3}$).

We applied the quantile g-computation (QGC) method, a novel developed approach, to assess the joint effects of $PM_{2.5}$ chemical components and gas pollutants, which were statistically significant ($P < 1.56 \times 10^{-3}$) on each condition. The analysis adjusted for the covariates used in Model 4. Hazard ratios (HRs) and 95% confidence intervals (CIs) in QGC models were estimated by bootstrap with 200 replications. This method, which integrates the weighted quantile sum [30] and g-computation, offers enhanced flexibility in estimating causal effects [31]. Detailed information on QGC is shown in Additional file 1: Supplementary methods [30, 31]. For this analysis, we used the R package "qgcomp" to apply the QGC.

Sensitivity analyses were performed by several strategies. First, we verified the Cox proportional hazards assumption via the examination of the Schoenfeld plots. Second, the E-value was computed to assess potential unmeasured confounders using the R package "EValue" [32]. Third, to assess the effects of temperature, we stratified the associations of mixture pollutants with health conditions by season (warm: April to September; cold: October to March). Fourth, to bolster the robustness of our findings, we (1) used stratified Cox proportional hazards models by age at recruitment (categorized in 5-year intervals) to further examine the possible violation of the

proportional hazards assumption and (2) excluded participants who were diagnosed within 2018 for each condition to evaluate the potential risk of reverse causality.

Results

Baseline characteristics

Table 1 shows the demographic characteristics of the cohort at baseline. The mean (standard deviation [SD]) age of the total participants was 51.4 (12.3) years, and over half were female. Among these participants, approximately one-third (31.3%) of the participants were diagnosed with hypertension at baseline, and 2282 (13.0%) had diabetes. Numbers of incident cases for 21 health conditions over an average follow-up of 4.2 years were shown in Additional file 1: Table S1. Additional file 1: Table S2 presents the distributions of AP, while the Spearman correlations and spatial distributions of pollutants are illustrated in Additional file 1: Fig. S3–S4. The mean (SD) 3-year average concentration of $PM_{2.5}$, NO_2, and O_3 was 55.2 (5.3) μg/m^3, 32.8 (8.8) μg/m^3, and 85.2 (4.7) μg/m^3, respectively. For the $PM_{2.5}$ chemical components, the mean (SD) exposure level ranged from 2.26 (0.2) μg/m^3 for chloride to 21.6 (3.4) μg/m^3 for OM. Among these pollutants, the positive correlations ranged from 0.06 (OM and O_3) to 0.87 (ammonium and sulfate), while negative correlations ranged from − 0.05 (BC and chloride) to − 0.22 (NO_2 and O_3).

Table 1 Basic characteristics of participants in the Sichuan cohort (n = 17,566)

Characteristic	
Age, year	51.40 ± 12.30
Sex, *n* (%)	
Male	7737 (44.0)
Female	9829 (56.0)
Education, *n* (%)	
Illiteracy	2185 (12.4)
Primary to middle school	9053 (51.5)
High school or above	6328 (36.0)
Annual household income, *n* (%)	
< 12,000	1681 (9.6)
12,000–19,999	2074 (11.8)
20,000–59,999	6498 (37.0)
60,000–99,999	3637 (20.7)
≥ 100,000	3676 (20.9)
Urbanicity, *n* (%)	
Rural	7893 (44.9)
Urban	9673 (55.1)
Smoke, *n* (%)	
Smoking	4394 (25.0)
Quitted	1270 (7.2)
Never	11,902 (67.8)
Second-hand smoke, *n* (%)	
No	8406 (47.9)
Yes	9160 (52.1)
Alcohol, *n* (%)	
No	8482 (48.3)
Yes	9084 (51.7)
Indoor air pollution, *n* (%)	
No	2696 (15.3)
Yes	14,870 (84.7)
Hypertension	
No	12,074 (68.7)
Yes	5492 (31.3)
Diabetes	
No	15,284 (87.0)
Yes	2282 (13.0)
Physical activity, MET-h/day	21.30 ± 14.91
BMI	24.32 ± 3.31
aMED index	25.73 ± 4.16

BMI Body mass index, *MET* Metabolic equivalent tasks, *aMED* Alternative Mediterranean diet index

Risk analyses

Figure 1 presents the HRs for 32 health conditions and their corresponding 95% CIs per interquartile range (IQR) higher exposure of each AP for Model 4. Detailed information on Models 1–3 can be found in Additional file 1: Fig. S5–S13. Figure 2 and S14 present the joint effects for each condition and corresponding positive weights for pollutants. After the Bonferroni correction, many associations, such as heart failure, were no longer statistically significant. Therefore, here we describe the results for Model 4 that were robust to correction and for QGC models without these conditions.

