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- The short-term effect of air pollution and disease burden of type 2 diabetes mellitus were estimated in Sichuan, China

Supporting Information:

Supporting Information may be found in the online version of this article.

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The Short-Term Effects and Burden of Ambient Air Pollution on Hospitalization for Type 2 Diabetes: Time-Stratified Case-Crossover Evidence From Sichuan, China

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Abstract Type 2 diabetes mellitus (T2DM), a complicated metabolic disease, might be developed or exacerbated by air pollution, resulting in economic and health burden to patients. So far, limited studies have estimated associations between short-term exposure to air pollution and disease burden of T2DM in China. Hence, we aimed to estimate the associations and burden of ambient air pollutants (NO_2, PM_{10}, $PM_{2.5}$, SO_2, and CO) on hospital admissions (HAs) for T2DM using a time-stratified case-crossover design. Data on HAs for T2DM during 2017–2019 were collected from hospital electronic health records in nine cities in Sichuan Province using conditional poisson regression. Totally, 92,381 T2DM hospitalizations were recorded. There were significant short-term effects of NO_2, PM_{10}, $PM_{2.5}$, SO_2 and CO on HAs for T2DM. A 10 μg/m^3 increment of NO_2, PM_{10}, $PM_{2.5}$, SO_2 and CO as linked with a 3.39% (95% CI: 2.26%, 4.54%), 0.33% (95% CI: 0.04%, 0.62%), 0.76% (95% CI: 0.35%, 1.16%), 12.68% (95% CI: 8.14%, 17.42%) and 79.00% (95% CI: 39.81%, 129.18%) increase in HAs for T2DM at lag 6. Stratified analyses modified by age, sex, and season showed old (≥65 years) and female patients linked with higher impacts. Using WHO's air quality guidelines of NO_2, PM_{10}, $PM_{2.5}$, and CO as the reference, the attributable number of T2DM HAs exceeding these pollutants exposures were 786, 323, 793, and 2,127 during 2017–2019. Besides, the total medical costs of 25.83, 10.54, 30.74, and 67.78 million China Yuan were attributed to NO_2, PM_{10}, $PM_{2.5}$, and CO. In conclusion, short-term exposures to air pollutants were associated with higher risks of HAs for T2DM.

Plain Language Summary Type 2 diabetes mellitus (T2DM) as complicated and severe metabolic disease, would be affected by air pollution, rendering numerous burdens on patients and society. In this study, the associations and burden of air pollutants (NO_2, PM_{10}, $PM_{2.5}$, SO_2, and CO) on hospital admissions (HAs) for T2DM were estimated using conditional poisson regression. Data on HAs for T2DM in nine cities in Sichuan Province during 2017–2019 were involved. In summary, there were 92,381 cases of T2DM hospitalizations. Results showed that significant short-term effects of air pollution on HAs for T2DM. In stratified analyses modified by age, sex, and season, higher impacts were linked with old (≥65 years) and female patients. When adopting WHO's air guidelines of NO_2, PM_{10}, $PM_{2.5}$, and CO, the attributable number and cost of HAs for T2DM exceeding air guidelines were estimated, posing central risks to public health. Continuous and further efforts should be taken to air pollution.

1. Introduction

Type 2 diabetes mellitus (T2DM), a complicated and severe metabolic disease, has escalated sharply during recent decades world-wide, resulting in massive burdens on both T2DM patients and society. According to the International Diabetes Federation, as the ninth cause of death, 537 million people were suffering from diabetes in 2021 globally. Among the diabetes patients, T2DM accounts for 90%, which was predicted to rise to 783 million in 2045 (Sun et al., 2022). When compared with people without diabetes, T2DM patients had a 15% increased risk of all-cause mortality (Tancredi et al., 2015). Considerable socioeconomic pressures from diabetes were for costs to global health economies, which were estimated at least US$966 billion in 2021, having increased 316% over the last 15 years (Sun et al., 2022). Heavy burden had brought for many countries, since the large quantity of diabetes patients. Specially, 140.9 million Chinese adult population had T2DM in 2021, having the most T2DM patients in the world (Sun et al., 2022). Since the China's healthcare reform in 2009, Chinese government has

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issued a series of policies and strategies to enhance the management of chronic diseases, like diabetes as one of the most typical chronic diseases (Jia & Tong, 2015).

Around the world, almost 99% people are breathing the air that are above the limits of World Health Organization (WHO, 2022). In recent years, various studies have investigated the associations between short-term exposure to ambient air pollution and T2DM incidence and burden (Liu et al., 2013, 2021a; Rajagopalan & Brook, 2012). Globally, 3.2 million cases of diabetes mellitus were linked with ambient air particle matter (PM), rendering to 8.3 million disability-adjusted life-years (Benjamin et al., 2018). A study in Chile reported that an interquartile range increase in particle matter (PM) with aerodynamic diameter ≤2.5 μm ($PM_{2.5}$), ≤10 μm (PM_{10}), nitrogen dioxide (NO_2), and sulfur dioxide (SO_2) were involved with relative risks of hospitalization for diabetes as 1.11 (95% confidence interval (CI): 1.06, 1.16), 1.11 (95% CI: 1.07, 1.15), 1.12 (95% CI: 1.05, 1.20), and 1.14 (95% CI: 1.06, 1.22), separately (Dales et al., 2012). Evidence from in vivo, in vitro and epidemiologic studies consistently supports the short exposure to air pollution to cause inflammation through further exacerbating systemic insulin resistance via over activity of the sympathetic nervous system (Li et al., 2012; Rajagopalan & Brook, 2012), which need to be further investigated with more relative studies.

