Short-term effects of gaseous pollutants on cause-specific cerebrovascular disease among patients with type 2 diabetes: case-crossover evidence from Beijing, China

Xiangtong Liu

Capital Medical University

Zhiwei Li

Capital Medical University

Moning Guo

Beijing Public Health Information Center

Feng Lu

Beijing Public Health Information Center

Aklilu Deginet

Capital Medical University

Mengmeng Liu

Capital Medical University

Xiaolin Xu

University of Queensland

Yanxia Luo

Capital Medical University

Yaoyu Hu

Capital Medical University

Yutong Li

Capital Medical University

Mengqiu Wu

Capital Medical University

Mengyang Liu

Capital Medical University

Lixin Tao

Capital Medical University

Xiuhua Guo (✉ statguo@ccmu.edu.cn)

School of Public Health, Capital Medical University <https://orcid.org/0000-0001-6657-6940>

Research

Keywords: Cerebrovascular diseases, Type 2 diabetes, Comorbidities, Gaseous pollutants, Distributed lag nonlinear model

Posted Date: April 5th, 2021

DOI: <https://doi.org/10.21203/rs.3.rs-384411/v1>

License: This work is licensed under a Creative Commons Attribution 4.0 International License.

[Read Full License](#)

Short-term effects of gaseous pollutants on cause-specific cerebrovascular disease among patients with type 2 diabetes: case-crossover evidence from Beijing, China

Xiangtong Liu ^{1,2,#}, Zhiwei Li ^{1,2,#}, Moning Guo ³, Feng Lu ³, Aklilu Deginet ^{1,2}, Mengmeng Liu ^{1,2}, Xiaolin Xu ^{4,5}, Yanxia Luo ^{1,2}, Yaoyu Hu ^{1,2}, Yutong Li ^{1,2}, Mengqiu Wu ^{1,2}, Mengyang Liu ^{1,2}, Lixin Tao^{1,2,*}, Xiuhua Guo ^{1,2,*}

¹ School of Public Health, Capital Medical University, Beijing, 100069, China.

² Beijing Municipal Key Laboratory of Clinical Epidemiology, Beijing, 100069, China.

³ Beijing Municipal Health Commission Information Center, Beijing, 100034, China.

⁴ The University of Queensland, Brisbane, Australia.

⁵ School of Public Health, Zhejiang University, Hangzhou, 310058, China.

[#]Xiangtong Liu and Zhiwei Li contributed equally to the work.

Corresponding authors:

Xiuhua Guo

School of Public Health, Capital Medical University, No.10 Xitoutiao, You'anmenWai, Fengtai District, Beijing 100069, China

Fax: +86-010-83911508, Tel.: +86-010-83911508

E-mail: statguo@ccmu.edu.cn

Lixin Tao

School of Public Health, Capital Medical University, No.10 Xitoutiao, You'anmenWai, Fengtai District, Beijing 100069, China

Fax: +86-010-83911778, Tel.: +86-010-83911778

E-mail: taolixin@ccmu.edu.cn

E-mail Address

Xiangtong Liu Ph.D

E-mail Address: xiangtongl@ccmu.edu.cn

Zhiwei Li Ph.D

28 E-mail Address: 15128472546@163.com
29 Moning Guo MD
30 E-mail Address: 13581627289@163.com
31 Feng Lu Ph.D
32 E-mail Address: lufeng@wjw.beijng.gov.cn
33 Aklilu Deginet Ph.D
34 E-mail Address: dgaklilu2006@gmail.com
35 Mengmeng Liu MD
36 E-mail Address: liumengmeng@ccmu.edu.cn
37 Xiaolin Xu Ph.D
38 E-mail Address: xiaolin.xu@uq.edu.au
39 Yanxia Luo Ph.D
40 E-mail Address: lyx100@ccmu.edu.cn
41 Yaoyu Hu MS
42 E-mail Address: huyaoyu499@163.com
43 Yutong Li MS
44 E-mail Address: 15210355177@163.com
45 Mengqiu Wu MS
46 E-mail Address: qiuwm00@163.com
47 Mengyang Liu Ph.D
48 E-mail Address: 18031864301@163.com
49 Lixin Tao Ph.D
50 E-mail Address: taolixin@ccmu.edu.cn
51 Xiuhua Guo Ph.D
52 E-mail Address: statguo@ccmu.edu.cn
53 **Word count of abstract: 280**
54 **Word count of text: 4836**

Highlights

- The health effect of gaseous pollutants pollution on cerebrovascular morbidity among the patients with comorbid type 2 diabetes in developing countries has remained largely unknown.
- Exposure to gaseous pollutants is associated an increased risk of cerebrovascular morbidity among the patient with comorbid type 2 diabetes.
- NO₂, SO₂, O₃ and CO presented non-linear and lagged effect on cerebrovascular disease among patients with type 2 diabetes, which may vary by gender and age.
- The study provided evidence of the risk of comorbid type 2 diabetes and cerebrovascular disease due to gaseous pollutants.

Abstract

Background: The association between gaseous pollutants and cerebrovascular morbidity has been widely studied; however, the association in patients with type 2 diabetes has remained unknown in developing countries.

Methods: A time-stratified case-crossover design combined with a distributed lag nonlinear model was adopted to estimate the short-term effects of gaseous pollutants (nitrogen dioxide [NO₂], sulfur dioxide [SO₂], ozone [O₃], and carbon monoxide [CO]) on cerebrovascular cases among patients with type 2 diabetes in Beijing. In addition, our study explored the variability across sex and age groups.

Results: A total of 223,216 (male 57.6% and elderly 61.7%) cerebrovascular cases were reported from 2014 to 2018. The cumulative exposure-response curves were U-shaped for NO₂, J-shaped for SO₂, and V-shaped for O₃ and CO. Extreme low-O₃, low-CO and high-CO increased the risk of cerebrovascular morbidity, with the maximum relative risk (RR) of 1.14 (95% CI: 1.01-1.28) (1st vs median), 1.02 (95% CI: 1.01-1.03) (1st vs median) and 1.25 (95% CI: 1.09-1.45) (99th vs median), respectively, appearing at lag0-13. Elderly individuals aged over 65 years were susceptible to extremely low-O₃ (maximum RR: 1.27, 95% CI: 1.08-1.48). Men and elderly individuals were more susceptible to extremely high-CO, and the maximum RR was 10% [1.31 (1.11-1.54) vs. 1.19 (1.00, 1.41)] and 26% higher [1.41(1.17-1.69) vs. 1.12 (0.97, 1.30)] than women and adults, respectively.

Conclusions: NO₂, SO₂, O₃ and CO presented nonlinear and lagged effects on cerebrovascular disease among patients with type 2 diabetes, which may vary by sex and age. Our study added to the limited evidence for the risk of cerebrovascular disease due to gaseous pollutants among patients with comorbid type 2 diabetes.

