Hongbing Xu and Jing Song contributed equally to this work.

Key Points:

- Extremely high levels of ambient black carbon and wood smoke-related particles were found during the study period
- Carbon particles, particularly from traffic, were associated with increased risks of childhood respiratory infections
- Greater risks were found among children older than 6 years

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Ambient Anthropogenic Carbons and Pediatric Respiratory Infections: A Case-Crossover Analysis in the Megacity Beijing

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Abstract Carbon loading in airway cells has shown to worsen function of antimicrobial peptides, permitting increased survival of pathogens in the respiratory tract; however, data on the impacts of carbon particles on childhood acute respiratory infection (ARI) is limited. We assembled daily health data on outpatient visits for ARI (bronchitis, pneumonia, and total upper respiratory infection [TURI]) in children aged 0–14 years between 2015 and 2019 in Beijing, China. Anthropogenic carbons, including black carbon (BC) and its emission sources, and wood smoke particles (delta carbon, ultra-violet absorbing particulate matter, and brown carbon) were continuously monitored. Using a time-stratified case-crossover approach, conditional logistic regression was performed to derive risk estimates for each outcome. A total of 856,899 children were included, and a wide range of daily carbon particle concentrations was observed, with large variations for BC (0.36–20.44) and delta carbon (0.48–57.66 $\mu g/m^3$). Exposure to these particles were independently associated with ARI, with nearly linear exposure-response relationships. Interquartile range increases in concentrations of BC and delta carbon over prior 0–8 days, we observed elevation of the odd ratio of bronchitis by 1.201 (95% confidence interval, 1.180, 1.221) and 1.048 (95% CI, 1.039, 1.057), respectively. Stronger association was observed for BC from traffic sources, which increased the odd ratio of bronchitis by 1.298 (95% CI, 1.273, 1.324). Carbon particles were also associated with elevated risks of pneumonia and TURI, and subgroup analyses indicated greater risks among children older than 6 years. Our findings suggested that anthropogenic carbons in metropolitan areas may pose a significant threat to clinical manifestations of respiratory infections in vulnerable populations.

Plain Language Summary Carbon air pollution has been linked to potential biological mechanisms responsible for respiratory diseases, but its impact on childhood respiratory infection remain sparse. In this study, we examined the associations of carbon particles with childhood hospital visits for acute respiratory infection in the megacity Beijing. The results indicated that recent exposure to ambient black carbon and wood smoke-related particles (delta carbon, ultra-violet absorbing particulate matter, and brown carbon) was associated with heightened risks of upper and lower respiratory tract infections in children. Greater detrimental respiratory effects were observed for carbon particles from traffic. Up to date, the global pandemic of pediatric respiratory infection and air pollution episodes occurs frequently under the context of climate crisis, our findings highlighted the importance of discerning adverse respiratory effects caused by source-specific carbon particles in real-world settings, particularly at the extreme levels of anthropogenic carbon exposures faced by billions of children living in urban areas worldwide today.

1. Introduction

Acute respiratory infection (ARI) is the most common childhood disease that can be life-threatening and worsen quality of life (Vos et al., 2020). The Global Burden of Disease study indicates that ARI, especially for infections of the lower respiratory tract (e.g., bronchitis and pneumonia) is a leading cause of globally mortality and rank second among causes of childhood disability-adjusted life-years (Vos et al., 2020). Environmental exposures

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such as ubiquitous air pollution may be important contributors to address in reducing ARI burden (Schraufnagel et al., 2019). As ambient fine particulate pollution substantially declined worldwide over the past decades following stringent emission regulations, combustion-derived carbon particles (e.g., black carbon [BC]) have become increasingly crucial drivers for air pollution episodes, particularly in urban environments (HEI, 2022). BC is the by-product from incomplete combustion of fossil fuels and biomass, and servers as the one of the most crucial triggers forcing climate warming (Anenberg et al., 2012). To implement cost-efficient abatement and targeted risk-reduction measures, growing evidence indicates that improvements of global air quality and public health benefits could be significantly achieved by BC emission controls (Anenberg et al., 2012). More recently, wood smoke episodes posed by anthropogenic activities (e.g., coal and biomass) are expected to occur more frequently under the context of climate crisis, along with emitting substantial amounts of carbon particles containing high levels of aromatic compounds (D'Evelyn et al., 2022). Carbon particles have been linked to pathogenesis of respiratory diseases, including pulmonary immune inflammation and oxidative stress (De Prins et al., 2014); however, data on the influence of ambient source-specific carbon particles (e.g., BC and wood smoke) on childhood ARI remain sparse.

Emerging experimental evidence supports that air population exposure can prompt host defense abnormalities, thereby might play an important role in colonization and transmission of bacterial or viral infections in the airways (Beentjes et al., 2022). Mechanistically, inhalation of carbon particles is capable of exhibiting potent abilities to worsen airway functions, including reduced ciliary beat frequency, inhibited bioactivity of antimicrobial peptides, and enhanced mucus production (Beentjes et al., 2022). Further, exposure to particles has been shown to suppress capacity of immune cells (e.g., alveolar macrophages) to internalize pathogens and increase pneumococcal colonization in the lungs (Yin et al., 2007; Zhou & Kobzik, 2007). Also, it is proven, both in animal and human studies, that carbon particles could be phagocytosed by macrophages in the airway, consequently leading to a high BC load in lower respiratory tracts (Saenen et al., 2017; Shimada et al., 2006). Thus far, few studies have examined associations of ambient carbon particles with bronchitis in children (Brauer et al., 2007; Kim et al., 2004; G. Wang et al., 2021). However, most these studies assessed the health impact of single carbon particle metric (e.g., BC) and were performed in study areas with lower pollutant levels. To our knowledge, the lag association pattern for relationship between carbon particles and ARI cases remains unclear because previous studies mainly focused on capturing chronic exposure effects. Further, the existing evidence of ambient BC-associated childhood ARI is mixed and inconclusive, and source contributions to BC varied across study locations have been hypothesized as a possible reason of heterogeneity in observational associations (JN et al., 2012). Indeed, toxic properties of BC can be determined by its compositions and emission sources (JN et al., 2012). Recent studies in vitro reported that alterations in pulmonary bacterial numbers and inflammatory cytokine levels responsive to diesel exhaust particles (a major source of traffic BC fraction) were larger than those of wood smoke (Samuelsen et al., 2009). Therefore, population-based investigations that link ambient source-specific carbon particles with clinical manifestations of ARI cases are urgently imperative to clarify the heterogeneous relationships observed previously.

Air quality worsened by anthropogenic activities has been of tremendous health concern in megacities, such as Beijing, China, where daily variations in ambient concentrations of carbon particles overlapped with levels measured in most urban areas worldwide. More recently, ambient particles are increasingly recognized as a crucial mediator for enhanced transmission of aerosolized microbial hazards, such as respiratory pathogens and antibiotic resistance genes (Abelenda-Alonso et al., 2021). Here, we hypothesized that recent exposure to elevated levels of ambient anthropogenic carbons (including BC and its sources, as well as wood smoke-related particles) would increase susceptibility to pediatric ARI. To this end, we conducted a case-crossover analysis to link carbon particle pollution measures with electronic medical records of outpatient visits in children under 14 years old, and examined the impacts of various carbon exposure metrics on ARI-related clinical manifestations, including bronchitis, pneumonia, and total upper respiratory infection (TURI).