Until now, limited studies were observed in developing countries, which were undergoing a marked aggravation in T2DM over the last decades with severer air pollution than developed countries (Nicole, 2015). However, there were gaps for the epidemiology evidence in developing countries, like the areas of China with high air pollution, which could lead to comparable health and cost (Jiang et al., 2022; Ma et al., 2016). For example, Sichuan Province was the fourth of high air levels in China in which the high $PM_{2.5}$ and PM_{10} levels was 47.7 and 75.9 μg/m^3 (Xiong et al., 2019), being about 9 and 5 times higher than the annual guideline (5 μg/m^3 for $PM_{2.5}$ and 15 μg/m^3 for PM_{10}) reported by World Health Organization (WHO, 2021). Situated in Sichuan Basin, in addition to high population densities and rich economies, Sichuan Province was linked with heavy air pollution from the intensive consumption of energy and unfavorable geographical conditions (Zhang et al., 2009). Particularly, a total of about 83 million residents in 2020 was in Sichuan Province, ranking as the fifth of population among all provinces (NBSC, 2021). Environment and meteorological conditions, like temperature or humidity would vary from city to city (Wang et al., 2021). Nonetheless, air pollution and health outcomes mainly pay attention to megacity of China, like Beijing (Bao et al., 2017). Few previous studies have confirmed the short-term effect of air pollution on multi-city scale in Sichuan. Besides, available studies have not evaluated the short-term effect of ambient air pollution on hospital admissions (HAs) for T2DM and related economic burden, which could serve as an evidence-based implications for chronic disease prevention in China.

Thus, the objective of this study is to estimate the associations between short-term exposure to ambient air pollution and hospital admissions (HAs) for T2DM in nine cities in Sichuan Province during 2017–2019. We also calculated the economic burden of T2DM owing to ambient air pollution.

2. Materials and Methods

2.1. Study Area

There are 21 cities in Sichuan Province. Considering the low data quality and limited availability of health data, some cities were no involved. In this study, 9 cities in Sichuan Province were included (Figure 1). Nine cities were Chengdu (CD), Mianyang (MY), Nanchong (NC), Guangan (GA), Meishan (MS), Zigong (ZG), Liangshanzhou (LSZ), Yibin (YB), and Luzhou (LZ), respectively.

2.2. Data

2.2.1. Hospitalization Data

The hospitalization data were obtained from the hospital electronic health records of 131 tertiary and secondary hospitals in nine cities of Sichuan Province. The International Classification of Disease 10th Revision (ICD-10: E11) codes of each hospitalization records were adopted to define as T2DM patients during the period of 1 January 2017 and 31 December 2019. The data include basic demographics, HAs time and primary discharge diagnosis.

2.2.2. Environmental Data

Ambient daily air pollution data of NO_2, SO_2, PM_{10}, $PM_{2.5}$, and CO were obtained from Sichuan Ecological Environmental Monitoring Station from 2017 to 2019, covering 82 air monitoring stations in the 9 cities with

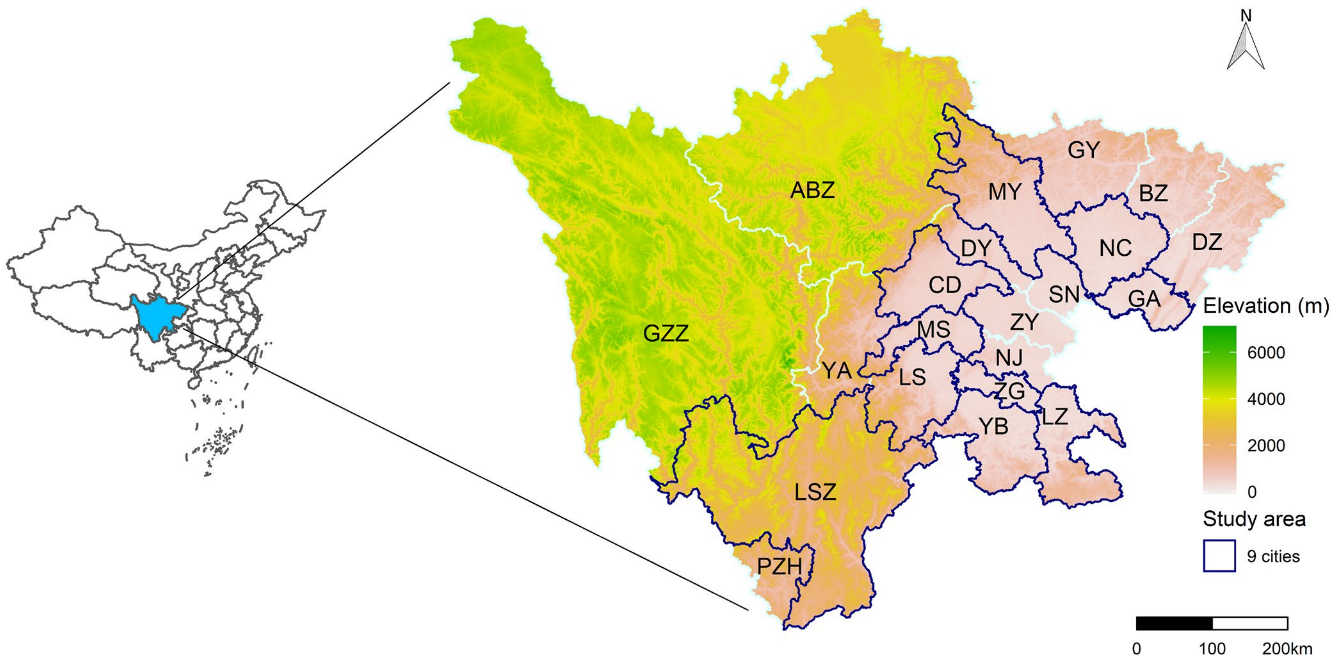

Figure 1. Geographical distribution of study areas, 9 cities of Sichuan Province.

19 in CD, 9 MY, 9 in NC, 6 in GA, 6 in MS, 6 in ZG, 17 LSZ and 10 YB. Meteorological data were collected from Sichuan Meteorological Bureau. Inverse distance weighting method (IDW) were involved to solve the missing data, which was a common and practical spatial interpolation method in environmental investigations (Byun & Schere, 2006). The calculation of IDW interpolation was based on the weighted average, which was applied to point source data like the environmental data from monitoring stations in this study (Shepard, 1968; Su et al., 2018). In addition, the AutoNavi Maps API (https://lbs.amap.com/) were involved to geocode the locations of all T2DM cases and monitoring stations. The individual exposure on the single day (from the current day to 7 days before: from lag 0 to lag 7) and multi-day moving average day (lag 01 to lag 07) could be calculated, which were used to estimate the average daily levels for the model.