Keywords: Cerebrovascular diseases; Type 2 diabetes; Comorbidities; Gaseous pollutants; Distributed lag nonlinear model

1. Introduction

Cerebrovascular disease remains a global challenge to public health and is the leading cause of mortality (Feigin et al., 2017). The cerebrovascular disease burden has increased in China (Wang et al., 2017), accounting for approximately one-quarter of the overall mortality (Zhou et al., 2016). One-third of cerebrovascular cases are comorbid with type 2 diabetes (T2D), leading to poor prognosis (Buddeke et al., 2017). To reduce the disease burden of comorbidity of cerebrovascular disease and T2D, it is crucial to determine modifiable risk factors.

Gaseous pollutants are common determinants for both T2D and cerebrovascular disease (Paul et al., 2020; Tian et al., 2018). Existing studies have proven that nitrogen dioxide (NO₂) is an important modifiable risk factor for cerebrovascular disease (Byrne et al., 2020; Maheswaran et al., 2016). Recently, the impact of gaseous pollutants on diabetes are attracting attention (Byrne et al., 2020; Sui et al., 2020). However, few studies have focused on the influence of gaseous pollutants on the incidence of cerebrovascular disease among people with comorbidities in the real world. Chiusolo *et al.* (Chiusolo et al., 2011) found that patients with preexisting diabetes appeared to confer a stronger susceptibility to NO₂ exposure. A recent study suggested that individuals with comorbidities, especially diabetes, tend to be more susceptible to air pollution (Li et al., 2019).

The disease burden of comorbidities has become a serious issue for public health in China. However, the short-term effects of ambient gaseous pollutant exposure on cerebrovascular disease onset among diabetic participants in China remain largely unknown. Additionally, these associations at the city-specific level have not been thoroughly investigated, particularly in Beijing.

In this study, we aimed to examine the associations between ambient gaseous

pollutants (NO₂, sulfur dioxide [SO₂], ozone [O₃] and carbon monoxide [CO]) and overall cerebrovascular disease onset among patients with comorbid T2D in Beijing. In addition, subgroups analysis of sex and age were adopted to explore the associations in susceptible subpopulations.

2. Materials and Methods

2.1 Study population

The data on cerebrovascular cases among patients with T2D during Jan 1st 2014 and Dec 31st 2018 were extracted from the Beijing Municipal Health Commission Information Center (<http://www.phic.org.cn/>). The data recording system in the study area has been proven to be of high validity and good representativeness, covering more than 95% of medical services for permanent residents in Beijing (Aklilu et al., 2020). The geographic locations of 258 hospitals included in the analysis have been described in our previous study (Li et al., 2018).

Data capture from the medical record system, including patient age, sex, date of admission, T2D status, and principal diagnosis on discharge. Based on the principal diagnosis, cause-specific cerebrovascular cases were identified according to the International Classification of Diseases, 10th Revision (ICD-10) codes: hemorrhagic stroke (ICD-10: I60-I62), ischemic stroke (ICD-10: I63), atherosclerosis (ICD-10: I65), intracranial aneurysm (ICD-10: I67) and apoplexy sequela (ICD-10: I69). Admissions caused by unintentional injuries or surgeries were excluded according to the principal diagnosis. In the study, overall cerebrovascular admissions were calculated as the sum of hemorrhagic stroke, ischemic stroke, atherosclerosis, intracranial aneurysm and apoplexy sequelae. A history of T2D was coded as E12 and was defined as having fasting plasma glucose ≥ 7.1 mmol/L and/or current treatment of diabetes with antidiabetic medication before admission. According to the living address of cases, only

cerebrovascular disease admissions among residents living in Beijing were included in this analysis (Figure S1).

2.2 Air pollution and meteorological data

Daily data of NO₂, SO₂, O₃, CO, fine particulate matter (PM_{2.5}) and inhalable particulate matter (PM₁₀), from Jan 1, 2014 to Dec 31, 2018, were obtained acquired from the Beijing Environmental Protection Bureau (<http://www.bjepb.gov.cn/>). Average daily temperature and relative humidity were acquired from the China Meteorological Data Sharing Service System (<https://data.cma.cn/en>).

2.3 Ethical Clearance

In this study, data were collected as part of health surveillance mandated by government and all data were desensitized. Since we only analyzed the aggregated data, which were typically used for administrative purposes, informed consent was waived. However, the study was approved by the Institutional Review Board of Capital Medical University with the IRB00009511 identification number.

2.4 Statistical Analysis

A time-stratified case-crossover design was adopted to remove control confounders and long-term trends (Liu et al., 2021). A distributed lag nonlinear model (DLNM) was applied to estimate the nonlinear and lagged influence of gaseous pollutants on cerebrovascular disease onset. Based on bidimensional functions called “cross-basis”, DLNM can reflect both lag structure of the association and the nonlinear exposure responses (Gasparrini, 2014). Therefore, the combination of the case-crossover design with DLNM was applied to simultaneously estimate the short-term, nonlinear, and lagged effects of gaseous pollutants on cerebrovascular disease onset.

In our study, a DLNM model combined with a time-stratified case-crossover design was built as follows:

$$\begin{aligned}
Y_t &\sim \text{Poisson}(\mu_t) \text{Log}(\mu_t) \\
&= \alpha + cb(\text{Pollutant}_{i,t}, 3) + PCA_i + cb(\text{Temp}_t, 3) + cb(RH_t, 3) \\
&\quad + \gamma \text{Holiday}_t + \lambda \text{Stratum}
\end{aligned}$$

where t is the specific day of observation; Y_t is the number of cerebrovascular cases on t ; μ_t is the expectation of Y_t ; α is the intercept; $\text{Pollutant}_{i,t}$, Temp_t , and RH_t are, respectively, the i^{th} concentration of gaseous pollutant, daily temperature and relative humidity on t ; $cb()$ is the cross-basis function for exposure-response natural spline for gaseous pollutant, daily temperature or relative humidity. Holiday is the indicator variable used to control the effect of public holidays, and Stratum represents the time stratum of the case-crossover design.

Sensitivity analyses were applied to check the robustness of the effect. First, a natural spline function of 3 df was added to the model (Chen et al., 2018). Second, principal component analysis was adopted to estimate the independent effects of gaseous pollutant (Feng et al., 2019). Principal component analysis is an appropriate statistical method to deal with collinearity among pollutants (Stafoggia et al., 2017). For example, to estimate the independent effects of NO_2 , we first substituted all primary pollutants (SO_2 , O_3 , CO , $\text{PM}_{2.5}$ and PM_{10}) with a composite latent variable, and then included this latent variable in the DLNM model. Additionally, the coefficient β' was transformed into the coefficient β of the original pollutants.

The 3D, slice and cumulative exposure-response curves were plotted between gaseous pollutants and cerebrovascular morbidity among patients with T2D. To identify the effect of extreme concentrations of gaseous pollutants, relative risk (RR) was estimated by comparing cerebrovascular cases of the 99th above or 1st below percentiles to the median concentration. We estimated the cumulative lag influence (lag 0-1, lag 0-3, lag 0-5, lag 0-7, lag 0-9, lag 0-11 and lag 0-13) to effectively describe the

associations between gaseous pollutants and cerebrovascular cases. Subgroup analyses were performed to test the variability across sex and age groups (adult: 18-64 years; elderly individuals: ≥ 65 years).

