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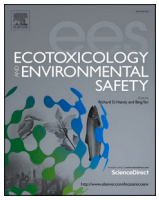

Air pollution and stroke: Short-term exposure's varying effects on stroke subtypes

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ABSTRACT

Background: Few studies have examined how air pollutants affect various stroke subtypes and how these effects differ with stroke severity, especially among European populations living in less polluted areas.
Methods: We conducted a time-stratified case-crossover study using 15 years of hospital-based stroke data from the University Hospital Augsburg in Southern Germany. Daily average air pollutants, including particulate matter (PM) with an aerodynamic diameter $< 10\mu m$ (PM_{10}), coarse particles (PM_{coarse}), fine particles ($PM_{2.5}$), ozone (O_3), nitrogen oxides (NO_2, NO), and meteorological data were obtained from local fixed urban background monitoring sites from 2006 to 2020. Conditional logistic regression was utilized to estimate the relationship between pollutants and daily stroke events, with modification effects being examined through stratified and interaction analyses.
Results: Based on 19,518 included stroke cases, each interquartile range (IQR) increase in $PM_{2.5}$, PM_{10}, PM_{coarse}, and NO_2 was associated with a 2.11 %, 2.55 %, 2.50 %, and 3.48 % rise in overall stroke events 5–6 days later. Positive associations were seen mostly for transient ischemic attacks and hemorrhagic strokes. Notably, people with severe stroke-induced disabilities were disproportionately affected by PM and NO_2, while those with mild disabilities were more affected by O_3 and NO. Moreover, damaging effects were amplified during warm seasons and the 2016–2020 five-year period.
Conclusion: Short-term air pollution exposure may trigger stroke events, with differential impacts depending on stroke subtype and severity of pre-existing disability. A coordinated effort is needed for stroke prevention in response to specific air pollutants, especially in the context of global warming.

1. Introduction

According to the World Stroke Organization, stroke remains the second leading cause of death and the third leading cause of disability-adjusted life-years lost throughout the world (Feigin et al., 2025; GBD, 2021). Global stroke burden has been increasing from 1990 to 2021 across the world (GBD, 2021). To date, a number of non-modifiable (age, sex, genetics, and race/ethnicity) and modifiable (hypertension,

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smoking, diet, and physical activity) risk factors are well established. Yet, the effect of outdoor air pollution has been identified, among other environmental factors, as a novel risk factor for stroke (Boehme et al., 2017).

Air pollution differs in chemical and physical properties depending on the type and size of chemical and biological contaminants. As a common proxy indicator for air pollution, outdoor particulate matter (PM) is mainly generated by traffic and transportation, industrial activities, power plants, construction sites, waste burning, fires, and agriculture (World Health Organization). Outdoor gaseous air pollutants are primarily produced by motor vehicles, industrial activities, and energy facilities (World Health Organization). About 8.1 million annual global deaths have been ascribed to air pollution, which was the second leading risk factor for deaths in 2021 worldwide (Health Effects Institute, 2024). Meanwhile, short-term air pollution exposure has been shown to trigger several diseases, including respiratory diseases (pneumonia or asthma) (Yee et al., 2021; Zheng et al., 2021), cardiovascular diseases (de Bont et al., 2022), and central nervous system disorders (Alhussaini et al., 2023).

An increasing number of studies have indicated the link between short-term exposure to ambient PM or gaseous pollutants and the incidence of strokes (de Bont et al., 2022; Lin et al., 2023; Toubasi and Al-Sayegh, 2023; Tian et al., 2023; Guo et al., 2023; Verhoeven et al., 2021; Choi et al., 2022). These studies have found that the effect of air pollution on stroke incidence varies by the type of air pollutant and the exposure window (Seposo et al., 2020). Research on different Chinese populations has consistently found positive associations between stroke-related hospital admissions and short-term exposure to air pollutants (Liu et al., 2017; Tang et al., 2021; Huang et al., 2017; Zeng et al., 2018; Li et al., 2023; Guo et al., 2020; Jiang et al., 2024; Lv et al., 2023; Fang et al., 2024; Chen et al., 2020). In contrast, short-term nitrogen dioxide (NO_2) exposure was negatively associated with stroke risk in a Korean cohort study (Kim et al., 2022). No effect of air pollution on strokes was found in New York City (Humphrey et al., 2023) and Thailand (Surit et al., 2023). The health effects of air pollution may change across subtypes of strokes (Verhoeven et al., 2021; Choi et al., 2022), but the findings of studies to date have remained inconclusive.