2. Methods

2.1. Study Population and Health Data Collection

Daily data on outpatient visits were extracted from Beijing Children's Hospital (BCH), which is the largest healthcare agency for children and adolescent population in Beijing, China and provides comprehensive medical care for approximately 3 million people each year. Individual-level information on sex, birth of date, residential district, date of outpatient visit, and International Classification of Diseases 10th edition (ICD-10) diagnosed

respiratory endpoints was collected for each ARI case. Participant age was computed from the date of birth to the date of outpatient visit. The study outcome measures were bronchitis (ICD-10 code: J40, J42, J44), pneumonia (ICD-10 code: J12–13, J15–18), and TURI (ICD-10 code: J10–11, J32, B00, B08). Assignment of the diagnosed disease to ICD-10 code categories was conducted by medically trained personnel from BCH. All electronic medical record data were recoded and de-identified to protect the privacy and confidentiality of each study participant. The final database included participants aged 14 years old and younger who resided in Beijing and had healthcare encounters for ARI-related clinical manifestations occurred between January 2015 and February 2019.

2.2. Air Pollution and Weather Data Collection

Ambient carbon particle pollution and meteorologic data were continuously determined at a long-term fixed air monitoring site on the campus of Peking University Health Science Center (PUHSC). The integrated sampling site has been set up on the roof of a 7-story teaching building (about 25 m above ground level) since 2014 and was approximately 8 km north of the BCH. Minute-to-minute concentrations of ambient carbon particle metrics, including BC, ultra-violet absorbing particulate matter (UVPM), delta carbon (Delta-C), and brown carbon (BrC), were simultaneously determined by Magee Scientific Aethalometer® Model AE-33 (CA, USA). The Aethalometer analyzed real-time sample of carbonaceous aerosols at optical wavelengths of 370, 470, 520, 590, 660, 880, and 950 nm. The defining standard for BC was determined by the absorption measurements at 880 nm; UVPM was determined by the light absorption at 370 nm; Delta-C was determined by the difference between BC measurements at 880 and 370 nm; BrC was estimated based on absorption coefficients of multi-wavelengths (e.g., 470 nm). Additionally, source contributions to BC measured at 880 nm, including traffic BC fractions and biomass burning, were also analyzed using the Aethalometer model. Previous studies have shown that UVPM contains high levels of organic materials (e.g., aromatic compounds) from wood smoke, and Delta-C is reliable marker of wood smoke (Deslauriers et al., 2022; Y. Wang et al., 2011). BrC represents a typical cluster of light-absorbing organic aerosol in the near-ultraviolet, which plays a role in the regional and global climate change (J. Wang et al., 2018).

Concurrently, we measured a variety of ambient copollutants (particulate and gaseous air pollution) at the same station. Hourly concentrations of ambient particulate matter in diameter <2.5 μm ($PM_{2.5}$) were measured by BAM-1020 beta attenuation mass monitor (Met One Instruments Inc., Washington). Minute-to-minute concentrations of carbon monoxide (CO), nitrogen dioxide (NO_2), sulfur dioxide (SO_2), and ozone (O_3) were monitored by EC9800 series analyzers (EcoTech Pty. Ltd., VIC, Melbourne, Australia). Hourly levels of ambient temperature (TEMP) and relative humidity (RH) were also monitored using a Met One unit (Met One Instruments, Inc). Daily averages were computed from 00:00 a.m. to 11:59 p.m. for all environmental exposure measures.

In China, carbon air pollution is not routinely monitored in the established network of air quality regulation. To assess the validity and plausibility of exposure assessment, daily averages of ambient criteria air pollutants ($PM_{2.5}$, CO, NO_2, SO_2, and O_3) and meteorologic parameters (TEMP and RH) were collected from national air quality and weather monitoring stations in urban regions operated by Beijing Municipal Ecology and Environment Bureau and China Meteorological Administration, respectively. As shown in Figures S1 and S2 in Supporting Information S1, high correlations of criteria air pollutants and meteorologic parameters measured at the fixed-location station on PUHSC campus and each national monitoring station indicated that environmental measurements from our fixed-location monitoring station may sufficiently capture potential variations of environmental factors exposures in the study area.

2.3. Statistical Analysis

Descriptive statistics were conducted for health outcomes and environmental factors. Spearman's correlation coefficients were calculated to evaluate correlations between measured air pollutants.

We assessed the linkages between ambient carbon particle pollution exposure and ARI cases using a time-stratified case-crossover study design, which allowed each ARI case to be her or his own control by examining acute air pollution exposure on the days (i.e., referent periods) neighboring the case day (Pirozzi et al., 2018). This design approach can control potential influences from time-invariant characteristics at the individual level (e.g., age, sex, pre-existing diseases, and socioeconomic status) and risk factors that did not vary substantially within study participants over a short time period (e.g., body mass index and indoor air pollution). For each ARI case, we

defined the date of outpatient visit as the case day, and the control days were chosen from other days with the same year, month, and day of week (DOW) as the case day, thus adjusting for time-dependent factors caused by long-term trend, season, and DOW. In this study, each case day was matched to 3 to 4 control days. For instance, if an outpatient visit for ARI occurred on Tuesday 11 September 2018, we defined Tuesday 11 September 2018 as the case day, then the control days were all other Tuesdays in September 2018 (4, 15, and 25 September). Using this design approach, 685,846, 878,869, and 1,342,415 control days were selected for outpatient cases of 202,401 pneumonia, 258,954 bronchitis, and 395,544 TURI, respectively.

Association of ambient carbon particle pollution exposure with each ARI measure was estimated using conditional logistic regression (clogit) models. Considering the existing literature on the impact of air pollution on respiratory health (WHO, 2021), the relationship between carbon particles and ARI was assumed as linearity. Polynomial distributed lag model (PDLM) was first applied to account for linear relationships and potential collinearities among different lag days of exposure. The lag structure was constrained by a third-degree polynomial in cross-basis matrices. For all clogit models, we adjusted for public holidays as a binary variable. To control potential impacts of meteorologic factors, 3-day averages of TEMP and RH prior to the day of hospital visit for each case were modeled using natural splines functions (6 degrees of freedom (df) for TEMP and 3 df for RH) (Chen et al., 2017). Single-pollutant clogit models coupled with PDLM were then implemented by including carbon particle metrics to examine the lagged associations by up to 8 days.