Fine particulate matter and gas pollutants

$PM_{2.5}$ was associated with a higher risk of total CVD (HR per 8.21 μg/m^3 higher exposure = 1.57, 95% CI = 1.46–1.69), hypertensive diseases (HTN) (1.58, 1.42–1.76), CAR (1.49, 1.28–1.73), arrhythmia (1.90, 1.55–2.33), cerebrovascular disease (CER) (1.77, 1.59–1.97), stroke (2.17, 1.78–2.65), ischemic stroke (2.23, 1.82–2.74), atherosclerosis (2.26, 1.86–2.75), diseases of veins, lymphatic vessels, and lymph nodes (VL) (1.53, 1.24–1.88), pneumonia (1.54, 1.25–1.90), type 2 diabetes (T2D) (1.75, 1.42–2.16), lipoprotein metabolism disorders (LMD) (2.21, 1.95–2.50), purine metabolism disorders (PMD) (2.02, 1.61–2.53), liver diseases (1.72, 1.55–1.92), anemia (1.52, 1.29–1.79), sleep disorders (1.97, 1.60–2.42), renal failure (1.68, 1.28–2.21), osteoarthritis (1.50, 1.36–1.65), and osteoporosis (1.69, 1.33–2.15). Compared to $PM_{2.5}$, NO_2 (per 15.75 μg/m^3 higher exposure) showed similar associations with these conditions, except for