All analyses were conducted in R software (version 4.0.2) and *dlnm* package was adopted for fitting the DLNM.

3. Results

A total of 223,216 cases for cerebrovascular disease were collected after excluding nonlocal admissions, of which 9,541 (4.27%), 149,757 (67.09%), 7,444 (3.33%), 31,356 (14.05%), and 23,912 (10.71%) were hospitalized for hemorrhagic stroke, ischemic stroke, atherosclerosis, intracranial aneurysm, and apoplexy sequela, respectively. In short, male participants and elderly individuals (≥ 65 years) accounted for 57.6% and 61.7%, respectively. [Table 1](#) summarizes the characteristics and distribution of daily cerebrovascular disease (overall and cause-specific), stratified by sex and age over the study period.

During the period, the 1st, 50th (median) and 99th percentiles of concentration, respectively, were 14.32, 43.66, 112.79 ($\mu\text{g}/\text{m}^3$) for NO_2 , 2.2, 7.35, 74.51 ($\mu\text{g}/\text{m}^3$) for SO_2 , 5.85, 54.91, 157.06 ($\mu\text{g}/\text{m}^3$) for O_3 , and 0.28, 0.89, 4.84 (mg/m^3) for CO. The average concentrations of NO_2 , SO_2 , O_3 and CO were 1.1, 0.1, 0.3 and 0.2 times of the limit of Chinese Ambient Air Quality guideline II, respectively. The differences in NO_2 , SO_2 , O_3 and CO between the four seasons were statistically significant ($F_{\text{NO}_2}= 76.62$, $P<0.001$; $F_{\text{SO}_2}= 188.1$, $P<0.001$; $F_{\text{O}_3}= 559.5$, $P<0.001$; $F_{\text{CO}}= 117.2$, $P<0.001$). During the study period, the median daily temperature was 14.4°C and the mean relative humidity was $54.3 \pm 19.2\%$. Gaseous pollutants except O_3 were strongly correlated with each other (coefficients ranged from 0.49 to 0.87) and moderately correlated with relative humidity and temperature (coefficients ranged from -0.41 to 0.33) ([Fig. 1](#)).

216 **Table 1. Characteristics and distribution of daily cerebrovascular cases in Beijing (2014-2018).**

	Total		Male		Female		<65 y		≥65 y	
	N	P ₂₅ -P ₇₅	N (%)	P ₂₅ -P ₇₅	N (%)	P ₂₅ -P ₇₅	N (%)	P ₂₅ -P ₇₅	N (%)	P ₂₅ -P ₇₅
Hemorrhagic stroke	9541	3-7	5692 (59.7)	2-4	3848 (40.3)	1-3	4218 (44.7)	1-3	5323 (55.3)	2-4
Ischemic stroke	149757	52-104	87285 (58.2)	30-61	62469 (41.8)	23-44	57454 (38.2)	21-40	92303 (61.8)	31-65
Atherosclerosis	7444	1-6	5460 (73.2)	1-4	1984 (26.8)	0-2	3412 (45.3)	0-3	4032 (54.7)	1-3
Intracranial aneurysm	31356	11-22	14876 (47.4)	5-11	16480 (52.6)	6-12	13068 (41.6)	4-10	18288 (58.4)	6-13
Apoplexy sequela	23912	3-21	14550 (61.0)	2-13	9361 (39.0)	1-8	7049 (30.5)	1-6	16863 (69.5)	2-15
Overall	223216	72-157	128508 (57.6)	41-91	94703 (42.4)	32-66	85726 (38.3)	30-60	137490 (61.7)	43-98

217 Note: N-counts of cases; P₂₅-P₇₅: 25th percentile and 75th percentile of daily cases.

Fig.1 Pearson correlation coefficients between gaseous air pollutants concentrations and weather conditions and daily admissions for cerebrovascular disease in Beijing, 2014-2018 (n = 1799). NO₂: nitrogen dioxide; SO₂: sulfur dioxide; O₃: ozone; CO: carbon monoxide. * 0.01 < P ≤ 0.05; ** 0.001 < P ≤ 0.01; *** P ≤ 0.001.

The results of the multipollutant models indicated that SO₂, NO₂, O₃ and CO were significantly associated with both overall and cause-specific cerebrovascular morbidity. Figure 2 show the relative risks of each gaseous pollutant on overall and cause-specific cerebrovascular morbidity using different lag structures. The maximum relative risk (RR) was 1.004 (95% CI: 1.003-1.004) for cerebrovascular cases, 1.003 (95% CI: 1.002-1.004) for ischemic stroke, 1.006 (95% CI: 1.003-1.009) for atherosclerosis, 1.005 (95% CI: 1.003-1.006) for intracranial aneurysm, and 1.007 (95% CI: 1.005-1.009) for apoplexy sequela. High SO₂ concentrations were associated with an increased risk of overall cerebrovascular cases (RR: 1.001; 95% CI: 1.0003-1.0017) at

Fig.2 Relative risk with 95% CI (confidence interval) in cerebrovascular morbidity associated with increase in concentrations of gaseous pollutants for different lag structures in multi-pollutant model: (a) SO₂: sulfur dioxide; (b) NO₂: nitrogen dioxide; (c) O₃: ozone; (d) CO: carbon monoxide.

lag0 day, intracranial aneurysm cases (RR: 1.0021; 95% CI: 1.0006-1.0037) at lag4 day, and apoplexy sequela cases (RR: 1.0022; 95% CI: 1.0001-1.0044) at lag0 day (Fig. 2a).

Positive associations were observed between NO₂ concentrations and risk for overall and cause specific cerebrovascular cases except hemorrhagic stroke (Fig. 2b).

High O₃ concentrations were associated with an increased risk of overall cerebrovascular cases (RR: 1.0101; 95% CI: 1.0099-1.0104) at lag0 day, hemorrhagic stroke cases (RR: 1.0386; 95% CI: 1.0373-1.040) at lag0 day, ischemic stroke cases (RR: 1.003; 95% CI: 1.0026-1.0033) at lag0 day, atherosclerosis cases (RR: 1.0017; 95% CI: 1.0002-1.0032) at lag5 day, and intracranial aneurysm cases (RR: 1.0441; 95% CI: 1.0434-1.0449) at lag0 day (Fig. 2c). High CO concentrations were associated with increased risk for overall cerebrovascular cases and ischemic stroke, atherosclerosis, intracranial aneurysm, and apoplexy sequela case morbidity, and the maximum RR and 95% CI were 1.048 (95% CI: 1.032-1.065), 1.047 (95% CI: 1.027-1.067), 1.144 (95% CI: 1.060-1.236), 1.050 (95% CI: 1.014-1.088), and 1.099 (95% CI: 1.056-1.144), respectively (Fig. 2d).