In exploratory analyses, we first derived cumulative exposure-response relationships between carbon particle pollution and ARI cases from clogit models coupled with PDLM. Further, subgroup analyses were conducted by age, sex (male, female), and season (warm periods [April–September], cool periods [October–March]). Given that children residing in urban areas generally go to kindergarten at 2–3 years old and primary school at 6 years old, study participants were stratified by the following age groups: 0–1, 2–5, and 6–14 years. The differences in subgroup-specific effect estimates were tested by a 2-sample z-test, and the statistical significance for comparisons was defined at p-value < 0.05 for two groups and 0.025 for three groups (Xu et al., 2022). Two-pollutant clogit models were constructed to evaluate whether the single-pollutant effects might be confounded by a second pollutant, including $PM_{2.5}$, CO, NO_2, SO_2, and O_3. Finally, we performed sensitivity analyses to check the robustness of the observational associations in main models by (a) repeating the regression analyses by modeling ambient TEMP and RH with natural splines function according to minimizing Akaike's information criterion and (b) additional adjustment for influenza epidemic (assigned one to epidemic condition or zero otherwise) based on information obtained from the Chinese National Influenza Center.

All association estimates are expressed as odds ratios (ORs) for ARI by interquartile range (IQR) increases in ambient carbon particle concentrations as ($e^{(\beta \times IQR)}$) with corresponding 95% confidence intervals (lower 95%CI: ($[e^{((\beta-1.96 \times SE) \times IQR)}$), upper 95%CI: ($e^{((\beta+1.96 \times SE) \times IQR)}$) for each outcome variable, where β and SE is the regression coefficient (namely log OR) and the corresponding standard error derived from clogit model, respectively. All calculations were performed using R, version 4.2.1 (R Project for Statistical Computing), with p-value < 0.05 indicating statistical significance.

3. Results

Descriptive statistics of included participant characteristics are presented in Table 1. We identified a total of 856,899 cases of childhood cause-specific ARI, including pneumonia, bronchitis, and TURI. For outpatient visits for bronchitis, nearly 58.3% were younger children aged 2–5 years, 42.7% were females, and 58.1% cases occurred in the cold period. Distributions of carbon particle air pollution exposure during the study period are summarized in Table S1 in Supporting Information S1. The mean (IQR) concentrations of daily ambient BC, UVPM, Delta-C, and BrC were 3.36 (2.91), 5.27 (4.16), 2.05 (1.68) μg/m³, and 15.40 (13.30) Mm⁻¹, respectively. Two major sources of BC were identified by the Aethalometer model from traffic and biomass burning, and source contributions to BC in this study area were dominated by traffic fractions. Further, the average exposure to measured carbon particles on control days was generally lower than that on case days (Table 1). As shown in Table S2 in Supporting Information S1, Spearman correlations of BC with co-exposure to gaseous pollutants were relatively high, especially with traffic-related air pollutants CO and NO_2. Daily concentrations of Delta-C and BrC were moderately correlated with traffic pollution.

Single lag day-specific risks of outpatient visits for ARI associated with IQR increases in ambient carbon particle pollution are shown in Figures 1a, 1c, and 1e. Overall estimated associations of BC and UVPM with risks for

Table 1
Demographics of Eligible Participants and Environmental Measures During the Study Period From 2015 to 2019

	Pneumonia	Bronchitis	TURI
Characteristics			
ICD-10	(J12–13, J15–18)	(J40, J42, J44)	(J10–11, J32, B00, B08)
Total (n)	202,401	258,954	395,544
Age, years			
0–1	60,772	55,602	60,676
2–5	103,767	150,951	115,984
6–14	37,862	52,401	21,884
Sex			
Male	113,684	148,424	225,359
Female	88,717	110,530	170,185
Season			
Warm	78,167	108,439	185,867
Cold	124,234	150,515	209,677
Case days (n)	202,401	258,954	395,544
Control days, (n)	685,846	878,869	1,342,415
Exposure measures, mean (SD) [IQR]			
Case days			
Pollutants			
BC ($\mu g/m^3$)	3.46 (3.00) [3.25]	3.25 (2.84) [3.02]	3.15 (2.69) [2.89]
UVPM ($\mu g/m^3$)	5.97 (6.39) [5.33]	5.42 (5.77) [4.67]	5.13 (5.33) [4.52]
Delta-C ($\mu g/m^3$)	2.60 (4.03) [2.48]	2.27 (3.54) [2.24]	2.08 (3.21) [1.97]
BrC, (Mm^{-1})	18.67 (28.67) [17.66]	16.81 (27.23) [16.50]	15.64 (26.38) [18.29]
Emission sources of BC ($\mu g/m^3$)			
Traffic fraction	2.38 (2.03) [2.25]	2.32 (2.01) [2.18]	2.29 (1.92) [2.13]
Biomass burning	1.08 (1.35) [1.05]	0.93 (1.20) [0.96]	0.86 (1.14) [0.86]
Control days			
Pollutants			
BC ($\mu g/m^3$)	3.41 (3.03) [3.14]	3.19 (2.83) [2.98]	3.07 (2.66) [2.86]
UVPM ($\mu g/m^3$)	5.87 (6.37) [5.01]	5.32 (5.76) [4.68]	5.02 (5.34) [4.38]
Delta-C ($\mu g/m^3$)	2.54 (3.97) [2.45]	2.23 (3.54) [2.18]	2.05 (3.25) [1.88]
BrC (Mm^{-1})	18.21 (28.63) [17.16]	16.42 (27.20) [16.17]	15.21 (26.07) [15.19]
Emission sources of BC ($\mu g/m^3$)			
Traffic fraction	2.36 (2.07) [2.22]	2.28 (2.00) [2.14]	2.22 (1.90) [2.10]
Biomass burning	1.05 (1.35) [1.03]	0.91 (1.20) [0.94]	0.85 (1.13) [0.84]

Note. TURI, total upper respiratory infection; IQR, interquartile range; BC, black carbon; UVPM, ultra-violet absorbing particulate matter; Delta-C, delta carbon; and BrC, brown carbon.