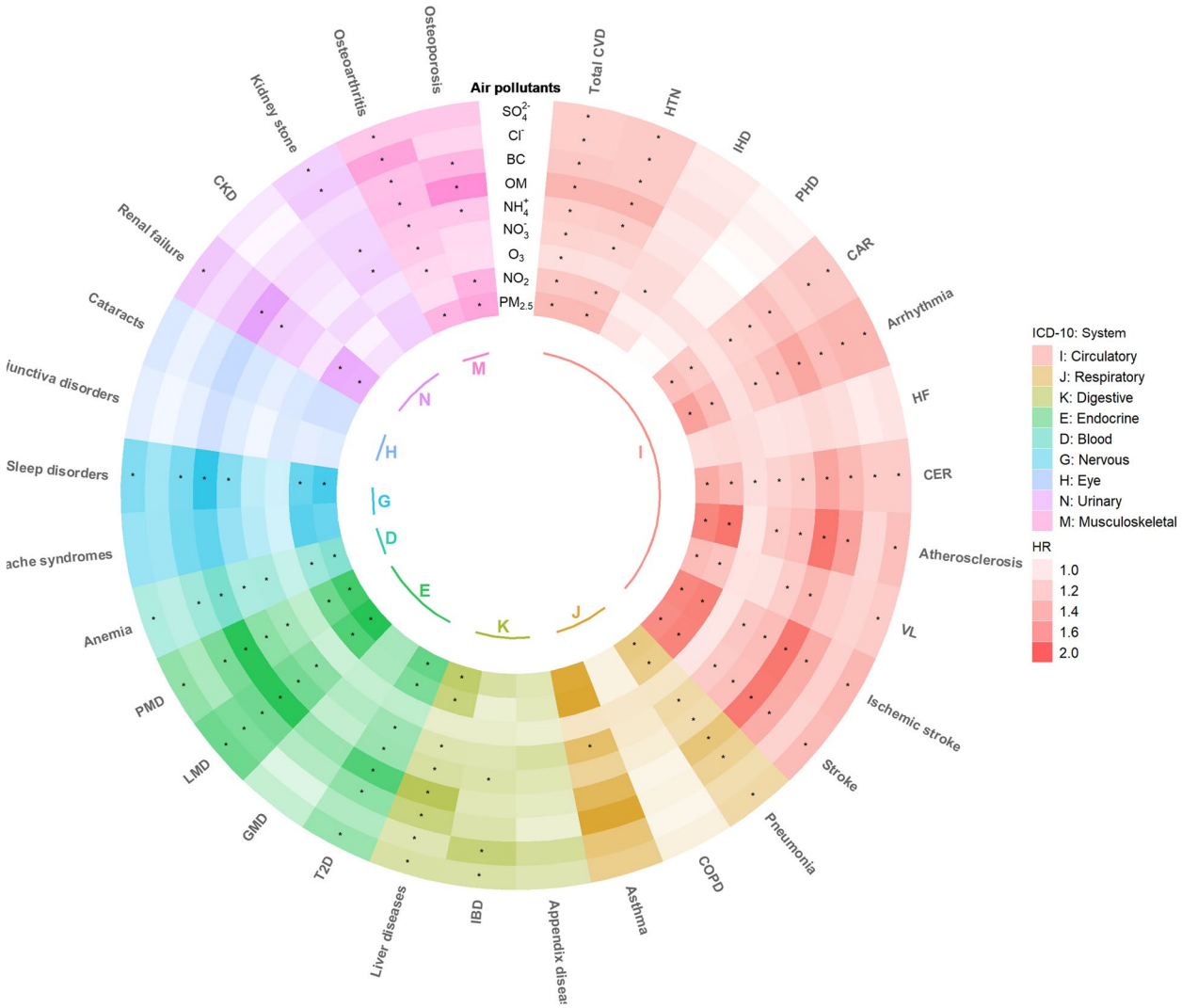

Fig. 1 Hazard ratios and corresponding 95% CI for associations between AP and 32 health conditions. Note: Units are per IQR increase in pollutants. An asterisk (*) indicates the $P < 1.56 \times 10^{-3}$. Models were adjusted for age, sex, education, annual household income, urbanicity, BMI, smoke, second-hand smoke, alcohol, indoor air pollution, physical activity, aMED index, hypertension, and diabetes. CVD, cardiovascular disease; HTN, hypertensive disease; IHD, ischemic heart disease; PHD, pulmonary heart disease; CAR, cardiac arrests; HF, heart failure; CER, cerebrovascular diseases; VL, diseases of veins, lymphatic vessels, and lymph nodes; COPD, chronic obstructive pulmonary disease; IBD, inflammatory bowel diseases; T2D, type 2 diabetes; GMD, glycoprotein metabolism disorders; LMD, lipoprotein metabolism disorders; PMD, purine metabolism disorders; CKD, chronic kidney disease; $PM_{2.5}$, particulate matter with aerodynamic diameter ≤ 2.5 μm; NO_2, nitrogen dioxide; O_3, ozone; NO_3^-, nitrate; NH_4^+, ammonium; OM, organic matter; BC, black carbon; Cl^-, chloride; SO_4^{2-}, sulfate; HR, hazard ratio

osteoarthritis. Unlike $PM_{2.5}$ and NO_2, O_3 (per 1.96 μg/m^3 higher exposure) was associated with a few diseases, including total CVD (1.06, 1.04–1.08), ischemic heart disease (IHD) (1.10, 1.06–1.15), CER (1.08, 1.05–1.10), and osteoarthritis (1.10, 1.08–1.13).

Chemical components of fine particulate matter

One or more chemical components of $PM_{2.5}$ were significantly associated with the conditions, except for heart failure (HF), pulmonary heart disease (PHD), chronic obstructive pulmonary disease (COPD), appendix diseases, glycoprotein metabolism disorders (GMD), headache syndromes, conjunctiva disorders, cataracts, and CKD. Among these associations of chemical components, OM (per 6.6 μg/m^3 higher exposure) was observed with largest HRs in total CVD (1.61, 1.47–1.77), HTN (1.63, 1.43–1.86), CAR (1.46, 1.20–1.76), arrhythmia (1.82, 1.43–2.32), CER (1.84, 1.61–2.10), stroke (2.43, 1.91–3.09), ischemic stroke (2.45, 1.92–3.14), atherosclerosis (2.46, 1.96–3.11), VL (1.61, 1.25–2.07), pneumonia