A recent systematic review and meta-analysis demonstrated strong and significant associations between short-term exposures to gaseous and ambient particulate air pollutants and the incidence and mortality of strokes (Toubasi and Al-Sayegh, 2023). However, the majority of these studies were implemented in Asia, primarily in low- and middle-income countries (58.8 %), whereas Europe only contributed 24.6 % of recent publications. More European population-based studies are therefore needed to further clarify these relationships within countries with comparatively lower air pollution levels. Furthermore, a systematic review revealed positive associations between short-term air pollution exposures and increased risks of ischemic strokes and intracerebral hemorrhage (Verhoeven et al., 2021). Transient ischemic attacks (TIAs), however, were poorly investigated, and the findings of these studies were inconsistent. Research demonstrating positive associations between short-term air pollution exposure and TIAs came from China (Zhang et al., 2021), Israel (Gaines et al., 2023), and the U.S (Lisabeth et al., 2008)., but no association was reported in Canada (Villeneuve et al., 2012).

Hence, we aimed to investigate the association between short-term exposures to several classical outdoor air pollutants and the occurrence of overall stroke and stroke subtypes in the area of Augsburg, Germany. Furthermore, we implemented effect modification analyses to identify individuals with high susceptibility, which could provide important evidence for the development of tailored prevention policies and treatment strategies.

2. Materials and methods

2.1. Study population

Data on daily stroke events were collected by the Department of Neurology at the University Hospital Augsburg between April 2006 and August 2020 (He et al., 2024). This research was conducted following guidelines set out in the Declaration of Helsinki and STROBE guidelines. According to the Bavarian Hospital Act, ethical approval was waived in the present study.

2.2. Assessment of outcomes and covariates

The Medical Informatics Department of the University Hospital Augsburg provided data on demographic characteristics (sex and age at admission), clinical details of patients (subtypes of strokes, disability, and severity), and some related covariates were collected during their hospital stay. Different types of strokes were defined according to the 10th version of the International Classification of Diseases (ICD-10) and classified as TIAs (code G45), hemorrhagic strokes (code I60, I61, I62), and ischemic strokes (code I63). In measuring functional independence after strokes, we utilized the modified Rankin Scale (mRS), which is a 7-level categorical scale (0–6 points), with the stroke severity being determined using the National Institutes of Health Stroke Scale (NIHSS), which ranges from 0 to 42 (Kasner, 2006).

2.3. Air pollution and meteorological data

The measurement details of ambient air pollution and meteorological parameters have been described elsewhere (Birmili et al., 2010; Wolf et al., 2015). Briefly, throughout the study period (2006–2020), we obtained the city-level daily 24-hour average concentrations of particulate matter (PM) with an aerodynamic diameter $< 10\mu m$ (PM_{10}), $< 2.5\mu m$ ($PM_{2.5}$), and PM_{coarse} (PM with an aerodynamic diameter between 2.5 and 10 μm) from the measurement stations operated by the Helmholtz Munich German Research Center for Environmental Health, Institute of Epidemiology (HMGU-EPI) in cooperation with the Environmental Science Center of the University of Augsburg (aerosol measurement station). The daily average concentrations of nitric oxide (NO), NO_2, and the daily maximum 8-hour average for ozone (O_3) were obtained from the network monitoring sites run by the Bavarian Environment Agency (LfU).