2.3. Modeling

The analysis involves three steps: confirming exposure-response function, estimating the number of HAs for T2DM due to ambient air pollution, and calculating corresponding economic cost of HAs for T2DM due to air exposure.

2.3.1. Statistical Methods

Time-series analysis was involved to evaluate the short-term effect of ambient air levels with HAs for T2DM (Zanobetti et al., 2014). Case-crossover study would compare the exposure in admissions with those from the same day of the week in the same month of this year as reference days, to evaluate the differences of exposure which might be influenced by the daily count of records (Janes et al., 2005). Based on case-crossover design framework, the influence of long-term tendency, seasonal effect, and day of week could be adjusted (Zanobetti et al., 2009). This study applied the time-stratified case-crossover design with conditional poisson regression to estimate main exposure from NO_2, PM_{10}, $PM_{2.5}$, SO_2, and CO on daily T2DM hospitalizations. In the model, temperature, relative humidity and city were taken as confounding factors. Daily T2DM cases were poisson distribution (Menzin et al., 2010). The Relative Risk (RR) and 95% CI were calculated for per 1 μg/m^3 increase of air concentrations.

The relative risk increase (RRI) in HAs for T2DM per 10 μg/m^3 increase of air levels were calculated by (RR-1), with details as follows:

$$\text{RRI}\% = \exp(\beta * 10) - 1 * 100\% \tag{1}$$

where β is the coefficient of air concentrations and HAs for T2DM from conditional poisson regression based on time-stratified case-crossover design. Besides, to make practicable comparison with previous study, the RRI in HA for per interquartile range increase was also estimated by using the interquartile data for air pollutants from different lag structure.

The short-term effects of air levels were confirmed by single pollutant models. When discerning the temporal effect with different lag structures, the single day (from the current day to 7 days before: from lag 0 to lag 7) and multi-day moving average day (from lag 01 to lag 07) were associated. The multi-day moving average lag exposures were the cumulative average from the current day (lag 0) to the lag day, like lag 02 is the cumulative average from lag 0, lag 1, and lag 2. Subgroups analyses were also involved to estimate the effects of stratified modification by age (<65 years and ≥65 years), gender (male and female) and season (warm season: April-September and cold season: October-March).

Pearson's correlation coefficients were estimated to confirm the correlation degree between air pollutants and meteorological data. All analyses were conducted using R (version 4.0.4). The amapGeocode package were adopted to geocode the locations. The gnm package were involved to apply the conditional poisson regression based on the time-stratified case-crossover design. The significance criterion was set at $p < 0.05$.

2.3.2. Calculating the Number of HAs for T2DM due to PM Pollution

The attributable number of HAs for T2DM was estimated from the coefficients of conditional poisson regression, with WHO's air quality guidelines for the 24 hr average setting as reference levels (25 μg/m^3 for NO_2, 45 μg/m^3 for PM_{10} and 15 μg/m^3 for $PM_{2.5}$, and 4 μg/m^3 for CO) (WHO, 2021). Since the concentrations of SO_2 were often below air guidelines, the attributable number of HAs for T2DM were excluded. The formula is as follows:

$$\mathrm{AN}i = (\exp(\beta * (x_i - x_0)) - 1)/\exp(\beta * (x_i - x_0)) * Ni \tag{2}$$

where ANi is the number of attributable HAs of T2DM to exceeding reference levels on day i; x_i (μg/m) is the observed level of air pollution on day i; x_0 is reference concentration from air quality guideline of WHO, which was setting as the theoretical minimum threshold levels. When air levels below the minimum threshold, there is no effect on HAs for T2DM (Evans et al., 2013); N_i is the number of HAs for T2DM on day i; AN is the sum of overall ANi during 2017–2019. In single pollutant model, the largest effect was adopted to estimate the attributable exposure to exceeding air guidelines (Wang et al., 2020).

2.3.3. Evaluating the Corresponding Hospitalization Economic Expense

The economic burden of HAs for T2DM due to air pollution were estimated, including the total HA expense and out-of-pocket cost. The formulas were as follows:

$$AC_{ytotal} = AN_y * Cost_{ytotal} * CPI_y \tag{3}$$

$$AC_{ypocket} = AN_y * Cost_{ypocket} * CPI_y \tag{4}$$

where AC_{ytotal} and $AC_{ypocket}$ are the total HA cost and out-of-pocket cost being attributable to exceeding air reference levels in year y; AN_y is the sum of overall AN_y during year y obtained from Equation 2; $Cost_{ytotal}$ and $Cost_{ypocket}$ indicate the case-average total HA expenses and out-of-pocket expenses in year y; CPI_y is the product of customer price indexes from year $y + 1$ to 2019; AC_{total} is the sum of AC_{ytotal}, and $AC_{ypocket}$ is the sum of $AC_{ypocket}$ during the study period.

2.4. Sensitivity Analysis

The robustness of major air pollutant influence on T2DM HAs in two-pollutant models were confirmed after adopting other air pollutant. In addition, the cases within circular areas of 50 km surrounding air measuring stations were estimated, which could represent the potential influence of distance (Liu, Pan, et al., 2021).