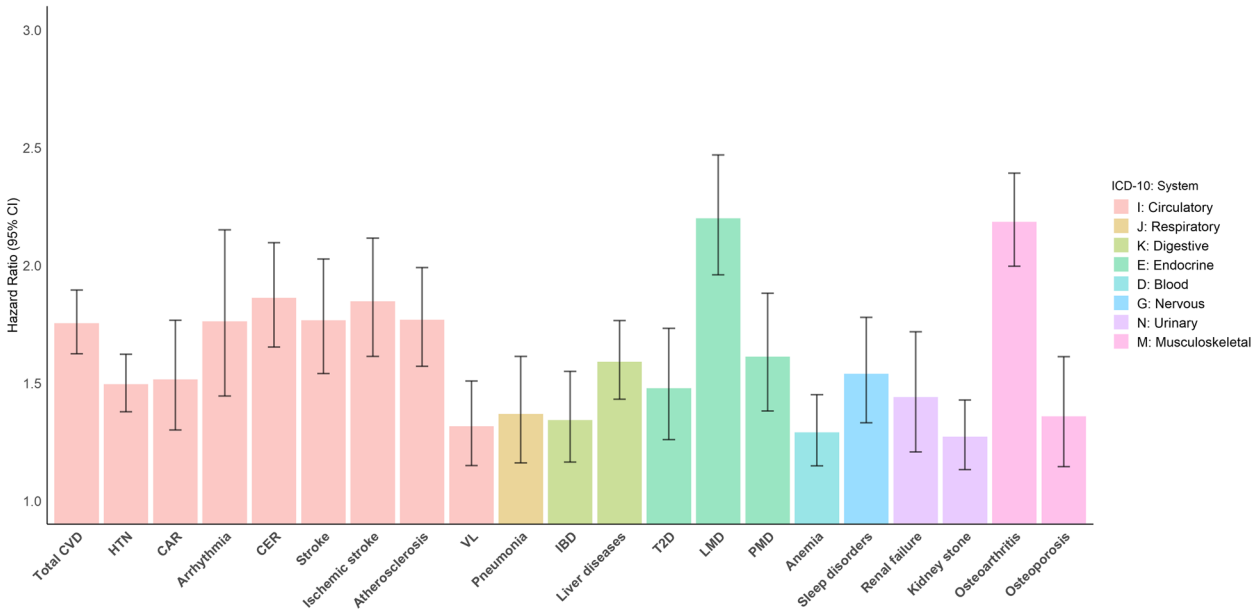

Fig. 2 Hazard ratios and corresponding 95% CI for associations between mixture pollutant and health conditions. Note: Units are per IQR increase in pollutants. Models were adjusted for age, sex, education, annual household income, urbanicity, BMI, smoke, second-hand smoke, alcohol, indoor air pollution, physical activity, aMED index, hypertension, and diabetes. CVD, cardiovascular disease; HTN, hypertensive disease; CAR, cardiac arrests; CER, cerebrovascular diseases; VL, diseases of veins, lymphatic vessels, and lymph nodes; IBD, inflammatory bowel diseases; T2D, type 2 diabetes; LMD, lipoprotein metabolism disorders; PMD, purine metabolism disorders

(1.60, 1.22–2.09), T2D (1.92, 1.50–2.45), LMD (2.18, 1.89–2.52), PMD (2.19, 1.67–2.87), liver diseases (1.85, 1.62–2.11), anemia (1.59, 1.29–1.95), sleep disorders (2.11, 1.65–2.71), renal failure (1.86, 1.32–2.61), and osteoporosis (1.97, 1.46–2.65). On the other hand, chloride has the largest HRs in inflammatory bowel diseases (IBD) (1.61, 1.30–1.99), kidney stones (1.32, 1.12–1.55), and osteoarthritis (1.71, 1.56–1.88). Further, nitrate was associated with asthma (1.72, 1.25–2.37).