pneumonia showed similar patterns over several days of exposure, with the largest effect estimates observed in the current day (Figure 1a). We found significant elevations of pneumonia by OR of 1.019 (95CI%, 1.013, 1.025) and 1.028 (95CI%, 1.019, 1.037), in association with IQR increases in BC and UVPM at lag day 0 of exposure, respectively. Higher Delta-C concentrations were also found in association with increased pneumonia risks by ORs of 1.006 (95CI%, 1.003, 1.009) to 1.007 (95CI%, 1.005, 1.010), whereas the lag structure was relatively flatter at all examined exposure periods. Further, the magnitude of the effect estimates of BrC, ORs ranging from 1.003 (95CI%, 1.002, 1.005) to 1.010 (95CI%, 1.008, 1.012), was comparable to those of Delta-C, but no
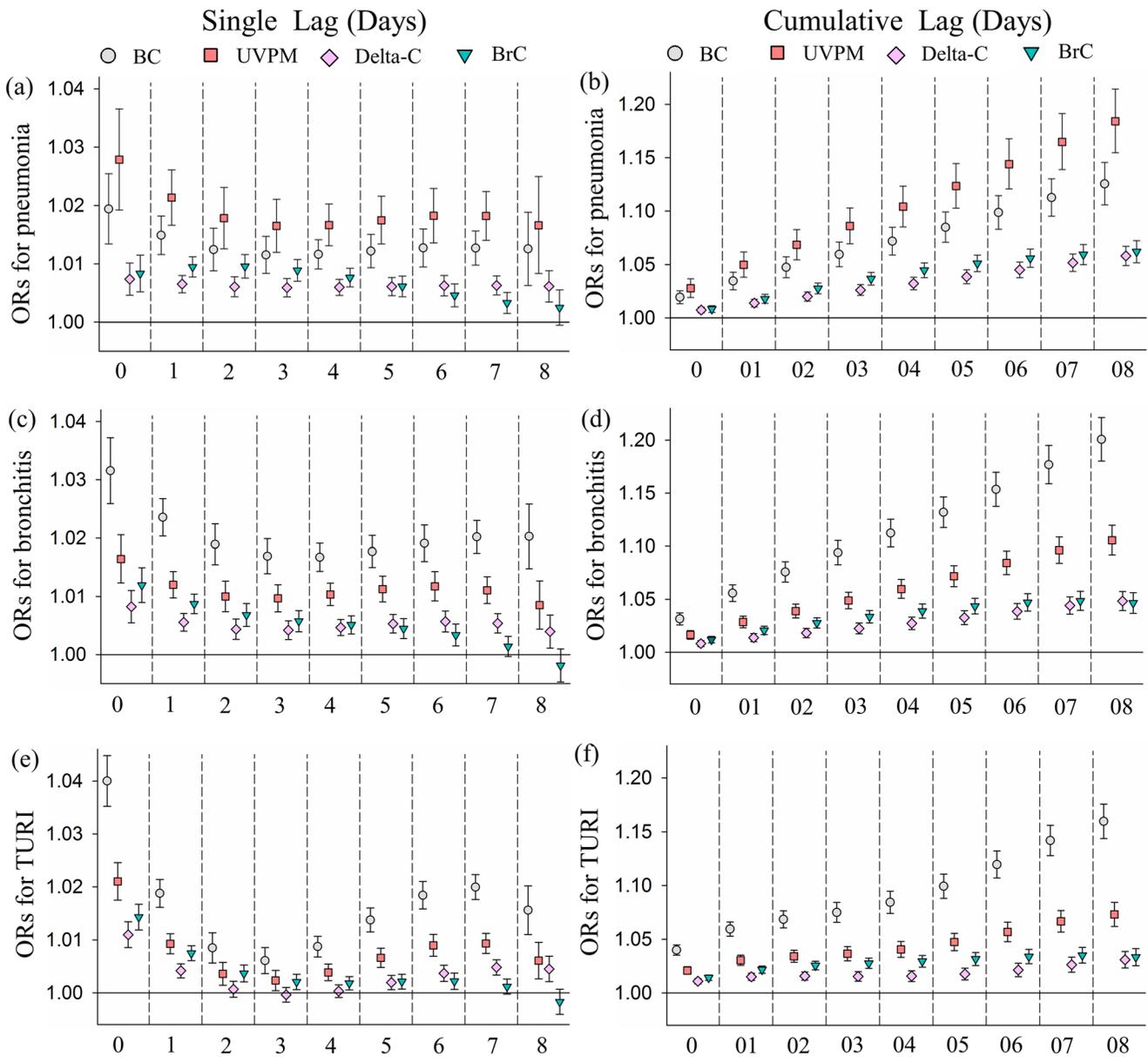
Figure 1. (a, c, e) *Single and* (b, d, f) *cumulative lag-specific risks of outpatient visits for respiratory infections associated with interquartile range increases in ambient carbon particle pollution exposure*. Abbreviation: TURI, total upper respiratory infection; BC, black carbon; UVPM, ultra-violet absorbing particulate matter; Delta-C, delta carbon; BrC, brown carbon; IQR, interquartile range; and OR, odds ratio.

significant effects were found at lag day 8 of exposure. For cases of bronchitis, the overall estimates for immediate association (lag0–3) were strong for exposure to BC, followed by UVPM, BrC, and Delta-C (Figure 1c). In specific, with IQR increases in concentrations of BC, UVPM, BrC, and Delta-C at lag day 0 of exposure, the corresponding OR for bronchitis was 1.032 (95CI%, 1.026, 1.037), 1.016 (95CI%, 1.012, 1.021), 1.012 (95CI%, 1.009, 1.015), and 1.008 (95CI%, 1.005, 1.011), respectively. We observed significant increases in TURI risks by ORs of 1.006 (95CI%, 1.004, 1.009) to 1.019 (95CI%, 1.016, 1.021) associated with exposure to BC at lag day 0–8, whereas the effect estimates appeared nonsignificant for Delta-C at lag day 2–3 and for BrC at lag day 6–7 (Figure 1e).

Cumulative lag day-specific risks of outpatient visits for ARI associated with IQR increases in ambient carbon particle pollution are shown in Figures 1b, 1d, and 1f. We observed consistently positive associations of BC, UVPM, BrC, and Delta-C with pneumonia cases, with the largest ORs ranging from 1.058 (95CI%, 1.049, 1.067)
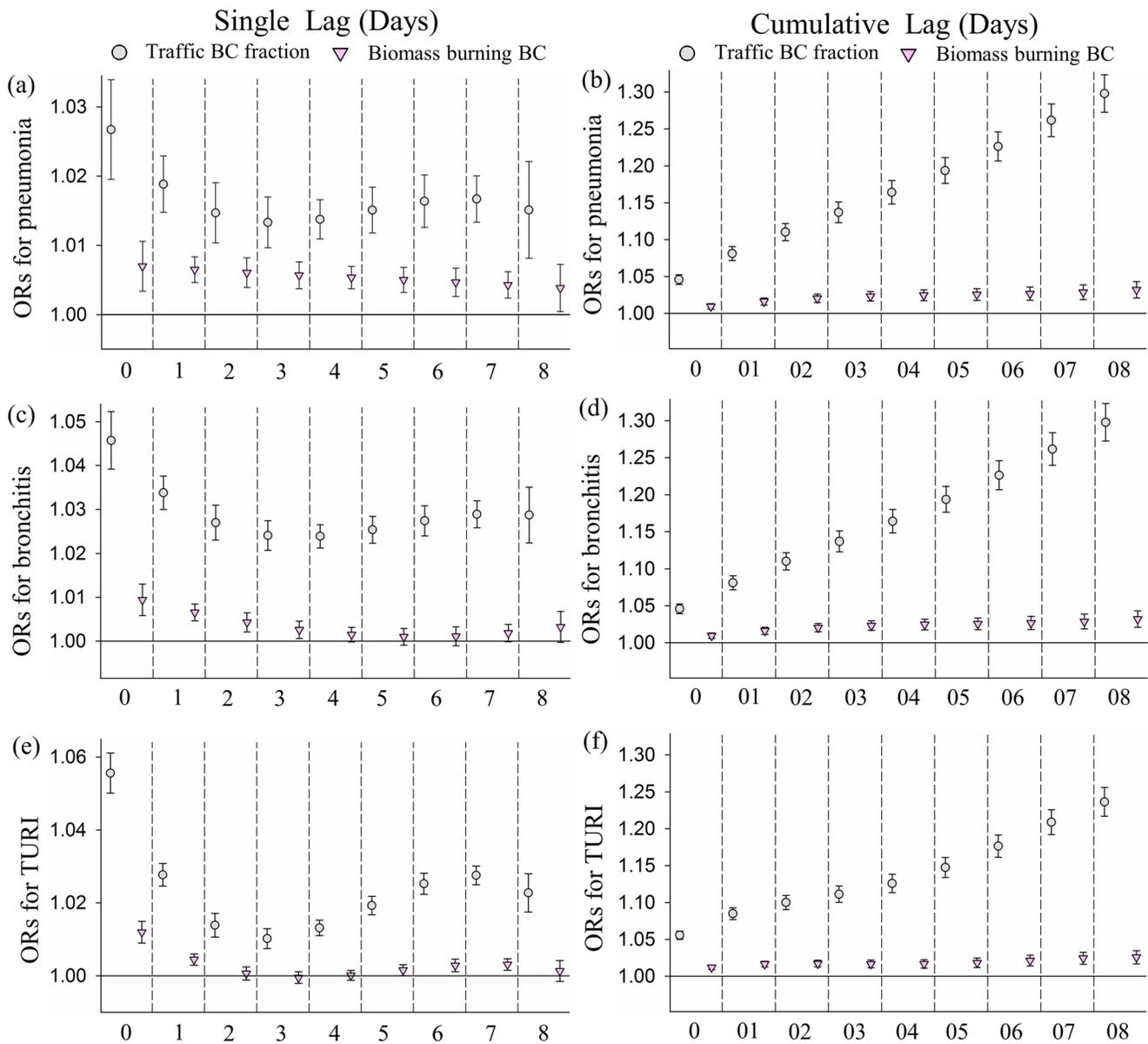
Figure 2. (a, c, e) *Single and* (b, d, f) *cumulative lag-specific risks of outpatient visits for respiratory infections associated with interquartile range increases in ambient sources of black carbon.* Abbreviation: TURI, total upper respiratory infection; BC, black carbon; IQR, interquartile range; and OR, odds ratio.