3. Results

3.1. Data Description

The descriptive results for T2DM hospitalization, air pollutant levels, and meteorological variables in Sichuan from 2017 to 2019 were listed in Table 1. In total, 92,381 T2DM cases were recorded, with 48,340 males and

Table 1
Summary Statistics of Hospital Admissions for Type 2 Diabetes Mellitus, Related Medical Expenses, Air Pollution Levels and Weather Conditions in the Nine Cities of Sichuan Province, 2017–2019

		Descriptive statistics for daily data					
Pollutant	Total number	Mean ± SD	Min	Max	P_{25}	P_{50}	P_{75}
T2DM (n)	92,381	69 ± 48	1	202	20	68	108
Total admission by age (*n*)							
<65	48,206	44 ± 19	1	116	29	43	57
≥65	44,175	40 ± 18	1	112	27	39	53
Total admission by sex (*n*)							
Male	48,340	44 ± 19	1	113	29	43	58
Female	44,041	40 ± 17	1	102	27	39	52
Total admission by season (*n*)							
Warm season	47,712	87 ± 35	18	200	59	86	112
Cold season	44,669	82 ± 36	1	202	56	80	106
Medical expenses[a]							
Total expenses		1 ± 1.3	0	140.3	0.5	0.8	1.2
Out-of-pocket cost		0.4 ± 0.7	0	81.8	0.1	0.2	0.4
Air pollution levels (μg/m^3)							
NO_2		29.3 ± 14.9	1	127.1	18.3	26.2	37.1
Warm season[b]		25.4 ± 12.8	1	109.2	16.4	22.3	31.5
Cold season[b]		33.4 ± 15.8	1.1	127.1	21.8	30.8	42.3
PM_{10}		65.3 ± 42	2.4	441.5	35.4	54.2	83.5
Warm season		49.3 ± 25.7	2.4	207.6	30.8	43.7	62.3
Cold season		82.4 ± 48.9	3.2	441.5	46.1	72.2	107.6
$PM_{2.5}$		41.3 ± 30.2	2	279.9	20.6	32.7	52.3
Warm season		28.4 ± 15	2	164.1	17.3	25.4	36.2
Cold season		55.1 ± 35.7	2	279.9	28.8	46.8	72.7
SO_2		10.8 ± 5.7	0	138.9	7.1	9.6	13
Warm season		10.2 ± 5.2	0	108.6	6.9	9.1	12.2
Cold season		11.5 ± 6.1	1	138.9	7.4	10.1	13.9
CO		84.1 ± 41.1	1.1	310.2	54.5	77	108.6
Warm season		106.4 ± 39.3	2.7	310.2	76.6	101.2	131.4
Cold season		60.2 ± 27.2	1.1	190.6	40.6	57.3	75.8
Meteorological measures							
Temperature (°C)		17.6 ± 7.2	0.1	34.5	11.2	18	23.6
Relative humidity (%)		76.7 ± 12.7	12.9	99.9	69.1	78.5	86.2

[a]Unit: case-average expenses, 10 thousand CNY. [b]warm season: April-September and cold season: October-March.

44,041 females. The age group of <65 and ≥65 years accounted for 52.2% and 47.8% separately. The number of HAs for T2DM in warm season were slightly higher than cold season. The overall total medical cost and self-paid cost was 935.8 million China Yuan (CNY) and 324.9 million CNY. And the case-average costs were 1.0 and 0.4 10 thousand CNY, respectively. Daily mean concentrations were 29.3 μg/m^3 for NO_2, 65.3 μg/m^3 for PM_{10}, 41.3 μg/m^3 for $PM_{2.5}$, 10.8 μg/m^3 for SO_2, 84.1 μg/m^3 for CO, 17.6°C for temperature, and 76.7% for relative humidity. The season-specific concentrations of air pollution were larger in cold season, except $PM_{2.5}$ and PM_{10}. Summary statistics of specific characteristics for 9 cities were displayed in Tables S1 and S2 in Supporting Information S1. Pearson correlation coefficients for all air levels and meteorological variables was illustrated in Figure S2 in Supporting Information S1.