Figure 3 presents the 3-D exposure-response surfaces of NO₂, SO₂, O₃ and CO on overall cerebrovascular cases along lag days, which indicated that the associations tended to be nonlinear. As shown in Figure 4, the cumulative exposure-response curves of the overall association between gaseous pollutants and cerebrovascular cases among T2D patients were almost nonlinear. Generally, the cumulative exposure-response curves for NO₂ were almost U-shaped, with a slight decline at concentrations lower than 43 µg/m³ and then a flattening off. Evidently, J-shaped increased risks were observed for high SO₂ concentrations, with steep slopes for concentrations ≥ 10 µg/m³ and becoming flat at 45 µg/m³. The cumulative exposure-response curves for O₃ were V-shaped, which meant that both high and low concentrations of O₃ may increase the

risk of cerebrovascular disease onset among patients with T2D. In addition, the cumulative exposure-response curves for CO were almost inverted V-shaped, increasing sharply at concentrations lower than 4 mg/m³ and then decreasing sharply, which indicated that the RR value peaked at a concentration of 3 mg/m³ and then decreased.

Fig.3 3D graphs of NO₂, SO₂, O₃ and CO effect on overall cerebrovascular cases: (a) overall effect of NO₂; (b) overall effect of SO₂; (c) overall effect of O₃; (d) overall effect of CO. NO₂: nitrogen dioxide; SO₂: sulfur dioxide; O₃: ozone; CO: carbon monoxide. RR (95% CI): relative risk and 95% confidence interval.

Fig.4 Cumulative exposure-response curves on overall cerebrovascular cases for gaseous pollutants (NO₂, SO₂, O₃ and CO) at lag0-7 using multi-pollutant models in Beijing, 2014-2018: (a) cumulative effect of NO₂; (b) cumulative effect of SO₂; (c) cumulative effect of O₃; (d) cumulative effect of CO. NO₂: nitrogen dioxide; SO₂: sulfur dioxide; O₃: ozone; CO: carbon monoxide. RR (95% CI): relative risk and 95% confidence interval.

The single day lag-response curves for extreme gaseous pollutant concentrations in cerebrovascular cases are shown in Figure 5. As shown in the figure, the curves of extremely high- NO₂, high- O₃ and high- SO₂ were almost straight lines through lag days, and no statistically significant associations were observed. The extremely high- CO showed a statistically significant hazardous effect from lag 2 to lag 7, and the RR value peaked at lag 4. The curves of the extremely low- NO₂, low- SO₂, and low- CO were S-shaped, and the RR values peaked at lag 3, lag 10, and lag 4, respectively. The extremely low-CO presented statistically significant hazardous effect from lag2 to lag7.

287

288 **Fig.5** Single day lag-response curves on overall cerebrovascular cases for extreme gaseous pollutants concentrations using multi-pollutant model
 289 in Beijing, 2014-2018: (a) overall effect of extreme high-NO₂; (b) overall effect of extreme high-SO₂; (c) overall effect of extreme high-O₃; (d)
 290 overall effect of extreme high-CO; (e) overall effect of extreme low-NO₂; (f) overall effect of extreme low-SO₂; (g) overall effect of extreme low-
 291 O₃; (h) overall effect of extreme low-CO. The high effect was estimated by the RR of cerebrovascular disease by comparing the 99th percentile to
 292 the median of daily concentration, whereas the low effect was estimated by comparing the 1st percentile to the median of daily concentration. NO₂:
 293 nitrogen dioxide; SO₂: sulfur dioxide; O₃: ozone; CO: carbon monoxide. RR (95% CI): relative risk and 95% confidence interval.

Table 2 lists the cumulative effect of extreme concentrations of gaseous pollutants on cerebrovascular disease among patients with T2D at different lag days. In short, extremely low- O₃, low- CO and high- CO presented statistically significant hazardous cumulative effects. However, no prominent cumulative effect of extreme NO₂ and SO₂ was observed. Specifically, low O₃ was significantly associated with an increased risk for cerebrovascular disease (RR=1.14, 95% CI: 1.01-1.28) (1st vs median) at lag0-13. Low- CO had a slight adverse effect (RR=1.02, 95% CI: 1.01-1.03) (1st vs median) at lag0-13. Extremely high CO presented a statistically significant cumulative hazardous effect on cerebrovascular cases, which increased with extended lag days, with a maximum RR value of 1.25 (95% CI: 1.09-1.45) (99th vs median), appearing at lag0-13. Differences were also observed among subgroups of the population. Subgroup analysis indicated that extremely low- O₃ only had a significant cumulative effect in the elderly population, with a maximum RR value of 1.27 (95% CI: 1.08-1.48) (1st vs median) on lag 0-13. Men and elderly individuals were more susceptible to extreme cumulative high-CO than women and adults, and the maximum RR value was 10% (1.31 (95% CI: 1.11-1.54) vs. 1.19 (95% CI: 1.00, 1.41)) and 26% higher (1.41(95% CI: 1.17-1.69) vs. 1.12 (95% CI: 0.97, 1.30)), respectively.

Table 2 Cumulative RRs and 95% CIs of extreme gaseous pollutants concentrations on cerebrovascular cases using multi-pollutant models.

Pollutant	Population	Extreme-low effect							Extreme-high effect						
		lag0-1	lag0-3	lag0-5	lag0-7	lag0-9	lag 0-11	lag 0-13	lag0-1	lag0-3	lag0-5	lag0-7	lag0-9	lag 0-11	lag 0-13
NO ₂	Total	0.99 (0.97, 1.02)	1.01 (0.97, 1.05)	1.03 (0.99, 1.08)	1.04 (0.98, 1.09)	1.03 (0.97, 1.10)	1.03 (0.96, 1.10)	1.03 (0.96, 1.10)	1.03 (0.96, 1.10)	1.05 (0.95, 1.17)	1.05 (0.94, 1.18)	1.03 (0.91, 1.17)	1.02 (0.89, 1.17)	1.03 (0.88, 1.20)	1.06 (0.89, 1.25)
	Men	1.00 (0.98, 1.03)	1.03 (0.99, 1.07)	1.05 (1.00, 1.11)	1.06 (1.00, 1.13)	1.06 (0.99, 1.13)	1.05 (0.97, 1.13)	1.05 (0.97, 1.14)	1.04 (0.96, 1.12)	1.06 (0.95, 1.20)	1.06 (0.92, 1.21)	1.04 (0.90, 1.20)	1.03 (0.87, 1.21)	1.04 (0.87, 1.25)	1.09 (0.89, 1.32)
	Women	0.98 (0.95, 1.01)	0.98 (0.94, 1.03)	1.00 (0.95, 1.06)	1.01 (0.94, 1.07)	1.00 (0.93, 1.07)	1.00 (0.92, 1.08)	1.00 (0.92, 1.09)	1.01 (0.94, 1.1)	1.04 (0.92, 1.17)	1.04 (0.91, 1.19)	1.03 (0.88, 1.19)	1.01 (0.85, 1.20)	1.01 (0.84, 1.21)	1.02 (0.84, 1.25)
	Adult	1.00 (0.97, 1.03)	1.02 (0.97, 1.07)	1.03 (0.97, 1.10)	1.04 (0.97, 1.12)	1.04 (0.96, 1.13)	1.04 (0.95, 1.14)	1.04 (0.94, 1.14)	1.05 (0.96, 1.15)	1.07 (0.93, 1.23)	1.06 (0.91, 1.24)	1.07 (0.91, 1.27)	1.09 (0.91, 1.32)	1.11 (0.90, 1.37)	1.12 (0.90, 1.41)
	The elderly	0.99 (0.96, 1.01)	1.00 (0.97, 1.04)	1.03 (0.98, 1.08)	1.03 (0.98, 1.09)	1.03 (0.96, 1.09)	1.02 (0.95, 1.09)	1.02 (0.95, 1.10)	1.01 (0.94, 1.08)	1.04 (0.93, 1.16)	1.04 (0.92, 1.18)	1.01 (0.88, 1.15)	0.97 (0.84, 1.13)	0.97 (0.83, 1.15)	1.02 (0.85, 1.22)
SO ₂	Total	0.99 (0.98, 1.01)	1.00 (0.97, 1.02)	1.00 (0.97, 1.03)	0.99 (0.96, 1.03)	0.99 (0.95, 1.03)	1.00 (0.96, 1.05)	1.03 (0.98, 1.08)	1.02 (0.96, 1.09)	1.05 (0.94, 1.16)	1.06 (0.93, 1.20)	1.07 (0.93, 1.24)	1.09 (0.92, 1.28)	1.10 (0.92, 1.32)	1.12 (0.93, 1.36)