to 1.184 (95CI%, 1.155, 1.214) at cumulative lags of 0–8 days (Figure 1b). In addition, we found significant elevations of bronchitis by ORs of 1.032 (95CI%, 1.026, 1.037) to 1.201 (95CI%, 1.180, 1.211), in association with IQR increases in BC over cumulative lags of multiple days (Figure 1d). We noted that the effect estimates of bronchitis attributable to BC were substantially stronger than those posed by other carbon particles (e.g., BrC and Delta-C). The association patterns were also found for TURI, with ORs of 1.040 (95CI%, 1.035, 1.045) to 1.160 (95CI%, 1.144, 1.176) for BC, 1.011 (95CI%, 1.009, 1.013) to 1.031 (95CI%, 1.023, 1.039) for Delta-C, and 1.014 (95CI%, 1.012, 1.017) to 1.305 (95CI%, 1.028, 1.042) for BrC (Figure 1f). As shown in Figure 2, the adverse respiratory events in relation to IQR increases in exposure to BC were mainly from traffic sources. We found significant increases in risks for pneumonia by OR of 1.161 (95% CI: 1.137, 1.186) responsive to traffic BC fractions at cumulative lags of 0–8 days of exposure, whereas the corresponding risk estimate was 1.049 (95% CI, 1.038, 1.060) for exposure to biomass BC burning.

In exploratory analyses, the concentration-response curves for ARI and carbon particle pollution are presented in Figure 3 and Figure S3 in Supporting Information S1. In general, the curves graphically illustrated a relationship
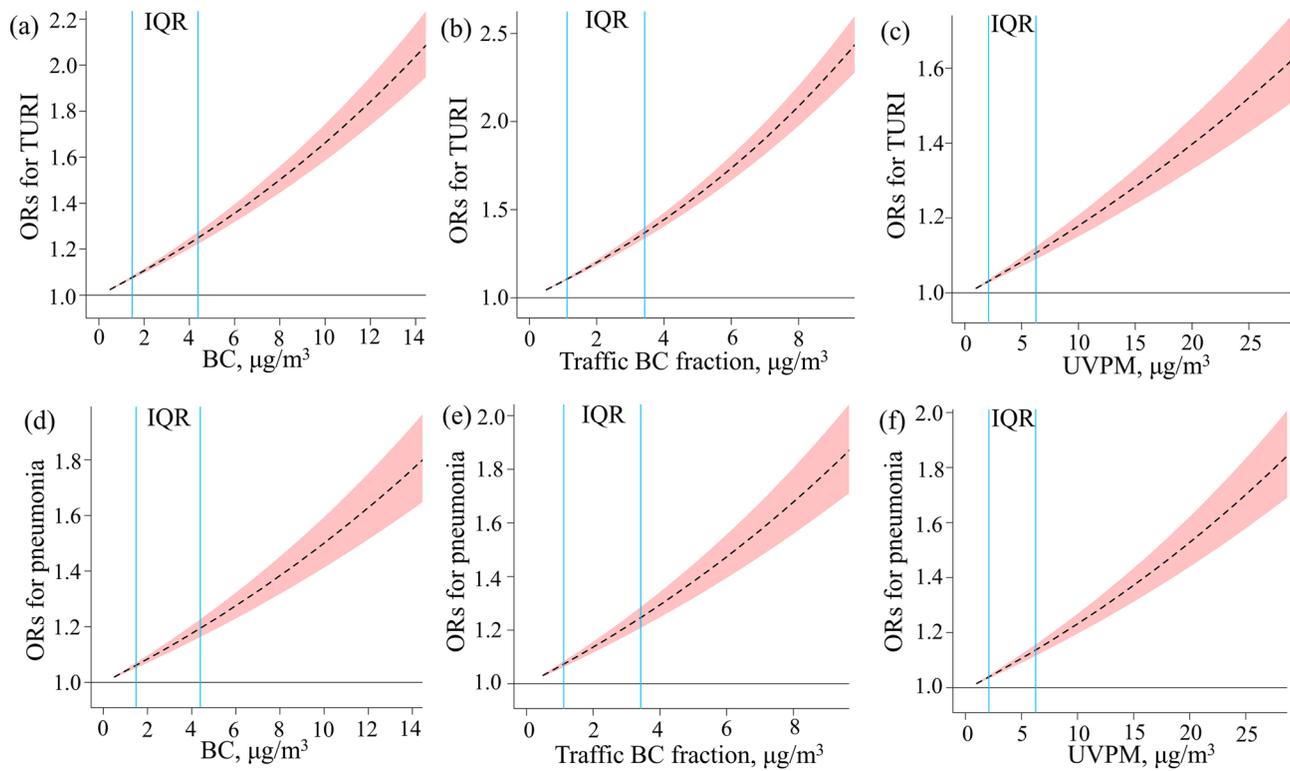
Figure 3. *Cumulative exposure-response curves of the associations between outpatient visits for respiratory infections and ambient carbon particle pollution over lags 0 to 8 days.* The interquartile range for black carbon (BC), traffic BC fraction, and ultra-violet absorbing particulate matter was 2.91, 2.30, and 4.16, respectively. In all analyses, participants experiencing the top 1% of carbon particle concentrations were trimmed for modeling exposure-response curves. Abbreviation: IQR, interquartile range; OR, odds ratio; BC, black carbon; and UVPM, ultra-violet absorbing particulate matter.