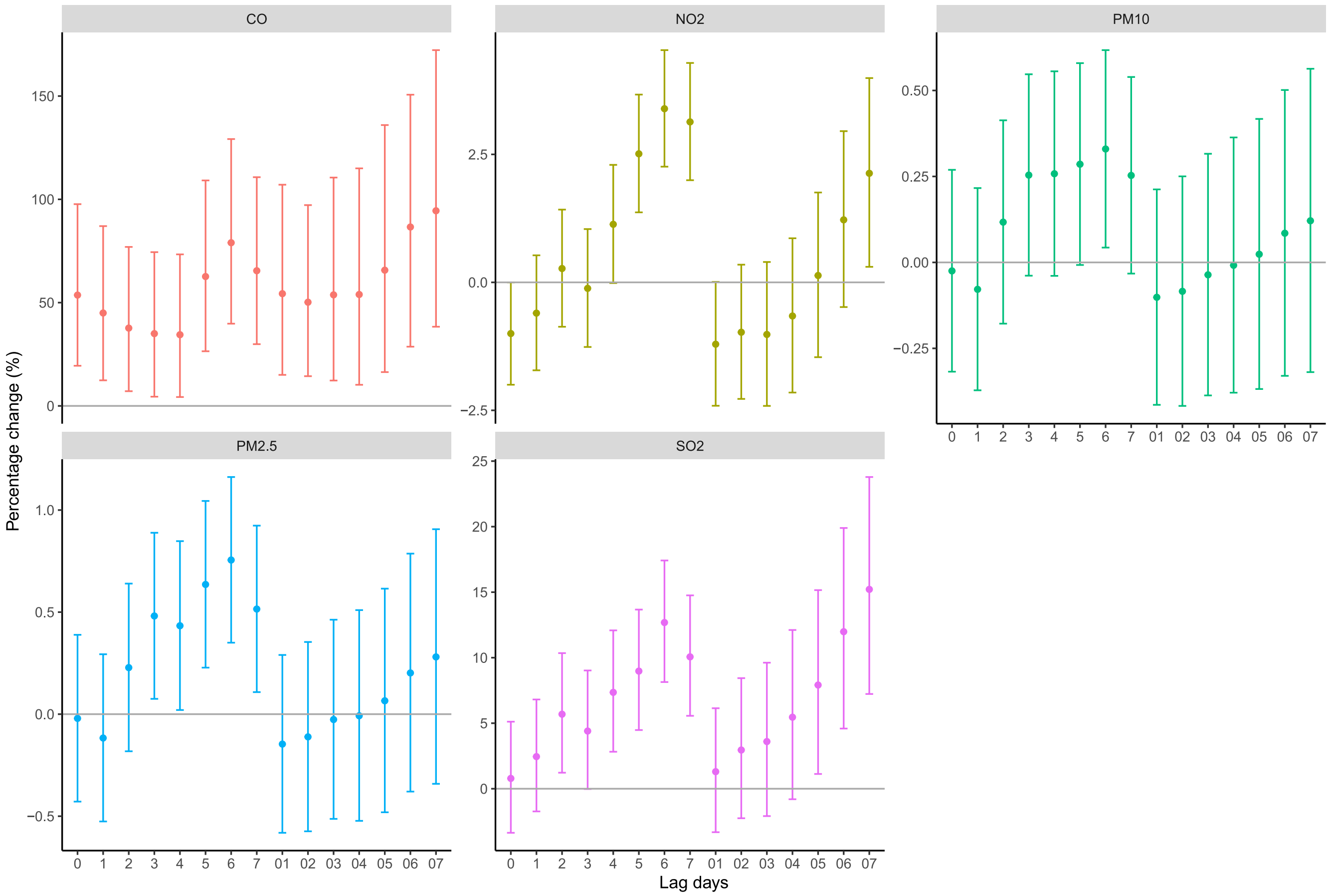

Figure 2. Percentage change (95% confidence interval) in hospital admissions for Type 2 diabetes mellitus associated with a 10 μg/m^3 increase in NO_2, PM_{10}, $PM_{2.5}$, and SO_2 on single day lags (from current day to 7 days before: lag 0–lag 7) and multi-day moving average lags (from lag 01 to lag 07) using single pollutant models.

3.2. Health Effects of PM Exposure in Overall and Subgroup Population

The associations of air pollutants with HAs for T2DM in single pollutant models along different lag structure were showed in Figure 2. Generally, except CO, the effect of air pollution on HAs for T2DM presented significantly at lag 5, lag 6 and lag 7 with the highest effect at lag 6. Per 10 μg/m^3 increase of NO_2, PM_{10}, $PM_{2.5}$, SO_2, and CO were linked with a RRI of 3.39% (95% CI: 2.26%, 4.54%), 0.33% (95% CI: 0.04%, 0.62%), 0.76% (95% CI: 0.35%, 1.16%), 12.68% (95% CI: 8.14%, 17.42%) and 79.00% (95% CI: 39.81%, 129.18%) in HAs for T2DM at lag 6, separately. The effect after adjusting individual city were estimated in Figure S1 in Supporting Information S1, since at lag 6 with strongest effect in single pollutant models. As shown, the effect of air pollution on T2DM would vary by cities.

The results of stratified analyses by age, sex, and season at lag 6 were displayed in Figure 3. Based on the results of the single pollutant model with the largest effects at lag 6, the subgroup analyses were presented at lag 6. As for the results of stratified analyses by age, the effects of air pollution on HAs for T2DM were significant for patients (≥65 years), except the correlations with PM10. While for the old (≥65 years), a RRI of 4.17% (95% CI: 2.67%, 5.71%), 0.71% (95% CI: 0.32%, 1.11%), 1.28% (95 CI%: 0.71%, 1.84%), 14.71% (95% CI: 8.35%, 21.44%), and 53.1% (95% CI: 21.42%, 114.50%) were estimated with an increase of 10 μg/m^3 of NO_2, PM_{10}, $PM_{2.5}$, SO_2 and CO. In gender-specific analysis, the female was exposed to higher air pollution risks. In terms of season analyses, except CO, the effects of air pollution were both positive in cold and warm season. Higher associations were found between NO_2 and SO_2 in cold season, while stronger effects were estimated in warm season for PM_{10} and $PM_{2.5}$.

3.3. Sensitivity Analysis

To estimate the coupled effects of other pollutants on the HAs for T2DM, the results of two-pollutant model was displayed in Table S4 in Supporting Information S1. Besides, the associated effects between $PM_{2.5}$ and PM_{10}