Given the different operating periods of monitoring sites (Birmili et al., 2010; Yao et al., 2023), we chose the site with the longest monitoring period for each air pollutant as the master site. Between 2006 and 2016, the daily averages of $PM_{2.5}$ were measured at the aerosol measurement station on the premises of the Fachhochschule Augsburg (FH; Technical University of Applied Sciences Augsburg), the representative of the urban background of Augsburg, which is located at 1 km southeast of the city center with a distance of 100 m to the main road in the north-east (Yao et al., 2023). Daily PM_{10} measurements were obtained from the urban background monitoring site located at Bourges Platz, which is located two kilometers to the north of the city center (Yao et al., 2023). Between 2017 and 2020, daily concentrations of both PM_{10} and $PM_{2.5}$ were mainly obtained from the network monitoring site located four kilometers south of the city center on the premises of the LfU. PM_{coarse} was calculated as the difference between PM_{10} and $PM_{2.5}$. Finally, PM data from FH and Bourges Platz monitoring sites (2006-2016) were calibrated with the data from the LfU monitoring site (2017-2020) to yield continuous levels of PM_{10}, $PM_{2.5}$, and PM_{coarse} throughout the whole study period (2006–2020). The daily maximum 8-hour O_3 level was measured at the LfU monitoring site, with NO and NO_2 being obtained from the Bourges Platz monitoring site. The missing values were imputed by the data obtained from the Bourges Platz (PM_{10} and $PM_{2.5}$) or LfU (NO and NO_2) sites. The selection of the measurement stations for data imputation depended on which station had a higher

explained variance (R^2) against data at the FH monitoring site (Yao et al., 2023; Cyrys et al., 2008). The daily 24-hour average air temperature and relative humidity were obtained from the LfU monitoring site. By combining all of these data sources, a continuous time series of all six ambient air pollutants and two meteorological indicators were derived for the full study period.

2.4. Statistical analysis

The time-stratified case-crossover study design was applied to estimate the association between air pollutants and stroke events. Case days were defined as the dates of stroke events, while control days were defined as the days in the same month and year that shared the same day of the week as the case day. Each stroke case day was therefore matched to 3 or 4 control days. By comparing the exposure levels on the case and control days, the case-crossover study minimizes potential confounding from long-term trends, seasonality, day of the week, and time-invariant confounders like sex and age (Carracedo-Martínez et al., 2010). Conditional logistic regression with a generalized additive model (GAM) was utilized to quantify the short-term effects of air pollution on stroke events. To keep alignment with existing evidence (Shah et al., 2015), the single-day lagged effect of air pollution was investigated from the case day (lag 0) to a maximum of six days before the case day (lag 1 to lag 6). The moving averages of air pollution were examined for periods 0–1, 2–4, 5–6, and 0–6 days before stroke events. To control for potential confounding by meteorological factors, we adjusted for daily mean air temperature and relative humidity for corresponding lag days and periods using natural splines with three degrees of freedom. Effect estimates were calculated as percent changes in daily stroke events with 95 % confidence intervals (CIs) based on the odds ratios (ORs) of stroke events corresponding to each IQR increase in air pollutant concentration. We further conducted subgroup analyses to explore the effect of air pollution on three stroke sub-types (TIAs, hemorrhagic strokes, and ischemic strokes), as well as stratified analyses based on the mRS for stroke-induced disability (no symptoms to slight disability [mRS = 0–2] *vs.* moderate disability to death [mRS = 3–6]) and stroke severity (no stroke to minor stroke [NIHSS = 0–3] *vs.* moderate to severe stroke [NIHSS = 4–42]).

Effect modification was explored by including an interaction term between air pollutants at each exposure window and potential modifiers, including sex (men *vs.* women) and age (<67.0, 67.0–78.0, ≥78.0 years), and daily average air temperature (tertiles 1–3). To further assess the time-varying effects of air pollutant values, the season of hospital admission was classified as warm (from May to October) or cold (from November to April). Admission years were divided into three five-year periods at an interval of five years (2006–2010, 2011–2015, 2016–2020), which were chosen due to their similar time durations and comparable total number of cases.