Mixture pollutant

The joint effects of AP were all positive and statistically significant in QGC models with largest HRs in LMD (2.20, 1.96–2.47), followed by osteoarthritis (2.18, 2.00–2.39), CER (1.86, 1.65–2.10), ischemic stroke (1.85, 1.61–2.12), atherosclerosis (1.77, 1.57–1.99), stroke (1.77, 1.54–2.03), arrhythmia (1.76, 1.44–2.15), total CVD (1.75, 1.62–1.89), PMD (1.61, 1.38–1.88), liver diseases (1.59, 1.43–1.77), sleep disorders (1.54, 1.33–1.78), CAR (1.52, 1.30–1.77), HTN (1.49, 1.38–1.62), T2D (1.48, 1.26–1.73), renal failure (1.44, 1.21–1.72), pneumonia (1.37, 1.16–1.61), osteoporosis (1.36, 1.14–1.61), IBD (1.34, 1.16–1.55), VL (1.32, 1.15–1.51), anemia (1.29, 1.15–1.45), and kidney stone (1.27, 1.13–1.43). Further, among these conditions, OM has the largest weight except for atherosclerosis (NO_2), IBD (chloride), kidney stone (chloride), and osteoarthritis (chloride).

Sensitivity analysis

Associations remain robust with main analyses when modified model settings or excluded participants' incident cases within 1 year (Additional file 1: Table S3–S35). The associations of the mixture pollutant with risks of health conditions were statistically significant in the warm season, with significant differences between warm and cold seasons observed in cardiometabolic diseases (Additional file 1: Table S36). Cox proportion hazard assumption was satisfied upon examining the Schoenfeld plots (results not shown). Additionally, E values for associations between AP and 32 health conditions indicate that any unmeasured confounder would need a substantial effect to erase the estimated associations.

Discussion

In this large, prospective cohort, we found that higher exposures to NO_2, O_3, and $PM_{2.5}$, as well as its chemical components, were associated with increased risks of various incident conditions. Briefly, these conditions involve the circulatory, respiratory, and digestive systems, among others. Moreover, our multi-pollutant models suggested that OM may play a primary role in the effects of AP mixtures on these conditions. To the best of our knowledge, this study might be the first to analyze both individual and joint effects of AP on a wide range of disease outcomes using an outcome-wide epidemiology framework

[17]. Within this framework, we included many other conditions in addition to common outcomes. This includes health conditions rarely reported in previous studies (i.e., osteoarthritis) because of the study designs or limited incident cases, as well as outcomes with inconsistent associations from previous research (i.e., COPD). This methodology aids in reducing potential biases and "P-hacking." The results of our study may shed new light on the understanding and intervention of air pollution to reduce risks of incident health conditions.

Circulatory diseases

A recent comprehensive review [2] summarized decades of evidence supporting the detrimental effects of AP on CVD, with the most robust findings associated with $PM_{2.5}$ and O_3. It also highlighted a significant gap in the literature regarding studies investigating the risks of multiple exposures. As far as we know, there has been only one recent study [9] that reported a positive association between the joint effects of AP on total CVD in a highly polluted region in China, where the concentration of $PM_{2.5}$ ranged from 67.7 to 77.9 $\mu g/m^3$. Importantly, this study indicated that OM accounted for approximately half of this joint effect. Our findings not only align with this study but are also consistent with the review. We observed similar associations and identified OM as the largest contributor. Furthermore, our study underscored the important role of OM in various CVD subtypes. OM has been associated with elevations in blood pressure, glucose, and lipids, all of which are established causal risk factors for CVD [14, 33]. With long-term exposure to OM, these abnormalities may accumulate, eventually leading to cardiovascular events and subsequent death [2]. However, the cardiac effects from each subtype of OM remain uncertain, warranting further research.

Respiratory diseases

Current epidemiological research on AP's relationship with chronic respiratory diseases largely focuses on its acute effects on COPD or asthma, while studies addressing its long-term effects on incident cases are not only limited but also yield inconsistent results[34]. For example, studies from Taiwan [35] and Italy [36], similar to ours, found no association between $PM_{2.5}$ and incident COPD, echoed by a recent meta-analysis [37]. In contrast, research conducted in Zhejiang [38] and Ontario [39] reported positive associations between $PM_{2.5}$ and incident COPD. Another meta-analysis reported a positive association, albeit with slight asymmetry in the funnel plot [40]. Similar inconsistent conclusions also occurred in studies related to asthma [39, 41]. Furthermore, current studies primarily explained the relationship between long-term exposure to $PM_{2.5}$ and COPD through oxidative stress and inflammation [2]. The accumulation of AP exposure can lead to frustrated phagocytosis, depletion of antioxidant defense systems, and unresolved inflammation [42]. However, detailed mechanisms still require further exploration.