O ₃	Men	0.99 (0.97, 1.01)	1.00 (0.97, 1.03)	1.01 (0.97, 1.05)	1.01 (0.97, 1.05)	1.01 (0.96, 1.06)	1.02 (0.97, 1.07)	1.04 (0.98, 1.10)	1.03 (0.96, 1.11)	1.06 (0.94, 1.20)	1.07 (0.92, 1.24)	1.08 (0.91, 1.28)	1.08 (0.90, 1.31)	1.08 (0.88, 1.33)	1.10 (0.88, 1.37)
	Women	0.99 (0.97, 1.01)	0.99 (0.96, 1.02)	0.99 (0.95, 1.03)	0.98 (0.93, 1.02)	0.97 (0.92, 1.02)	0.98 (0.93, 1.04)	1.01 (0.95, 1.07)	1.01 (0.94, 1.09)	1.03 (0.91, 1.16)	1.04 (0.89, 1.21)	1.06 (0.89, 1.26)	1.09 (0.90, 1.32)	1.13 (0.92, 1.39)	1.16 (0.93, 1.46)
	Adult	1.00 (0.98, 1.02)	1.00 (0.97, 1.04)	1.00 (0.96, 1.04)	0.99 (0.94, 1.04)	0.99 (0.93, 1.04)	1.01 (0.95, 1.07)	1.04 (0.98, 1.12)	1.01 (0.93, 1.10)	1.00 (0.87, 1.15)	0.99 (0.84, 1.18)	1.02 (0.84, 1.23)	1.05 (0.84, 1.30)	1.07 (0.85, 1.36)	1.08 (0.84, 1.39)
	The elderly	0.99 (0.97, 1.01)	0.99 (0.97, 1.02)	1.00 (0.97, 1.04)	1.00 (0.96, 1.04)	0.99 (0.95, 1.04)	1.00 (0.95, 1.05)	1.02 (0.96, 1.07)	1.03 (0.97, 1.11)	1.08 (0.96, 1.21)	1.10 (0.96, 1.26)	1.11 (0.95, 1.29)	1.11 (0.93, 1.32)	1.12 (0.93, 1.36)	1.15 (0.94, 1.41)
	Total	1.02 (0.98, 1.05)	1.05 (0.98, 1.12)	1.08 (0.99, 1.17)	1.09 (1.00, 1.20)	1.10 (1.00, 1.22)	1.12 (1.00, 1.25)	1.14 (1.01, 1.28)	1.04 (0.98, 1.09)	1.05 (0.97, 1.13)	1.04 (0.95, 1.15)	1.04 (0.93, 1.17)	1.04 (0.92, 1.19)	1.03 (0.89, 1.19)	1.00 (0.85, 1.17)
	Men	1.01 (0.97, 1.06)	1.04 (0.97, 1.12)	1.07 (0.97, 1.17)	1.08 (0.97, 1.21)	1.10 (0.97, 1.23)	1.12 (0.98, 1.27)	1.15 (1.00, 1.32)	1.04 (0.98, 1.10)	1.06 (0.97, 1.16)	1.05 (0.94, 1.17)	1.02 (0.90, 1.16)	0.99 (0.85, 1.15)	0.96 (0.81, 1.14)	0.95 (0.79, 1.13)
	Women	1.02 (0.98, 1.07)	1.06 (0.98, 1.14)	1.09 (0.99, 1.20)	1.10 (0.99, 1.23)	1.12 (0.99, 1.26)	1.12 (0.98, 1.28)	1.13 (0.98, 1.30)	1.04 (0.98, 1.10)	1.03 (0.94, 1.13)	1.03 (0.92, 1.16)	1.08 (0.94, 1.23)	1.12 (0.96, 1.31)	1.12 (0.94, 1.33)	1.07 (0.89, 1.29)