We conducted sensitivity analyses to assess the robustness of our findings. First, two-pollutant models were implemented for all air pollutant pairs that were not strongly correlated (r_S <0.7). Second, we used a restricted cubic spline with three degrees of freedom to assess the potential nonlinear relationship between daily mean air pollution and stroke events. The linearity of the exposure-response curves for air pollutants was determined by the visual inspection and likelihood ratio tests. All statistical analyses were done with R software (version 4.1.2); 2-sided P values < 0.05 were considered statistically significant, with a P < 0.10 being regarded as marginally significant.

3. Results

3.1. Study population characteristics

A total of 19,518 stroke patients aged 18 and older were recruited after excluding patients with missing exposure and outcome data. As shown in Table 1, the mean age and standard deviation (SD) of patients at enrollment was 70.9 (13.3) years, and 44.0 % of them were women. Most patients were diagnosed with ischemic strokes (67.8 %). In most cases, stroke patients were diagnosed with a moderate disability to death (31.8 %) or no stroke to minor stroke severity (42.0 %). Half of the strokes (50.6 %) occurred during cold seasons, and more than one third of stroke patients (35.7 %) were diagnosed during the second five-year period (2011–2015) (S.Fig 1).

Table 1
Basic characteristics of stroke survivors (N = 19,518) included in our study in Augsburg, Germany, from 2006 to 2020.

Characteristics	Mean±SD / n (%)
Sex	
Men	6290 (32.2)
Women	8585 (44.0)
Unknown	4643 (23.8)
Age (y)	70.9±13.3
Type of strokes[a]	
Transient ischemic attack	5024 (25.7)
Hemorrhagic stroke	1208 (6.2)
Ischemic stroke	13,242 (67.8)
Not specified stroke	44 (0.2)
Disability due to strokes (by mRS score)	
No symptoms to slight disability[b]	5879 (30.1)
Moderate disability to death[c]	6214 (31.8)
Unknown	7425 (38.0)
Stroke severity (by NIHSS score)	
No to minor stroke[d]	8189 (42.0)
Moderate to severe stroke[e]	5425 (27.8)
Unknown	5904 (30.2)
Seasons[f]	
Warm seasons	9667 (49.5)
Cold seasons	9851 (50.5)
5-year periods[g]	
2006–2010	6649 (34.1)
2011–2015	6966 (35.7)
2016–2020	5903 (30.2)

Abbreviations: mRS, Modified Rankin scale (a scale ranging from 0 to 6, with higher scores indicating greater disability); NIHSS, National Institutes of Health Stroke Scale (a scale ranging from 0 to 42, with higher scores indicating greater stroke severity).
Note: [a] Types of strokes were defined based on the ICD-10 code; [b] the mRS score of 0–2 is "no symptoms to slight disability"; [c] mRS 3–6 is "moderate disability to death". [d] NIHSS score of 0–3 is "no to minor stroke"; [e] NIHSS score of 4–42 is "moderate to severe stroke"; [f] Seasons: warm seasons: May to October; cold seasons: November to April; [g] 5-year periods: the year of admission.

3.2. Outdoor air pollutants

Distributions of daily exposure levels are displayed in Table 2. There were 3227 (58.9 %) days for NO_2, 1580 (28.8 %) days for $PM_{2.5}$, 157 (2.9 %) days for PM_{10}, and 35 (0.6 %) days for O_3 that exceeded World Health Organization (WHO) daily air quality standards (NO_2: 25 μg/m^3; $PM_{2.5}$: 15 μg/m^3; PM_{10}: 45 μg/m^3; 8-hour O_3: 100 μg/m^3) (World Health Organization, 2021), respectively. There was little change in the levels of most air pollutants during the study period of 2006–2020 (S.Fig 2). Following stratification of the data according to seasons, our analysis revealed significantly elevated concentrations of PM_{coarse} and O_3 during warmer compared to colder periods. Conversely, $PM_{2.5}$, PM_{10}, NO, NO_2, and relative humidity exhibited higher atmospheric levels in cold seasons (S.Table 1).