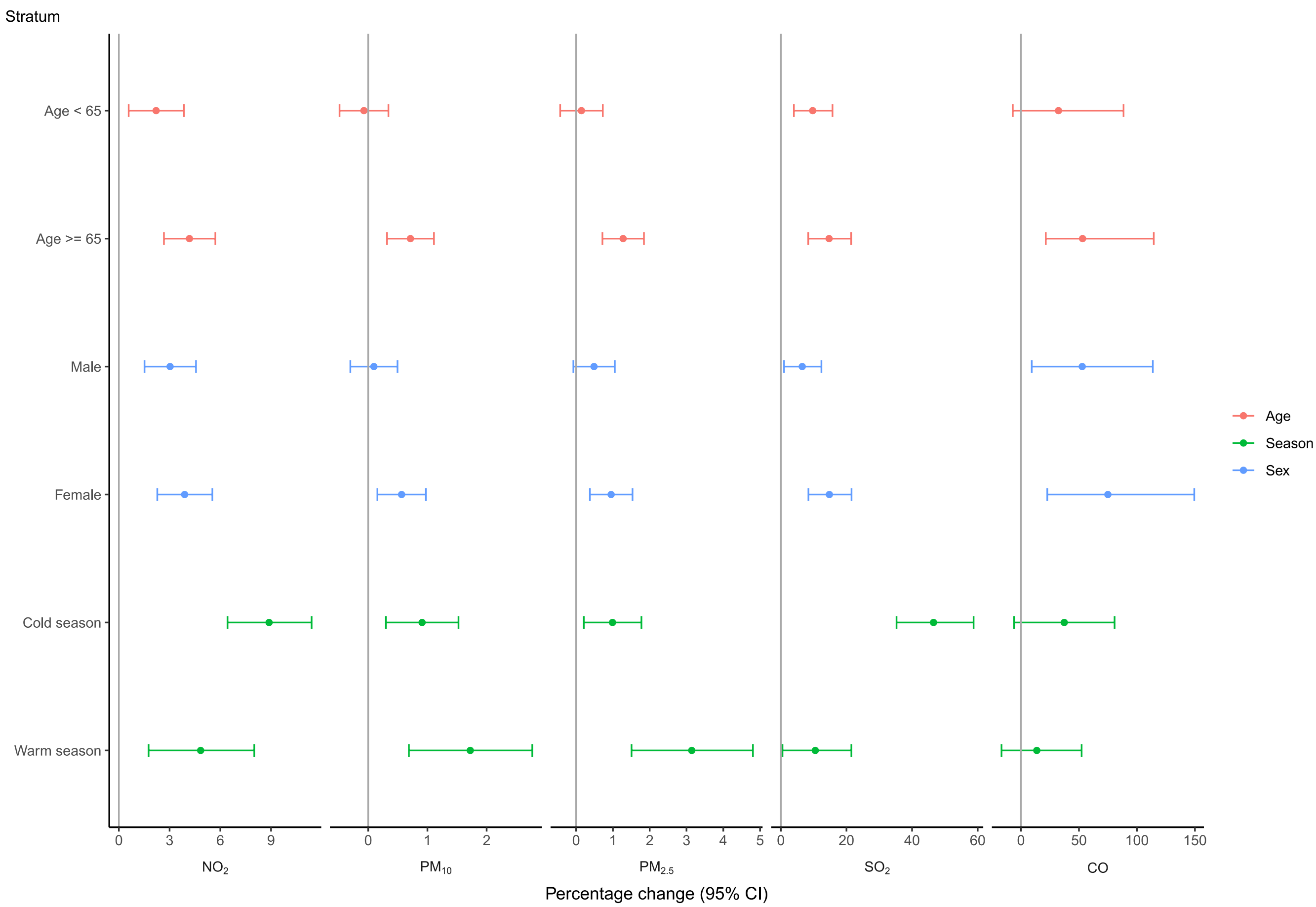

Figure 3. Percentage change (95% confidence interval) of age, sex, and season group in overall hospital admissions for Type 2 diabetes mellitus associating with a 10 μg/m^3 increase in NO_2, PM_{10}, $PM_{2.5}$, and SO_2 at lag 6 in Sichuan Province in 2017–2019.

were excluded since the high correlation ($r = 0.95$). The results of two-pollutant models were listed in Table S4 in Supporting Information S1. After the adjustment of the second pollutant, the effect of a single pollutant would vary to some extent. Some would be weakened, while the other would be enhanced. Like, the effect of $PM_{2.5}$ and PM_{10} would be decreased after the introduction of the second pollutant, while the impact of SO_2 would be increased after the introduction of PM_{10} or $PM_{2.5}$. In addition, to test the robustness of main models, the percentage change (95% CI) of air pollutants per 10 μg/m^3 increase at various lag structure within the circular areas of 50 km from the nearest air monitoring stations were displayed in Figure S3 in Supporting Information S1.

3.4. Attributable Health Risks and Economic Costs due to PM Pollution

The attributable number of HAs for T2DM and associated economic expense in Sichuan Province during 2017–2019 were displayed in Table 2, which were caused by exceeding the WHO air quality standard. As shown, 786, 323, 793 and 2127 total cases of HAs for T2DM could be owing to exceed the air guidelines of NO_2, PM_{10}, $PM_{2.5}$ and CO. Associating with exceeding exposure of NO_2, PM_{10}, $PM_{2.5}$, and CO during 2017–2019, 25.83, 10.54, 30.74, and 67.78 million CNY were estimated for the total medical expense, and 10.27, 4.15, 12.19, and 26.93 were confirmed for the out-of-pocket cost, separately.

4. Discussion

4.1. Summary of Findings

This study is the first to estimate the associations between levels of NO_2, PM_{10}, $PM_{2.5}$, SO_2, and CO and risks of HAs for T2DM in short-term exposure in nine cities in Sichuan Province from 2017 to 2019. As shown,

Table 2
The Attributable Number of Hospital Admissions for Type 2 Diabetes Mellitus and Corresponding Economic Cost due to Exceeding Air Pollution Exposure Using WHO Air Quality Standard in Sichuan Province, 2017–2019

	NO_2			PM_{10}			$PM_{2.5}$			CO		
Year	AN_y	AC_{ytotal}[a]	$AC_{ypocket}$[a]	AN_y	AC_{ytotal}[a]	$AC_{ypocket}$[a]	AN_y	AC_{ytotal}[a]	$AC_{ypocket}$[a]	AN_y	AC_{ytotal}[a]	$AC_{ypocket}$[a]
2017	216	8.14	3.81	78	2.92	1.36	202	7.59	3.55	444	16.70	7.81
2018	405	12.94	4.60	175	5.58	1.98	380	12.15	4.32	802	25.62	9.10
2019	164	4.75	1.87	71	2.04	0.80	211	10.99	4.32	881	25.46	10.1
Total	786	25.83	10.27	323	10.54	4.15	793	30.74	12.19	2127	67.78	26.93

Note. AN_y, AC_{ytotal}, $AC_{ypocket}$ were calculated based on the largest effect estimates in single pollutant models (lag 6).
[a]Unit: million CNY. The annual economic costs were measured at the CPI from 2019.

significant associations between air pollution exposure and HAs for T2DM were discerned. In stratified analysis, the old (≥65), female patients and in cold season might expose to higher effect of outdoor air pollution, which is consistent with prior studies (Rao et al., 2015; Wang et al., 2018). In addition, taking the WHO's air quality as reference, exceeding NO_2, PM_{10}, $PM_{2.5}$, and CO exposure associated with massive total economic cost to HAs for T2DM, with 25.83, 10.54, 12.19 and 26.93 million CNY during 2017–2019.