CO	Adult	1.01 (0.97, 1.05)	1.03 (0.97, 1.11)	1.05 (0.96, 1.14)	1.05 (0.95, 1.16)	1.05 (0.94, 1.17)	1.06 (0.94, 1.19)	1.06 (0.94, 1.21)	1.05 (1.00, 1.11)	1.06 (0.98, 1.15)	1.03 (0.93, 1.14)	1.01 (0.89, 1.14)	1.01 (0.88, 1.16)	1.00 (0.86, 1.17)	0.99 (0.84, 1.17)
	The elderly	1.02 (0.97, 1.08)	1.08 (0.99, 1.17)	1.12 (1.01, 1.25)	1.16 (1.03, 1.31)	1.19 (1.04, 1.37)	1.23 (1.06, 1.43)	1.27 (1.08, 1.48)	1.01 (0.94, 1.08)	1.03 (0.93, 1.14)	1.06 (0.94, 1.21)	1.10 (0.95, 1.28)	1.10 (0.93, 1.32)	1.06 (0.88, 1.29)	1.01 (0.82, 1.25)
	Total	1.00 (1.00, 1.01)	1.01 (1.00, 1.01)	1.01 (1.00, 1.02)	1.01 (1.01, 1.02)	1.02 (1.01, 1.02)	1.02 (1.01, 1.03)	1.02 (1.01, 1.03)	1.04 (0.98, 1.10)	1.08 (0.99, 1.18)	1.11 (1.01, 1.23)	1.15 (1.03, 1.28)	1.19 (1.05, 1.35)	1.22 (1.07, 1.40)	1.25 (1.09, 1.45)
	Men	1.00 (1.00, 1.01)	1.01 (1.00, 1.02)	1.01 (1.01, 1.02)	1.02 (1.01, 1.03)	1.02 (1.01, 1.03)	1.02 (1.01, 1.03)	1.02 (1.01, 1.03)	1.06 (0.99, 1.13)	1.12 (1.01, 1.24)	1.15 (1.02, 1.29)	1.19 (1.04, 1.35)	1.23 (1.07, 1.42)	1.27 (1.09, 1.49)	1.31 (1.11, 1.54)
	Women	1.00 (1.00, 1.01)	1.00 (1.00, 1.01)	1.01 (1.00, 1.01)	1.01 (1.00, 1.02)	1.01 (1.00, 1.02)	1.01 (1.00, 1.02)	1.01 (1.00, 1.02)	1.01 (0.94, 1.08)	1.04 (0.93, 1.15)	1.07 (0.95, 1.21)	1.10 (0.97, 1.26)	1.14 (0.98, 1.32)	1.17 (0.99, 1.37)	1.19 (1.00, 1.41)
	Adult	1.00 (1.00, 1.01)	1.01 (1.00, 1.01)	1.01 (1.00, 1.01)	1.01 (1.00, 1.02)	1.01 (1.00, 1.02)	1.01 (1.00, 1.02)	1.02 (1.00, 1.03)	1.01 (0.95, 1.08)	1.04 (0.95, 1.15)	1.06 (0.96, 1.18)	1.08 (0.96, 1.21)	1.09 (0.96, 1.25)	1.12 (0.97, 1.30)	1.17 (1.00, 1.36)
	The elderly	1.00 (1.00, 1.01)	1.01 (1.00, 1.02)	1.01 (1.00, 1.02)	1.02 (1.01, 1.03)	1.02 (1.01, 1.03)	1.02 (1.01, 1.04)	1.02 (1.01, 1.04)	1.08 (1.00, 1.16)	1.15 (1.02, 1.29)	1.20 (1.05, 1.37)	1.28 (1.10, 1.48)	1.36 (1.15, 1.60)	1.41 (1.17, 1.69)	1.41 (1.16, 1.71)

4. Discussion

To the best of our knowledge, this is the first study to examine the associations between gaseous pollutants and cerebrovascular case onset among patients with comorbid T2D in China. In this study, we observed significant nonlinear and lagged effects of NO₂, SO₂, O₃ and CO on the morbidity of cerebrovascular disease among patients with T2D. The extreme effect of high and low concentrations was not consonant, depending on sex, age, and type of gaseous pollutants. Our study added to the limited evidence for the risk of comorbidities of T2D and cerebrovascular disease due to gaseous pollutants in developing countries.

The nonlinear and lagged effects of gaseous pollutants were robust when adjusting for co-pollutants using principal component analysis in multipollutant models. T2D is the leading risk factor for cerebrovascular cases and related death in Chinese adults. Note that China had the largest disease burden of T2D worldwide in 2019 ([Saeedi et al., 2019b](#)). Even if the adverse effect in an individual might be small, the overall attributable risk of gaseous pollution might be considerably high, given the large population with T2D in China ([Maji et al., 2017](#); [Maji et al., 2018](#)).

During the study period, the average concentrations of NO₂ (43.66 µg/m³) in Beijing slightly exceeded the Chinese National Ambient Air Quality guideline II (40 µg/m³). The major anthropogenic sources of NO₂ were motor vehicle exhaust and industrial emissions in Beijing ([Gao et al., 2017](#)). Consistent with existing studies ([Wang et al., 2020](#)), we have added evidence for a U-shaped nonlinear NO₂-cerebrovascular disease association, where morbidity leveled off at low exposure levels and increased sharply with higher exposure. Another recent time-series study estimated an increased risk of 1.054 (95% CI: 1.031, 1.077) in stroke morbidity per 10 µg/m³ increase in NO₂ across lag 0-3 days ([Guo et al., 2020](#)). It is difficult to directly compare

the nonlinear and lag effects across cities due to the different study designs and model specifications. However, these findings of associations between high NO₂ concentration and cerebrovascular case onset were similar as a whole.

Our results show a V-shaped CO-cerebrovascular case association at levels below the current China air quality standard. During the study period, the average daily CO concentrations (0.89 mg/m³) across Beijing were well below the current Chinese National Ambient Air Quality guideline II (4 mg/m³); however, the CO-cerebrovascular disease association remained present despite this. Furthermore, our study suggested that both low- CO and high- CO exposure may increase the risk of cerebrovascular cases. Aligning with our study, Shah and colleagues ([Shah et al., 2015](#)) found that a 1 ppm increase in CO concentrations [relative risk (*RR*) and 95% *CI*: 1.015 (1.004, 1.026)] was significantly associated with morbidity or mortality for stroke. Another national study reported that increases of 1 mg/m³ in CO concentrations were associated with a 3.24% (95% *CI*: 2.05%-4.43%) increase in ischemic stroke morbidity; however, the associations were not statistically significant when adjusting for other pollutants ([Tian et al., 2018](#)).

The concentrations of SO₂ (7.35 µg/m³) and O₃ (54.91 µg/m³) were far below the limit of Chinese Ambient Air Quality guideline II (60 µg/m³ and 160 µg/m³, respectively). SO₂ and O₃ are gaseous pollutants mainly emitted by fuel combustion and regional transport in urban Beijing. A growing body of research has suggested that incrementally increased concentrations of SO₂ and O₃ exposure may increase cerebrovascular morbidity ([Chen et al., 2019](#)). Contrary to previous studies, however, in our research, we observed increased cerebrovascular cases associated with high- SO₂, low- O₃ and high- O₃ under the air quality limit of China. Note that over 2013-2018, the air quality of Beijing had a measurable improvement, of which SO₂ decreased the most,

and O₃ showed a fluctuating increase (Li et al., 2020).

Our study found that exposure to extreme NO₂ and CO may have a stronger impact on the risk for morbidity of cerebrovascular disease than SO₂ and O₃. This finding is almost in accordance with another national study of 172 cities in China, which reported that NO₂ [1.82% (1.45%-2.19%)], CO [3.24% (2.05%-4.43%)], SO₂ [1.37% (1.05%-1.70%)] and O₃ [0.01% (-0.14%-0.16%)] were significantly associated with increases in hospital admissions for ischemic stroke (Tian et al., 2018). Although the potential reasons remain unknown, we suppose that traffic gaseous pollutants may have become the major sources of air pollutants in Beijing. Oxidative stress is supposed to be a key pathway for the different cardiovascular actions of NO₂ and CO pollution (Miller, 2020). A recent study found that exposure to high- O₃ was associated with decreased nitrotyrosine, a marker of the reaction product of superoxide and NO (Balme et al., 2019).