We noticed a very high positive correlation between $PM_{2.5}$ and PM_{10} ($r_S = 0.95$). NO exhibited high correlations with NO_2 ($r_S = 0.81$) and O_3 ($r_S = -0.70$), but in opposite directions. Both $PM_{2.5}$ and PM_{10} were moderately positively correlated with NO and NO_2. O_3 was moderately positively correlated with air temperature ($r_S = 0.59$) but negatively correlated with relative humidity ($r_S = -0.64$) (S.Table 2).

Table 2
Summary of daily ambient air pollutants and meteorological parameters in Augsburg, Germany, from 2006 to 2020.

Variables	Mean ± SD	Min	P25	P50	P75	Max	IQR
$PM_{2.5}$ (μg/m^3)	13.0 ± 10.6	0.0	6.4	10.4	16.3	126.4	9.9
PM_{10} (μg/m^3)	17.3 ± 12.2	0.0	9.3	14.6	21.8	138.7	12.5
PM_{coarse} (μg/m^3)	4.3 ± 3.7	0.0	1.7	3.5	5.8	50.6	4.1
O_3 (μg/m^3)	46.1 ± 23.3	0.6	27.6	48.0	63.4	127.8	35.8
NO (μg/m^3)	11.9 ± 18.7	0.0	2.5	5.4	13.2	238.8	10.7
NO_2 (μg/m^3)	29.1 ± 12.9	3.6	19.7	27.7	36.4	113.3	16.7
Air temperature (°C)	10.4 ± 8.1	−13.9	3.9	10.5	16.7	30.3	12.8
Relative humidity (%)	74.2 ± 11.9	38.4	65.1	74.9	84.0	99.0	18.9

Abbreviations: SD, Standard deviation; IQR, interquartile range; $PM_{2.5}$, particulate matter with an aerodynamic diameter below 2.5 μm; PM_{10}, particulate matter with an aerodynamic diameter below 10 μm; PM_{coarse}, coarse particulate matter with an aerodynamic diameter between 2.5 and 10 μm; O_3, ozone; NO, Nitric oxide; NO_2, nitrogen dioxide.
Note: Ambient air pollutants and meteorology were consecutively measured between 2006 and 2020.

3.3. Association between outdoor air pollution and overall stroke events

As shown in Fig. 1, we observed statistically significant, albeit small, delayed effects for most air pollutants at lag 5 and 6 days. An IQR increase in $PM_{2.5}$, PM_{10}, PM_{coarse}, and NO_2 at lag 5 and 6 days was associated with increased odds of overall stroke events. By contrast, a delayed decrease in the odds of stroke was observed for O_3 at lag 6 days (percent change = −4.28 [–8.36; −0.02]). More numeric data are available in S.Table 3.

A similar pattern was found in the lagged moving average model (Fig. 2). During the peak lag of 5–6 days, each IQR increase in moving averages of $PM_{2.5}$, PM_{10}, PM_{coarse}, and NO_2 was positively associated with overall stroke events (all $P < 0.05$). Additionally, NO_2 showed a significantly positive association with stroke at the lag of 0–6 days, while O_3 showed a marginally negative association ($P < 0.10$). See S. Table 4 for further details.

3.4. Subgroup / stratified analyses

The relationships between air pollution and stroke events varied by their subtypes. In the single-day lagged model, there was a 6-day delayed effect of four air pollutants on TIAs. Each IQR increase in $PM_{2.5}$, PM_{10}, and NO_2 was positively associated with TIA events at a 6-day lag, whereas each IQR increase in O_3 was negatively associated with TIAs (percent change = −12.49 [–19.73; −4.60]). For hemorrhagic strokes, 5- and 6-day delayed effects were both observed for $PM_{2.5}$, and lag 4- and 5-day delayed effects were found for NO_2 (S.Fig. 3). In particular, we found an isolated association between ischemic stroke