Digestive diseases

Previous studies have explored the associations of AP with liver diseases, including cirrhosis [43] and metabolic-associated fatty liver disease [44]. Consistent with these findings, our study found positive associations between $PM_{2.5}$ and NO_2 and liver diseases. Regarding diseases of the appendix, we are not aware of any studies that explore the long-term effects of air pollution on it [45], and we also found no significant association. As for IBD, recent research indicated an association between $PM_{2.5}$ and IBD [46, 47], whereas we did not find a significant result between them after applying the Bonferroni correction. However, we did observe associations between specific $PM_{2.5}$ chemical components and IBD, including chloride, ammonium, and sulfate. On the one hand, research has reported that sulfate may play an important role in producing highly acidic fine aerosols to facilitate the transition process of other particles [48]. On the other hand, some hypotheses have been raised suggesting that particles can enter the gastrointestinal tract via mucociliary transport, subsequently affecting the gastrointestinal microbiome [49]. However, the mechanisms underpinning the associations between these components and the microbiome remain unclear. Additionally, similar to circulatory diseases, we noted a significant contribution of OM in joint effects of AP on liver diseases, further highlighting the necessity to reduce OM concentrations.

Other diseases

Echoed with previous studies, we identified positive associations of $PM_{2.5}$ and NO_2 with risks of several health conditions, including T2D [6, 35, 50], LMD [51, 52], PMD [53], anemia [54], sleep disorders [55, 56], renal failure [57], and osteoporosis [58]. Further, recent prospective research indicated that AP increases the risk of hyperuricemia [53]. This may explain the observed associations between chemical components and kidney stones in our study. However, current research on the association between long-term exposure to AP and osteoarthritis and osteoporosis is limited. To our knowledge, this is the first prospective study exploring the link between AP and osteoarthritis. We are only aware of one animal study that found that exposure to either PM or a combination of PM and gas pollutants led to a significant reduction in osteoarthritis biomarkers, including cartilage oligomeric protein and N-telopeptides of type I collagen [59]. Given

the limited research on this topic, additional evidence is needed to support these findings.

For subgroup analysis, a similar result was found in another study conducted in Sichuan, which reported higher hospital admission risks related to particulate matter in the warm season [60]. However, caution is needed when drawing conclusions. Although the CMEC survey period was from May 2018 to September 2019 [20], the recruitment for the Sichuan cohort was completed at the end of 2018, resulting in most of the data collection occurring during the warm season. This may have led to the survey avoiding the coldest and most polluted periods [61].

Potential mechanisms

Previous studies focused on $PM_{2.5}$, NO_2, and O_3, whereas mechanistic evidence on components is limited. It is widely recognized that exposure to AP initially triggers oxidative stress and inflammation, which then transmit into the circulation, subsequently leading to vascular dysfunction, endothelial damage, and epigenomic changes [2]. These changes may accumulate and fail to resolve in the context of the long-term effects of AP, potentially contributing to various health conditions [6, 62]. Since $PM_{2.5}$ is mainly involved in these processes, certain components may play an important role [63]. For example, a panel study [64] conducted among 76 students in Taipei showed that sulfate and O_3 were associated with markers of inflammation (high-sensitivity C-reactive protein), oxidative stress (8-hydroxy-2′-deoxyguanosine), fibrinolytic (plasminogen activator inhibitor-1), and coagulation (fibrinogen). For chloride, a repeated-measure study [65] conducted among healthy adults in Beijing found it to be associated with extracellular superoxide dismutase and glutathione peroxidase 1, suggesting it may be involved in antioxidant processes. Because chloride is closely related to sea salt and wind-blown dust [66–69], and dust contains metal elements such as calcium and potassium ions, it may be associated with adverse health effects [70, 71]. Notably, our multiple exposure analyses suggested that OM is an important pollutant. Previous studies [72–74] have reported that polycyclic aromatic hydrocarbons, such as Benzo[a]pyrene, which are primarily produced by the incomplete combustion of organic materials [75, 76], are associated with the aryl hydrocarbon receptor and may be involved in lipid peroxidation and tissue damage processes. However, most current evidence focuses on OM detected in urine, such as polycyclic aromatic hydrocarbons [77]. It is worth noting that OM in urine can come from various sources, including food, soil, dust, water, and more [73]. Given the different sources, the mechanisms may differ. Consequently, there should be a pressing need for more studies on airborne components in the future.