whereby exposure to high levels of carbon particles could contribute to greater magnitudes of adverse respiratory events. Results derived from subgroup analyses by participant characteristics (age and sex) and season are presented in Figure 4 and Figures S4–S6 in Supporting Information S1. We found that the pollutants-associated increases in risks of ARI were greater among older children (Figure 4 and Figure S4 in Supporting Information S1). Specifically, the OR of pneumonia and BC exposures at cumulative lag of 0–8 days was 1.064 (95CI%, 1.032, 1.098) in children aged 0–1 year, whereas the effect from individuals aged 6–14 years was relatively high (OR 1.194 [95CI%, 1.144, 1.245]). We did not find consistent association patterns between carbon particles and respiratory events among sex- and season-specific groups. Additionally, our main results of carbon particles remained robust in two-pollutant models after controlling copollutants (Table S3 in Supporting Information S1) and in repeating analyses with controlling meteorologic factors using natural spline functions or additional adjustments for potential impacts of influenza epidemic (Figure S7 in Supporting Information S1).

4. Discussion

In this case-crossover analysis of pediatric respiratory diseases in megacity Beijing, we have shown that recent exposure to ambient BC and wood smoke (UVPM, Delta-C, and BrC) is significantly associated with increased risks of cause-specific ARI, including pneumonia, bronchitis, and TURI. Specifically, the risk estimates posed by ambient BC were predominantly driven by its emission sources originating from traffic. Concentration-response curves indicated that increased risks for ARI were consistently found across measured spectrum of carbon particle concentrations, with no apparent detrimental effect thresholds. Subgroup analyses further showed that deleterious respiratory effects were stronger among older children. To our knowledge, our current study is the first to systematically reveal the influences of ambient BC and its sources, as well as wood smoke-related particles on childhood ARI, suggesting that carbon particle pollution may pose potential respiratory risks to vulnerable population, such as children, in megacities with dense population and anthropogenic activities. Future studies implicated in the biological pathogenesis of pediatric respiratory infection diseases responsive carbon air pollution exposure are urgently needed.
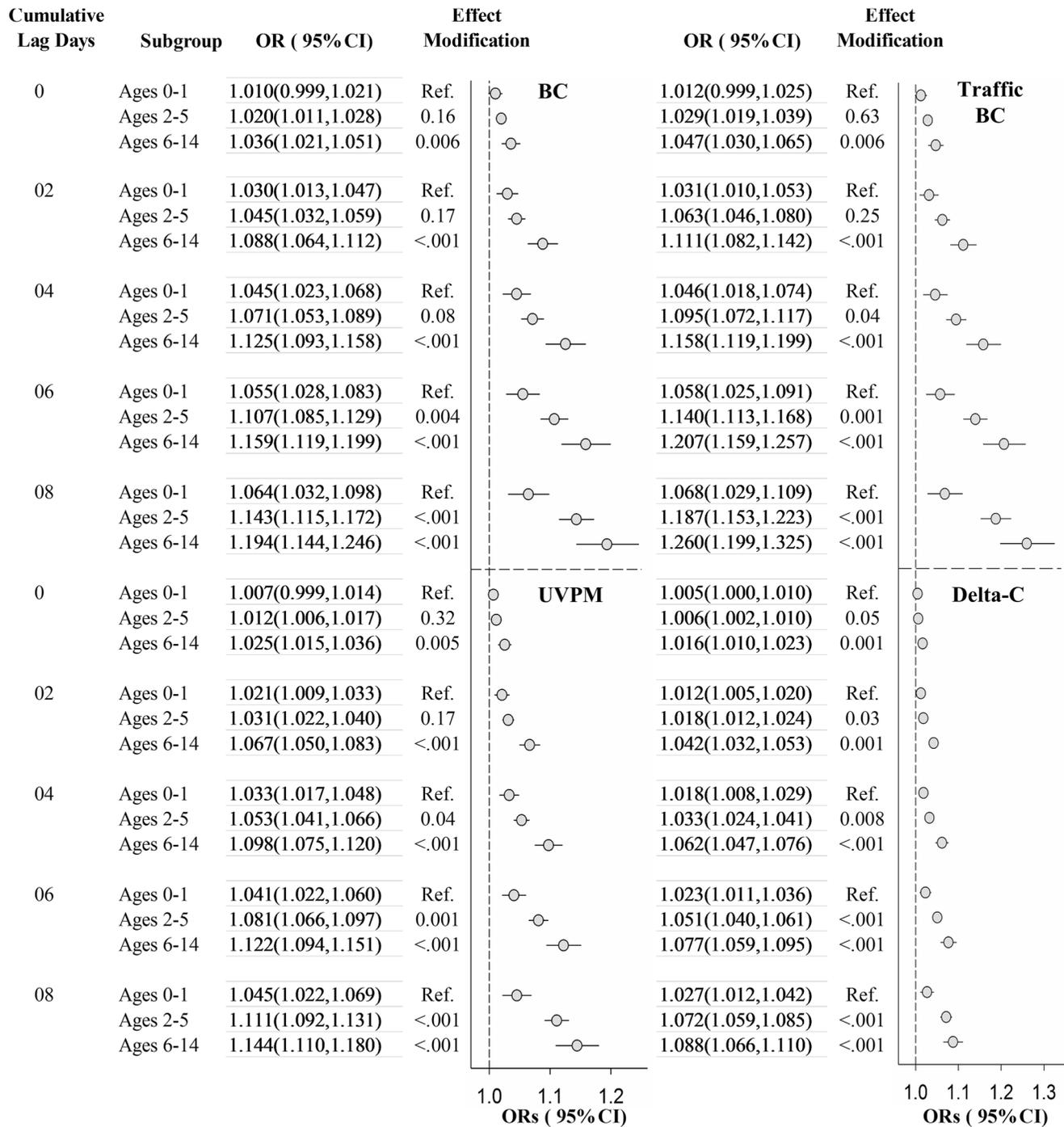
Cumulative Lag Days	Subgroup	OR (95% CI)	Effect Modification	OR (95% CI)	Effect Modification
BC				**Traffic BC**	
0	Ages 0-1	1.010(0.999,1.021)	Ref.	1.012(0.999,1.025)	Ref.
	Ages 2-5	1.020(1.011,1.028)	0.16	1.029(1.019,1.039)	0.63
	Ages 6-14	1.036(1.021,1.051)	0.006	1.047(1.030,1.065)	0.006
02	Ages 0-1	1.030(1.013,1.047)	Ref.	1.031(1.010,1.053)	Ref.
	Ages 2-5	1.045(1.032,1.059)	0.17	1.063(1.046,1.080)	0.25
	Ages 6-14	1.088(1.064,1.112)	<.001	1.111(1.082,1.142)	<.001
04	Ages 0-1	1.045(1.023,1.068)	Ref.	1.046(1.018,1.074)	Ref.
	Ages 2-5	1.071(1.053,1.089)	0.08	1.095(1.072,1.117)	0.04
	Ages 6-14	1.125(1.093,1.158)	<.001	1.158(1.119,1.199)	<.001
06	Ages 0-1	1.055(1.028,1.083)	Ref.	1.058(1.025,1.091)	Ref.
	Ages 2-5	1.107(1.085,1.129)	0.004	1.140(1.113,1.168)	0.001
	Ages 6-14	1.159(1.119,1.199)	<.001	1.207(1.159,1.257)	<.001
08	Ages 0-1	1.064(1.032,1.098)	Ref.	1.068(1.029,1.109)	Ref.
	Ages 2-5	1.143(1.115,1.172)	<.001	1.187(1.153,1.223)	<.001
	Ages 6-14	1.194(1.144,1.246)	<.001	1.260(1.199,1.325)	<.001
UVPM				**Delta-C**	
0	Ages 0-1	1.007(0.999,1.014)	Ref.	1.005(1.000,1.010)	Ref.
	Ages 2-5	1.012(1.006,1.017)	0.32	1.006(1.002,1.010)	0.05
	Ages 6-14	1.025(1.015,1.036)	0.005	1.016(1.010,1.023)	0.001
02	Ages 0-1	1.021(1.009,1.033)	Ref.	1.012(1.005,1.020)	Ref.
	Ages 2-5	1.031(1.022,1.040)	0.17	1.018(1.012,1.024)	0.03
	Ages 6-14	1.067(1.050,1.083)	<.001	1.042(1.032,1.053)	0.001
04	Ages 0-1	1.033(1.017,1.048)	Ref.	1.018(1.008,1.029)	Ref.
	Ages 2-5	1.053(1.041,1.066)	0.04	1.033(1.024,1.041)	0.008
	Ages 6-14	1.098(1.075,1.120)	<.001	1.062(1.047,1.076)	<.001
06	Ages 0-1	1.041(1.022,1.060)	Ref.	1.023(1.011,1.036)	Ref.
	Ages 2-5	1.081(1.066,1.097)	0.001	1.051(1.040,1.061)	<.001
	Ages 6-14	1.122(1.094,1.151)	<.001	1.077(1.059,1.095)	<.001
08	Ages 0-1	1.045(1.022,1.069)	Ref.	1.027(1.012,1.042)	Ref.
	Ages 2-5	1.111(1.092,1.131)	<.001	1.072(1.059,1.085)	<.001
	Ages 6-14	1.144(1.110,1.180)	<.001	1.088(1.066,1.110)	<.001