In stratified analyses, the short-term effect of ambient air levels with HAs for T2DM distributed not equally among subgroups. In age-specific analyses, the patient with age ≥65 years were more susceptive to the air pollution, which was in line with previous studies (Sun et al., 2016). Higher mortality or morbidity risks related to air pollution being found in the elderly than the young. Since that the old were more vulnerable to air pollution, this introduced more greater exposure associated from more outdoor time than the young with work necessities (Tong et al., 2015). As for the gender-specific effects, females were associated with higher exposure to air pollution than males, linking with prior studies (Wang et al., 2018). For instance, a cross-sectional study found that females were exposed to high levels of NO_2 with a 4% increase in diabetes prevalence while not for males in the US (Brook et al., 2008). Not only biological but also non-biological factors might result in this difference. Like, female has greater deposition of particle pollution in the lung and smaller airway diameter than men (Mitsakou et al., 2007). Under such susceptibility to health conditions, airway reactivity would be elevated through favoring particulate deposition (Bennett et al., 1996). In addition, females and males were involved with different life stress and socioeconomic status (Seeman et al., 2002). A study reported that health and behavior of female are more vulnerable to various residential environmental factors (Wen & Zhang, 2009). The effects of air pollutants with T2DM hospitalizations were stronger in cold season for NO_2 and SO_2, while contrary results for PM_{10} and $PM_{2.5}$. So far, the evidence was not consistent about the modification effects of season on air pollution (Wang et al., 2018). Different pronounced effects in cold and warm seasons may be owing to various characteristic of air pollution, climate conditions and pollutant sources. Previous studies have found stronger association between air pollution and T2DM HAs in cold season (Luo et al., 2023). With less rain and wind during cold season, the higher levels of particle pollutants are associated with slower diffusion. Besides, there might be some common biological pathways for low temperature and air pollution, like elevated inflammation and oxidative stress by increasing the susceptibility to air pollution (Halonen et al., 2010). As for warm season, heat exposure is more likely linked with increasing risks of diabetes-related HAs (Xu et al., 2019). Because the pollutant sources and climate conditions would vary. NO_2 and SO_2 are precursors of secondary particles. In China, coal combustion was the primary source of particulate and gaseous pollutants in cold season, like NO_2 and SO_2. As for particle pollutants, mainly from industrial production and vehicles, higher levels were estimated in warm season (Zhao et al., 2018). Like a previous study found that NO_2 and PM_{10} all were relative with insulin resistance increasing, while PM_{10} with higher effect of 18.7% than NO_2 of 17.0%. Besides, recent studies reported that the development and progression of cardio-metabolic diseases might link with systemic oxidative stress and low-grade inflammation which were involving with the pathogenesis of T2DM, when exposed to traffic related air pollution (Rajagopalan & Brook, 2012).

The RR of T2DM per interquartile range increase of NO_2, SO_2, PM_{10}, and $PM_{2.5}$ is 1.34% (95% CI: 0.90%, 1.79%), 4.89% (95% CI:3.18%, 6.63%), 0.13% (95% CI: 0.02%, 0.25%), and 0.30% (95% CI: 0.14%, 0.46%) on lag 6, respectively. Interestingly, higher impact was found in gaseous pollutants (NO_2, SO_2, and CO) when compared with particulate air pollutants (PM_{10} and $PM_{2.5}$) in lag 5–7, which was associated with a meta-analysis on the associations between air pollution and diabetes risk (Janghorbani et al., 2014) and time-series studies addressed the effects of air pollutants on mortality in China (Wong et al., 2008; Wu et al., 2021). Whereas the findings from Europe and US were not accordant, reporting that higher effects of PM_{10} and NO_2 on morbidity than SO_2 (Milojevic et al., 2014; Woodruff et al., 2008). In prior studies on health outcomes, stronger effects were also found in gaseous pollutants than particulate pollutants, with different values that might owing to the diversity in population sensitivity and hygiene conditions for different areas (Liang et al., 2019; Zhang et al., 2017). Overall, exposure to ambient air pollutants is likely more than one pollutant since the mixture of air pollutants.

4.2. Selected Review of Relevant Literature

In the past few decades, increasing studies observed the significant associations between air pollutants and HAs for T2DM, from developed areas like Europe or North America to developing countries like China (Kloog et al., 2012; Song et al., 2018). Only limited multi-city studies reported the associations of air pollution with T2DM hospitalizations. For example, a multi-city study in the US found that a 10 μg/m^3 of $PM_{2.5}$ corresponded to a 1.14% (95% CI: 0.56%, 1.73%) increase in hospitalization risks for diabetes in the moving average of lag 2 (Zanobetti et al., 2014). Particularly, the large quantity of studies was conducted in single-city level. Song et al. reported that an increase of 10 μg/m^3 of NO_2, PM_{10}, $PM_{2.5}$, SO_2 and CO corresponded to increment in T2DM hospitalization of 1.27% (95% CI: 0.33%, 2.22%), 0.32% (95% CI: 0.10%, 0.55%), 0.53% (95% CI: 0.22%, 0.83%), 0.55% (95% CI: 0.04%, 1.07%) and 0.04% (95% CI: 0.02%, 0.06%) in Shijiazhuang, China (Song et al., 2018). A study reported that a 10 μg/m^3 increase in NO_2 was coincided with an increase in morbidity for diabetes by 1.22% (95% CI: 0.51, 2.96) in Tianjin, China (Tong et al., 2015). A study conducted in Shanghai found that a 10 μg/m^3 increase in PM_{10}, SO_2 and CO were involved with a 0.6% (95% CI: 0.1%, 1.2%), 1.1% (95% CI: −0.10%, 3.2%), and 1.3% (95% CI: 0.00%, 2.6%) increase in RR of diabetes mortality (Kan et al., 2004). We also summarized the relative studies on the short-term effect between air pollutants and T2DM incidence or prevalence in Table S5 in Supporting Information S1, which could give insights to support the short-term effect of air pollution on diabetes.

There were some relative studies conducted in developed countries. A study presented that the United States adults would increase hospitalizations of diabetes when exposed to higher levels of air pollutants (Zanobetti et al., 2009). A study conducted in Los Angeles found that higher exposure to traffic related $PM_{2.5}$ and NO_2 were likely associated with diabetes development (Coogan et al., 2012). The results from Chile reported that increased concentrations of air pollutants would contribute to increasing the risks of diabetes (Dales et al., 2012). These studies provided the effects of air pollutants on HAs for T2DM for various region, facilitating the abundance and insights of relative studies globally.