Subgroup analysis of sex supported that male participants were more susceptible to extremely high- CO exposure than females. A study from Shenzhen showed that males were vulnerable to extremely high- SO₂, high- NO₂ and low- O₃, and females were vulnerable to extremely high- O₃ (Wang et al., 2020). Another study found that among stroke patients male were more vulnerable than female to changes in concentrations of SO₂ and NO₂ (Wang et al., 2016). In short, the potential sex differences in the associations between gaseous pollutants and cerebrovascular cases remain to be determined.

Subgroup analysis of age showed that elder individuals were more susceptible to extremely high- CO and low- O₃ exposure and were at higher risk of cerebrovascular-related hospitalizations. Unsurprisingly, compared with younger adults, elderly participants are more vulnerable to gaseous pollutants and have a higher risk of

cerebrovascular diseases. Wang and colleagues found that younger adults were more immune to extremely low- NO₂ than elderly adults (Wang et al., 2020). Another study of Beijing also supported that increased concentrations of NO₂ and O₃ were associated with higher increased risks of cerebrovascular hospitalizations in elder individuals (Huang et al., 2017).

There are some strengths of our study. First, the data on cerebrovascular cases has been proven to be of high validity and good representativeness, covering more than 95% of permanent residents in Beijing, and the sample size was relatively large. Therefore, the present results may be representative of the authentic associations between gaseous pollution and cerebrovascular cases in the study area. Second, to the best of our knowledge, this was the first time that a nonlinear and lagged association were observed between NO₂, SO₂, and O₃ and cerebrovascular cases in a population with T2D, which may have important implications for the prevention and treatment of cerebrovascular cases.

However, several limitations should be addressed. First, we could not collect data on the relationships between patients owing to the limitation of the available data. However, there might be few family aggregation cases, which may affect population sensitivity (Yang et al., 2018). Second, the date of diagnosis, rather than the time of cerebrovascular symptom onset, was used in the analysis, which may result in temporal misalignment between gaseous pollution and cerebrovascular incidence and the underestimation of exposure effects (Lokken et al., 2009). However, because cerebrovascular disease is a kind of disease requiring prompt hospitalization and treatment, temporal misalignment is expected to play a minor role in our estimation. As admission or diagnosis may occur in the days after the onset of symptoms, it is important to explain the lag influence of air pollution on cerebrovascular disease onset.

Third, we used the arithmetic mean from 35 fixed-site monitor measurements as a proxy for individual exposure, which may result in exposure measurement errors and underestimate the influence of gaseous pollution (Dionisio et al., 2016). Fourth, caution should be taken when extrapolating our results to other areas although Beijing is representative of cities with advanced economies and relatively high levels of air pollution.

Although the adverse effect of cerebrovascular disease might be small for each individual, public health implications are very important given the large population with T2D in China exposed to unavoidable air pollution. Further studies with more accurate times of cerebrovascular symptom onset are needed to further validate our findings.

Conclusion

NO₂, SO₂, O₃ and CO presented nonlinear and lagged effects on cerebrovascular disease among patients with type 2 diabetes. Men were more susceptible to extremely high- CO, and elderly individuals aged over 65 years were susceptible to both extremely low- O₃ and high- CO. Our study added to the limited evidence for the risk of comorbidities of T2D and cerebrovascular disease due to gaseous pollutants.

Abbreviations

T2D: type 2 diabetes; NO₂: nitrogen dioxide; SO₂: sulfur dioxide; O₃: ozone; CO: carbon monoxide; ICD-10: International Classification of Diseases, 10th Revision; PM_{2.5}: fine particulate matter with an aerodynamic diameter < 2.5 µm; PM₁₀: inhalable particulate matter with an aerodynamic diameter <10 µm; DLNM: distributed lag nonlinear model; *df*: degrees of freedom; 95% CI: 95% confidence interval; RR: relative risk.

Declarations

Acknowledgments

We acknowledge the Beijing Municipal Health Commission Information Center and the Beijing Air Pollution and Metrological Data Center.

Funding

This study was supported by National Natural Science Foundation of China (No. 82003559), Nature Science Foundation of Capital Medical University (No. PYZ2018046), Beijing Municipal Training Project of Excellent Talents. The funding was neither used for the study design nor data collection but to cover for the publication fees.

Availability of data and materials

The data can be accessed from the Beijing Municipal Health Commission Information Center with permission via direct request.

Authors' contributions

Xiangtong Liu and Zhiwei Li conceived and designed the study. Moning Guo and Feng Lu advised the retrieval of clinical data. Xiuhua Guo and Lixin Tao supervised the progress of the study. Xiangtong Liu prepared the draft manuscript, and Xiuhua Guo improved the drafted manuscript. Xiangtong Liu, Zhiwei Li, Aklilu Deginet, Mengmeng Liu, Xiaolin Xu, Yanxia Luo, Yaoyu Hu, Yutong Li, Mengqiu Wu and Mengyang Liu advised on the overall data analysis and the development of the manuscript. All authors were involved with the critical revision of the manuscript and approved the final version.

Ethics approval

In this study, informed consent was not specifically required because we did not use

personal data identifiers. However, the study was approved by the Institutional Review Board of Capital Medical University with the IRB00009511 identification number.

Consent for publication

Not applicable.

Competing interests

The authors declare that they have no competing interests.

References

Aklilu, D., et al., 2020. Short-term effects of extreme temperatures on cause specific cardiovascular admissions in Beijing, China. *Environ Res.* 186, 109455.

Balmes, J. R., et al., 2019. Ozone effects on blood biomarkers of systemic inflammation, oxidative stress, endothelial function, and thrombosis: The Multicenter Ozone Study in oldEr Subjects (MOSES). *PLoS One.* 14, e0222601.

Buddeke, J., et al., 2017. Trends in comorbidity in patients hospitalised for cardiovascular disease. *Int J Cardiol.* 248, 382-388.

Byrne, C. P., et al., 2020. Short-Term Air Pollution as a Risk for Stroke Admission: A Time-Series Analysis. *Cerebrovasc Dis.* 1-8.

Chen, C., et al., 2018. Ambient air pollution and daily hospital admissions for mental disorders in Shanghai, China. *Sci Total Environ.* 613-614, 324-330.

Chen, C., et al., 2019. The effect of air pollution on hospitalization of individuals with respiratory and cardiovascular diseases in Jinan, China. *Medicine (Baltimore).* 98, e15634.

Chiusolo, M., et al., 2011. Short-Term Effects of Nitrogen Dioxide on Mortality and

482 Susceptibility Factors in 10 Italian Cities: The EpiAir Study. *Environ Health*
483 *Perspect.* 119, 1233-8.

484 Dionisio, K. L., et al., 2016. A simulation study to quantify the impacts of exposure
485 measurement error on air pollution health risk estimates in copollutant time-
486 series models. *Environ Health.* 15, 114.