Figure 4. *Risks of outpatient visits for pneumonia associated with interquartile range increases in ambient carbon particle concentrations over cumulative lags 0 to 8 days stratified by age.* Abbreviation: IQR, interquartile range; OR, odds ratio; BC, black carbon; UVPM, ultra-violet absorbing particulate matter; and Delta-C, delta carbon.

Extensive investigations have examined the associations between air pollution and respiratory infections over the past decades, however, the evidence of linking ambient BC exposures with pediatric ARI is largely sparse. BC represents the elemental carbon core of particles from incomplete combustions, vehicular traffic (particularly diesel-powered) is crucial source of BC, but activities of biomass burning (e.g., use of wood or coal) can also contribute to ambient BC (JN et al., 2012). A prior cross-sectional investigation assessing impact of air pollution on respiratory diseases has shown that the adjusted OR for bronchitis symptoms in association with IQR

(0.15 μg/m³) increases in BC concentrations of was 1.04 (95%CI, 1.00, 1.08) in 1,109 children from urban area near busy roads of the San Francisco Bay Area (Kim et al., 2004). In comparison, the Prevention and Incidence of Asthma and Mite Allergy study including 2,578 children showed null associations between ambient soot (a measure of elemental carbon) and bronchitis during the first 4 years of life in a population of children residing in both rural and urban areas of the Netherlands (Brauer et al., 2007). Also, a cross-sectional study conducted in 30,315 Chinese children reported that no significant effects of pneumonia were found for lifetime ambient BC exposures (Shi et al., 2021). The disparate findings might be partially explained by the heterogeneity in study contexts, including population characteristics and exposure assessments. Report from the WHO indicated that interpreting results of BC exposures from epidemiologic observations should consider the primary sources of BC in study areas (JN et al., 2012). Recent evidence indicated that the source contributions to daily ambient BC concentrations in Beijing were predominated by anthropogenic emission sectors (e.g., transportation) and biomass burning emissions (Mao et al., 2020). To date, no studies have specifically examined whether the adverse respiratory effects of BC exposures could be attributed to its potential sources, whereas health effects for cardio-vascular responses caused by source-specific BC have been identified (Ljungman et al., 2019). The authors have reported that the linkages between ambient BC and stroke incidence are most apparent for exposure from traffic sources (Ljungman et al., 2019). The present study showed the clear lag association patterns of respiratory infections with ambient BC and its well-characterized BC emission sources, included traffic and biomass burning. Interesting, in two-pollutant models with adjustment for $PM_{2.5}$, the magnitude of estimated effects of BC and traffic BC fractions on bronchitis became stronger, whereas the effects attenuated after controlling for NO_2. One potential explanation is that BC effects were confounded by other combustion products contributing to $PM_{2.5}$, and BC may share similar emission sources with pollutants originating from traffic (e.g., NO_2) (Janssen et al., 2011). It is noteworthy that in the region of this study, the IQR for carbon particles such as BC was 2.91 μg/m³ among exposed young children, whereas in other studies IQRs ranged from 0.15 to 0.90 μg/m³ (Brauer et al., 2007; Kim et al., 2004; Shi et al., 2021). Given that a positive linear relationship was found at IQR concentrations of BC exposures, our findings suggested that significant reductions in ambient BC might generate enormous public health benefits, particularly mitigating the ARI burden in children.

In addition, we found that exposure to wood smoke-related particles was associated with clinical manifestations of ARI. Delta-C has been used a specific indicator for wood smoke pollution, and both UVPM and BrC represent a typical cluster of organic fractions (e.g., aromatic compounds from biomass burning) of BC particles (Deslauriers et al., 2022; J. Wang et al., 2018; Y. Wang et al., 2011). While household pollutants, such as wood fuel use for cooking, have been closely correlated with adverse respiratory events (Raju et al., 2020), few studies have examined the impact of ambient wood smoke on pediatric ARI. In this study, by comprehensive assessment of various ambient wood smoke metrics in real-world exposure settings, we provided clear evidence showing that ambient wood smoke-related particles were significantly associated with elevated risks of childhood respiratory diseases caused by infection of lower and upper respiratory tracts. For Delta-C at cumulative exposure periods, we obtained risk estimates of outpatient visits for pneumonia, bronchitis, and TURI in exposed children, ranging from 0.7% to 5.8%, 0.3% to 4.8%, and 1.1% to 3.1%, respectively. To date, wood smoke-related particles from anthropogenic activities (e.g., wildfires) have been found to be an increasing source of particulate air pollution worldwide (D'Evelyn et al., 2022). Prior evidence showed that increases in days of wood smoke exposures were associated with heightened risks of bronchiolitis by 4%–11% in children (Karr et al., 2009). A comparable study indicated that risks of respiratory admissions increased by nearly 7% during smoke days of exposure with high levels of wildfire-specific pollutants relative to the nonsmoker days (Liu et al., 2017). Although the magnitude of the estimated effects caused by wood smoke-related particles found in the present study might be relatively small, its adverse impacts would pose a tremendous threat to burden of pediatric respiratory infection diseases as wood smoke episodes occur frequently in the context of global climate crisis (Reid & Maestas, 2019).