4.3. Pathophysiologic Mechanisms of T2DM and Air Pollution

So far, the mechanisms of T2DM and air pollution is plausible, with several hypotheses existing. Strong evidence supported the triggering of inflammation in T2DM (Donath & Shoelson, 2011), specifically when chronic activation of inflammatory may be linking with chronic insulin resistance and subsequent T2DM, which is associated with air pollution (Liu et al., 2013; Rajagopalan & Brook, 2012). There are also other two possible mechanisms in mediating T2DM, namely pulmonary and systemic inflammation. One is involved with directly releasing cytokines, altering in glucose homeostasis by defective insulin signaling in tissues, and activating in visceral adipose tissues potentiating inflammation (Sun et al., 2009; Xu et al., 2010; Yan et al., 2011). While the other one is related with endoplasmic reticulum stress in the lung and liver associated with hepatocyte and alveolar cells (Liu et al., 2013; Rajagopalan & Brook, 2012).

In addition, $PM_{2.5}$ as a hypothalamic stressor could cause peripheral inflammation and abnormalities in glucose metabolism (Liu et al., 2013; Yan et al., 2011), mediate dysfunctional brown adipose and mitochondrial tissues rendering one of the systemic pathologies in T2DM (Lowell & Shulman, 2005). Besides, positive effect of PM_{10}, NO_2 and CO on insulin resistance among children in Iran were reported (Kelishadi et al., 2009). As a supplement, a later study in Germany found residential proximity to traffic, PM_{10}, NO_2, and CO play positive roles in the risks of insulin resistance for Children. Exposure to traffic related air pollution could impair glucose tolerance in pregnancy (Fleisch et al., 2014). Sulfate was linked with decreased vascular reactivity for T2DM patients (O'Neill et al., 2007). Air pollutants were statistically significant with the increase of subcutaneous abdominal adipose tissue, especially $PM_{2.5}$ and NO_2 (Sun et al., 2009).

4.4. Economic Burden Assessment

In this study, the burden of HAs for T2DM attributable to PM exposure was calculated. T2DM as one of the major chronic disease, it ranked eighth among top 25 causes of disability-adjusted life-years (Zhou et al., 2019). Particularly, exposure to air pollutants was unavoidable when compared with other risk factors, like obesity and lifestyle. In low-income and lower-to-middle income countries, the demographic expansion, rapid industrialization and aging might increase the burden of health loss owing to air pollution (Li et al., 2019). As shown, the air pollution-related burden of T2DM could be a notable public health problem in China. Proportional benefits in reducing the cost of T2DM can be achieved by abatement of air pollution, which is critical for cost-effective policymaking and T2DM prevention (Yang et al., 2014).

When assessing the corresponding economic burden of exceeding PM exposures, both AN and AC are significant indicators, which could provide data to verify the underlying effects of air pollution on health (Lin et al., 2016). Such method was associated with a study that confirmed the diabetes death in China on national scale, which reported that 5,878 diabetes deaths being attributable to the total PM_{10}. When Chinese National Ambient Air Quality Standards and WHO target level were adopted in PM_{10}-related diabetes deaths, 2016 and 5,528 deaths could be saved (Yang et al., 2020). Zhao et al. (2022) adopted different methods to estimate the rates of diabetes-related ANs, with crude rates of diabetes-related ANs being 247.10 and 272.37 in 2016 and 2017 in Sichuan Province, respectively (Zhao et al., 2022). As aforementioned, positive associations between economic burden and PM pollution were discerned. Tighter control policies and stricter regulation on decreasing air pollution end emission in China, more profound hospitalizations and economic lost could be avoided. The quantity of health and economic cost fell from 2018, owing to the various measures to control air pollution by Chinese government since 2015 (Council, 2013). As the first study associating the estimation on attributable burden of HAs for T2DM owing to exceeding PM exposure in Sichuan Province, this might bring about evidence for public health implications.

4.5. Strengths and Limitations of the Present Study

There were several characteristics of this study. (a) The comparable cases of T2DM hospitalizations were collected, involving 92381records across the Sichuan Province, which enabled to reveal credible results. (b) This is the first investigation to estimate the association between exposure to ambient air pollution (NO_2, PM_{10}, $PM_{2.5}$, SO_2, and CO) and HAs for T2DM in Sichuan Province, based on time-stratified case-crossover design, a dependable method to confirm the short-term effects of air pollution (Jaakkola, 2003). (c) The total medical expenses and out-of-pocket cost attributable to air pollution were estimated, which could support the society and individuals on economic burden.

There were also some limitations. (a) Only 9 cities of Sichuan Province were involved since the unavailability to the data for other cities. (b) Not all potential effect modifiers were involved, like family income, education level, due to the limit to the availability of data. (c) The real economic cost of T2DM hospitalizations due to PM pollution could be underestimated, only with total medical expenses and out-of-pocket cost and excluding the outpatient expenses and indirect medical cost.

5. Conclusions

In summary, exposures to air pollutants (NO_2, PM_{10}, $PM_{2.5}$, SO_2, and CO) were associated with HAs for T2DM in nine cities in Sichuan Province during 2017–2019, based on the time-stratified case-crossover analysis. Given the associations and burden of air pollutants on HAs for T2DM, the enhanced risks and burden of T2DM were in severe air pollution areas, manifesting the strategies of public health promotion on air pollution. Besides, higher risks were found in old (≥65 years) and female patients. Continuous and further efforts should be taken to air pollution and its induced health risks in China, which is possible and should be involved with national prevention programs.

Data Availability Statement

The raw/processed patient data involve individual information, which are not accessible to the public due to Medical Ethics Committee of the Affiliated Hospital of Chengdu University of Traditional Chinese Medicine's data policy.

Conflict of Interest

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

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