487 Feigin, V. L., et al., 2017. Global Burden of Stroke. *Circ Res.* 120, 439-448.

488 Feng, W., et al., 2019. Short-term PM10 and emergency department admissions for
489 selective cardiovascular and respiratory diseases in Beijing, China. *Sci Total*
490 *Environ.* 657, 213-221.

491 Gao, J., et al., 2017. Haze, public health and mitigation measures in China: A review of
492 the current evidence for further policy response. *Sci Total Environ.* 578, 148-
493 157.

494 Gasparri, A., 2014. Modeling exposure-lag-response associations with distributed lag
495 non-linear models. *Stat Med.* 33, 881-99.

496 Guo, Y., et al., 2020. Short-term associations between ambient air pollution and stroke
497 hospitalisations: time-series study in Shenzhen, China. *BMJ Open.* 10, e032974.

498 Huang, F., et al., 2017. Gaseous Air Pollution and the Risk for Stroke Admissions: A
499 Case-Crossover Study in Beijing, China. *Int J Environ Res Public Health.* 14.

500 Li, H., et al., 2018. Effects of ambient carbon monoxide on daily hospitalizations for
501 cardiovascular disease: a time-stratified case-crossover study of 460,938 cases
502 in Beijing, China from 2013 to 2017. *Environ Health.* 17, 82.

503 Li, J., et al., 2019. Association between ambient particulate matter air pollution and ST-

504 elevation myocardial infarction: A case-crossover study in a Chinese city.
 505 Chemosphere. 219, 724-729.

506 Li, W., et al., 2020. Air quality improvement in response to intensified control strategies
 507 in Beijing during 2013-2019. Sci Total Environ. 744, 140776.

508 Liu, L., et al., 2021. Intraday effects of ambient PM(1) on emergency department visits
 509 in Guangzhou, China: A case-crossover study. Sci Total Environ. 750, 142347.

510 Lokken, R. P., et al., 2009. Air pollution and risk of stroke: underestimation of effect
 511 due to misclassification of time of event onset. Epidemiology. 20, 137-42.

512 Maheswaran, R., et al., 2016. Air Pollution and Subtypes, Severity and Vulnerability to
 513 Ischemic Stroke-A Population Based Case-Crossover Study. PLoS One. 11,
 514 e0158556.

515 Miller, M. R., 2020. Oxidative stress and the cardiovascular effects of air pollution.
 516 Free Radic Biol Med. 151, 69-87.

517 Paul, L. A., et al., 2020. The impact of air pollution on the incidence of diabetes and
 518 survival among prevalent diabetes cases. Environ Int. 134, 105333.

519 Shah, A. S., et al., 2015. Short term exposure to air pollution and stroke: systematic
 520 review and meta-analysis. Bmj. 350, h1295.

521 Stafoggia, M., et al., 2017. Statistical Approaches to Address Multi-Pollutant Mixtures
 522 and Multiple Exposures: the State of the Science. Curr Environ Health Rep. 4,
 523 481-490.

524 Sui, X., et al., 2020. The short-term effect of PM(2.5)/O(3) on daily mortality from
 525 2013 to 2018 in Hefei, China. Environ Geochem Health.

526 Tian, Y., et al., 2018. Association between ambient air pollution and daily hospital
527 admissions for ischemic stroke: A nationwide time-series analysis. PLoS Med.
528 15, e1002668.

529 Wang, W., et al., 2017. Prevalence, Incidence, and Mortality of Stroke in China: Results
530 from a Nationwide Population-Based Survey of 480 687 Adults. Circulation.
531 135, 759-771.

532 Wang, X. D., et al., 2016. Short-term effects of air pollution on acute myocardial
533 infarctions in Shanghai, China, 2013-2014. J Geriatr Cardiol. 13, 132-7.

534 Wang, Z., et al., 2020. Association between short-term exposure to air pollution and
535 ischemic stroke onset: a time-stratified case-crossover analysis using a
536 distributed lag nonlinear model in Shenzhen, China. Environ Health. 19, 1.

537 Yang, Y., et al., 2018. Ambient fine particulate pollution associated with diabetes
538 mellitus among the elderly aged 50 years and older in China. Environ Pollut.
539 243, 815-823.

540 Zhou, M., et al., 2016. Cause-specific mortality for 240 causes in China during 1990-
541 2013: a systematic subnational analysis for the Global Burden of Disease Study
542 2013. Lancet. 387, 251-72.

Figures

Figure 1

Pearson correlation coefficients between gaseous air pollutants concentrations and weather conditions and daily admissions for cerebrovascular disease in Beijing, 2014-2018 (n = 1799). NO₂: nitrogen dioxide; SO₂: sulfur dioxide; O₃: ozone; CO: carbon monoxide. * 0.01 < P ≤ 0.05; ** 0.001 < P ≤ 0.01; *** P ≤ 0.001.

Figure 2

Relative risk with 95% CI (confidence interval) in cerebrovascular morbidity associated with increase in concentrations of gaseous pollutants for different lag structures in multi-pollutant model: (a) SO₂: sulfur dioxide; (b) NO₂: nitrogen dioxide; (c) O₃: ozone; (d) CO: carbon monoxide.

Figure 3

3D graphs of NO_2 , SO_2 , O_3 and CO effect on overall cerebrovascular cases: (a) overall effect of NO_2 ; (b) overall effect of SO_2 ; (c) overall effect of O_3 ; (d) overall effect of CO. NO_2 : nitrogen dioxide; SO_2 : sulfur dioxide; O_3 : ozone; CO: carbon monoxide. RR (95% CI): relative risk and 95% confidence interval.

Figure 4

Cumulative exposure-response curves on overall cerebrovascular cases for gaseous pollutants (NO₂, SO₂, O₃ and CO) at lag0-7 using multi-pollutant models in Beijing, 2014-2018: (a) cumulative effect of NO₂; (b) cumulative effect of SO₂; (c) cumulative effect of O₃; (d) cumulative effect of CO. NO₂: nitrogen dioxide; SO₂: sulfur dioxide; O₃: ozone; CO: carbon monoxide. RR (95% CI): relative risk and 95% confidence interval.

Figure 5

Single day lag-response curves on overall cerebrovascular cases for extreme gaseous pollutants concentrations using multi-pollutant model in Beijing, 2014-2018: (a) overall effect of extreme high-NO₂; (b) overall effect of extreme high-SO₂; (c) overall effect of extreme high-O₃; (d) overall effect of extreme high-CO; (e) overall effect of extreme low-NO₂; (f) overall effect of extreme low-SO₂; (g) overall effect of extreme low-O₃; (h) overall effect of extreme low-CO. The high effect was estimated by the RR of cerebrovascular disease by comparing the 99th percentile to the median of daily concentration, whereas the low effect was estimated by comparing the 1st percentile to the median of daily concentration. NO₂: nitrogen dioxide; SO₂: sulfur dioxide; O₃: ozone; CO: carbon monoxide. RR (95% CI): relative risk and 95% confidence interval.

Supplementary Files

This is a list of supplementary files associated with this preprint. Click to download.

- [3supplementalfile21.4.1.docx](#)