On the other hand, the findings of our study can assist policymakers in mitigating health risks. By identifying important pollutants associated with each disease, policymakers can develop targeted pollution control strategies. For instance, they can focus on reducing key pollutants such as OM and develop specific strategies for different diseases. Additionally, attention can be given to patients from areas with high concentrations of specific pollutants.

Study strengths and limitations

According to the information we have, this is the first outcome-wide study of AP and the risks of multiple health conditions. Besides the large size and prospective design of the cohort, our study has several additional strengths. These include a comprehensive set of covariates (which were corrected based on recordings to minimize measurement errors), outcomes based on national records with ICD-10 codes (which are objective and help minimize selective loss to follow-up), and the application of methodologies that are widely accepted in the context of environmental multiple exposures. Furthermore, we carried out a series of sensitivity analyses to ensure the robustness of the results, which consistently demonstrated reliability with the assumption of proportional hazards being satisfied.

Nevertheless, some limitations should be acknowledged when interpreting our results. First, observational studies may inevitably involve issues with unmeasured confounding. Hence, we calculated the E-values to assess the robustness of the associations against the influence of unmeasured confounding. Second, although we applied Bonferroni correction to address multiple testing concerns, some true associations may not meet the threshold and were therefore overlooked. Third, some conditions, like diabetes, might only require hospital admission at later stages. While we excluded self-reported conditions prior to the baseline to ensure the incident cases, some admissions might reflect more severe cases. Fourth, we assessed individuals' exposure levels based on their residential addresses without detailed activity patterns. This is a common limitation in long-term air pollution research. However, since the living and working areas of the participants may not be far apart, this measurement error may be limited to some extent.

Conclusions

Our findings from this large, prospective study in Southwest China show that AP, including $PM_{2.5}$ and its components, NO_2, and O_3, are associated with higher risks of several health conditions. The joint effects of AP on these

conditions reflect the important role of OM. Additional research is needed for the detailed effects of OM subtypes to ascertain specific resources to curb.

Abbreviations

aMED	Alternative Mediterranean Diet
AP	Air pollutants
BC	Black carbon
BMI	Body mass index
CAR	Cardiac arrests
CER	Cerebrovascular disease
CIs	Confidence intervals
CKD	Chronic kidney disease
CMEC	China Multi-Ethnic Cohort
COPD	Chronic obstructive pulmonary disease
CVD	Cardiovascular diseases
GMD	Glycoprotein metabolism disorders
HF	Heart failure
HRs	Hazard ratios
HTN	Hypertensive diseases
IBD	Inflammatory bowel diseases
ICD-10	International Classification of Diseases 10th revision
IHD	Ischemic heart disease
IQR	Interquartile range
LMD	Lipoprotein metabolism disorders
NO_2	Nitrogen dioxide
OM	Organic matter
O_3	Ozone
PHD	Pulmonary heart disease
PMD	Purine metabolism disorders
$PM_{2.5}$	Particles ≤ 2.5 μm in diameter
QGC	Quantile g-computation
SD	Standard deviation
T2D	Type 2 diabetes
VL	Diseases of veins, lymphatic vessels, and lymph nodes
4D-STDF	Four-dimensional spatiotemporal deep forest

Supplementary Information

The online version contains supplementary material available at https://doi.org/10.1186/s12916-024-03596-5.