Our collective findings were in line with existing mechanistic evidence that carbon particles can be capable of impairment in pulmonary host defense through several pathways, consequently heightened respiratory infections following air pollution exposure (Beentjes et al., 2022). Studies have revealed that carbon particles as biologically active stimuli can swiftly elicit pulmonary and systemic inflammatory responses (De Prins et al., 2014). Animal models indicated exacerbations of respiratory virus-induced inflammation (e.g., elevated neutrophils in broncho-alveolar lavage), chemokine expressions, and airway hyperresponsiveness after ultrafine carbon black exposures (Lambert et al., 2003). Further, inhalation of carbon particles impairs phagocytic action of alveolar macrophages and capacity of viral uptake by macrophages, then prompting colonization and infection of the pathogens in

respiratory tracts (Loaiza-Ceballos et al., 2022). Laboratory studies reported that BC could affect airway bacterial ecosystems and the tolerance of bacterial biofilms to antibiotics, such as enhancing replication and survival of Streptococcus pneumoniae against antibacterial agents (Hussey et al., 2017). It has been demonstrated that the antimicrobial activities of cathelicidin, including antibacterial and antiviral actions, are substantially suppressed by exposure to carbon particles (Findlay et al., 2017). Studies in vitro showed that traffic-related particles could enhance pneumococcal adhesion to the airway via up-regulated expressions of platelet-activating factor receptor (Miyashita et al., 2022). A recent clinical study showed that ambient combustion-related particles (e.g., BC and Delta-C) were associated with alterations in the transcriptomic of respiratory infection-related immune responses in patients hospitalized with ARI (Croft et al., 2021). Here, the overall magnitude of the estimated effects posed by carbon particles found in this population significantly reduced in single-day lag exposure metrics with the largest OR on lag day 0; however, the cumulative effects were greater during prolonged exposure period. The stronger health impacts of traffic BC fractions were supported by growing evidence indicating that carbon particles may contain absorb a variety of toxic compounds and consequently penetrate into the lungs (Long & Carlsten, 2022). This association pattern was also largely consistent with previous findings of the impact of BC inhalation on respiratory inflammation in children (Lin et al., 2011), suggesting that repeated air pollution exposures could play a more prominent role on the respiratory health. Another crucial factor for toxicological effects of particles is the ability to deposit into the lungs (Olesiejuk & Chałubiński, 2023). A prior analysis has shown that the number deposition of inhaled particles depends strongly on its emission sources, and nearly 69% of traffic particles and 38% of the wood combustion could be deposited in the respiratory tract (Kristensson et al., 2013). The difference in respiratory-tract deposition of particles might help explain our findings of deferential association patterns posed by source-specific carbon particles exposures. More recently, an in vitro study reported that the changes in pulmonary bacterial numbers and inflammatory cytokines posed by diesel exhaust particles (a major source of traffic BC fraction) were larger than those of wood smoke (Samuelsen et al., 2009). Given that the precise biological pathway underlying the linkage between air pollution exposure and ARI remains poorly elucidated, further studies are warrant to explain potentially mechanism involved.

This study has a number of strengths. First, a broad array of carbon particle metrics was simultaneously measured using a state of the art of monitor instrument, which enabled us to assess comprehensive impacts of BC and its sources, as well as wood smoke exposures on adverse respiratory events. Second, unlike studies performed in North American and European countries, the wide spectrum of carbon particle concentrations captured by long time-series measurements in this study area with poor air quality provided a unique opportunity to examine respiratory effects of ambient BC and wood smoke in relatively wider exposure ranges. Third, using PDLM models allowed to identify multiple-day health effects of an individual day's exposure and offered detailed information on estimation of effects showing that cumulative exposures might contribute to stronger effects. Despite these strengths, we also recognized several limitations. Results from correlations between ambient criteria air pollutants measured at our fixed-location station and national monitoring stations suggested that the spatiotemporal distribution characteristic of daily pollutants in this study area displayed similar change patterns. Nevertheless, using single monitor based carbon pollutant data as surrogates for population's exposure, a common assessment approach applied in epidemiologic studies, might have introduced potential nondifferential exposure misclassification to underestimate the observational associations. Further, BCH is the largest facility for children and adolescents in Beijing, and thus collected outcomes might represent respiratory events of the general pediatric population, but potential selection bias was inevitable. Moreover, although time-stratified case-crossover design was adequate to control covariates relevant to time-invariant and time-dependent factors (e.g., sex, indoor air pollution, and season), lifestyle-related confounders may not be fully adjusted; however, this type of confounder was not likely to change considerably over the month for individuals. Also, air pollution exposure metrics were assigned to each participant based on the date of outpatient visits, which might bias the effects of air pollution due to lack of exact time from onset to outpatient visits. Although all cause-specific ARI cases were carefully reviewed by the expertise physicians and classified based on ICD-10 codes to ensure consistency of disease diagnosis; however, the diagnosis classification for each case without confirmation by laboratory analyses (e.g., PCR), which might have engendered disease case misclassification. Another possible limitation is that the choice to study younger subjects (children aged 0–14 years) could have reduce the generalizability of the observational effects to a broader population (e.g., young adults and the elderly). Here, we found robust and consistent associations between pediatric ARI and carbon particle pollution exposure in this study, which are of public importance because growing clinical evidence has shown that childhood respiratory events (e.g., pneumonia and bronchitis) could be linked to multiple detrimental respiratory outcomes in their middle age (Perret et al., 2020).

5. Conclusions

We have shown here that ambient anthropogenic carbons during prior days of exposure is significantly associated with heightened risks of upper and lower respiratory tract infections in children. Given that global pandemic of pediatric ARI and air pollution episodes occurs more frequently under the global context of climate change, our findings highlight the importance of discerning adverse respiratory effects caused by anthropogenic source-specific carbon air pollution (e.g., traffic and wood smoke), thereby protecting vulnerable individuals during the early life.

Conflict of Interest

The authors declare no conflicts of interest relevant to this study.

Data Availability Statement

The data on health outcomes used in this study are not publicly available due to confi-dentiality of individual information. The data on environmental measures from the fixed-site monitoring on PUHSC used in this study are not publicly available due to protection of property right. The data on concentrations of ambient air pollution used in this study were collected from Beijing Municipal Ecology and Environment Bureau and are available at http://zx.bjmemc.com.cn/getAqiList.shtml?timestamp=1668402696544. The data on meteorological parameters used in this study were collected from Daily Timed Data from automated weather stations in China and are available at http://data.cma.cn/en/?r=data/detail&dataCode=A.0012.0001. The data on weekly reports of influenza used in this study were collected from the Chinese National Influenza Center and are available at https://ivdc.chinacdc.cn/cnic/en/Surveillance/.

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