Additional file 1: Supplementary methods. Figure S1 - Participant inclusion process for the study. Figure S2 - Timeline of our study assessment. Figure S3 - Spearman correlation matrix among three-year average AP concentrations. Figure S4 - The study area (Sichuan province) and spatial distribution of air pollutants in this study. Figure S5 - Hazard ratios (95% CIs) of 32 health conditions risks associated with per IQR increase in PM2.5 mass. Figure S6 - Hazard ratios (95% CIs) of 32 health conditions risks associated with per IQR increase in NO2. Figure S7 - Hazard ratios (95% CIs) of 32 health conditions risks associated with per IQR increase in O3. Figure S8 - Hazard ratios (95% CIs) of 32 health conditions risks associated with per IQR increase in nitrate. Figure S9 - Hazard ratios (95% CIs) of 32 health conditions risks associated with per IQR increase in ammonium. Figure S10 - Hazard ratios (95% CIs) of 32 health conditions risks associated with per IQR increase in OM. Figure S11 - Hazard ratios (95% CIs) of 32 health conditions risks associated with per IQR increase in BC. Figure S12 - Hazard ratios (95% CIs) of 32 health conditions risks associated with per IQR increase in chloride. Figure S13 - Hazard ratios (95% CIs) of 32 health conditions risks associated with per IQR increase in sulfate. Figure S14- Positive weight estimations of AP associated with risks of conditions by QGC method. Table S1 - Inclusion and exclusion criteria of outcomes in the analysis. Table S2 - Summary distributions of three-year average AP concentrations. Table S3 - Sensitivity analyses for associations of AP with risks of total CVD. Table S4 - Sensitivity analyses for associations of AP with risks of HTN. Table S5 - Sensitivity analyses for associations of AP with risks of IHD. Table S6 - Sensitivity analyses for associations of AP with risks of PHD. Table S7 - Sensitivity analyses for associations of AP with risks of CAR. Table S8 - Sensitivity analyses for associations of AP with risks of arrhythmia. Table S9 - Sensitivity analyses for associations of AP with risks of HF. Table S10 - Sensitivity analyses for associations of AP with risks of CER. Table S11 - Sensitivity analyses for associations of AP with risks of stroke. Table S12 - Sensitivity analyses for associations of AP with risks of ischemic stroke. Table S13 - Sensitivity analyses for associations of AP with risks of atherosclerosis. Table S14 - Sensitivity analyses for associations of AP with risks of VL. Table S15 - Sensitivity analyses for associations of AP with risks of pneumonia. Table S16 - Sensitivity analyses for associations of AP with risks of COPD. Table S17 - Sensitivity analyses for associations of AP with risks of asthma. Table S18 - Sensitivity analyses for associations of AP with risks of appendix diseases. Table S19 - Sensitivity analyses for associations of AP with risks of IBD. Table S20 - Sensitivity analyses for associations of AP with risks of liver diseases. Table S21 - Sensitivity analyses for associations of AP with risks of T2D. Table S22 - Sensitivity analyses for associations of AP with risks of GMD. Table S23 - Sensitivity analyses for associations of AP with risks of LMD. Table S24 - Sensitivity analyses for associations of AP with risks of PMD. Table S25 - Sensitivity analyses for associations of AP with risks of anemia. Table S26 - Sensitivity analyses for associations of AP with risks of headache syndromes. Table S27 - Sensitivity analyses for associations of AP with risks of sleep disorders. Table S28 - Sensitivity analyses for associations of AP with risks of conjunctiva disorders. Table S29 - Sensitivity analyses for associations of AP with risks of cataracts. Table S30 - Sensitivity analyses for associations of AP with risks of renal failure. Table S31 - Sensitivity analyses for associations of AP with risks of CKD. Table S32 - Sensitivity analyses for associations of AP with risks of kidney stone. Table S33 - Sensitivity analyses for associations of AP with risks of osteoarthritis. Table S34 - Sensitivity analyses for associations of AP with risks of osteoporosis. Table S35 - Sensitivity analyses for associations of mixture pollutant with risks of health conditions. Table S36 - The associations of Mixture pollutant with risks of health conditions stratified by season.

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Authors' contributions

H.Z. and F.H. conducted statistical analyses and wrote the original draft. H.Z. wrote the additional file 1. L.W., X.T., and B.G. revised the manuscript and performed data visualization. Y.L. and H.Y. helped with the linkage of the medical records database. D.M., T.L., Y.F., and Y.B. acquired the baseline data and searched the literature. J.Z. and X.Z. designed the study, contributed to the cohort data, and supervised this work.

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Availability of data and materials

The data that support the findings of this study are available upon reasonable request to the corresponding author.

Declarations

Ethics approval and consent to participate

This study was granted by the Sichuan University Medical Ethical Review Board (K2016038 and K2020022). All participants provided informed consent.

Consent for publication

Not applicable.

Competing interests
The authors declare no competing interests.

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