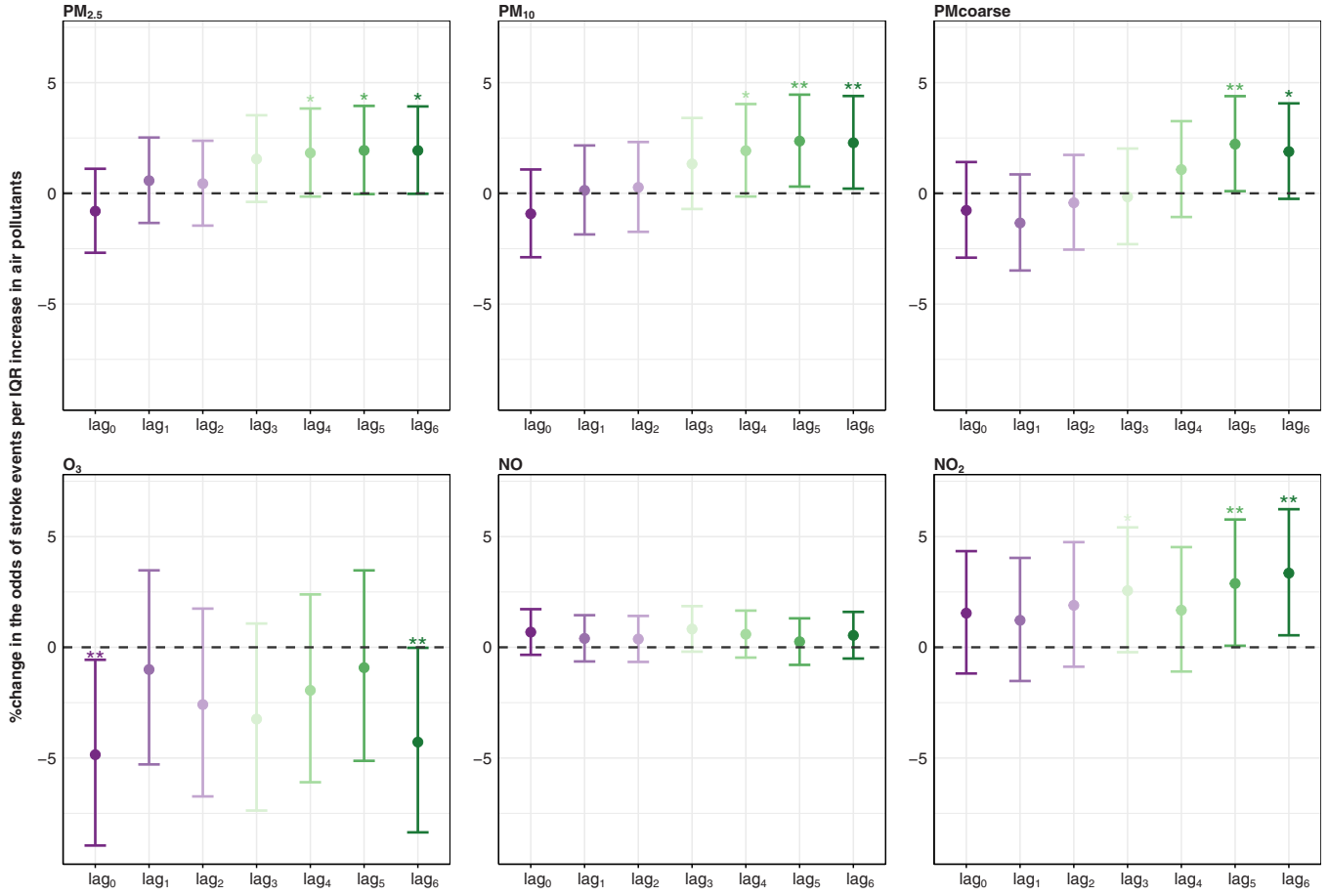

Fig. 1. Percent change (95 % CI) in the odds of overall stroke events in each interquartile range (IQR) increase in single-day lagged air pollutants. **Note**: * , $P < 0.10$; * *, $P < 0.05$.

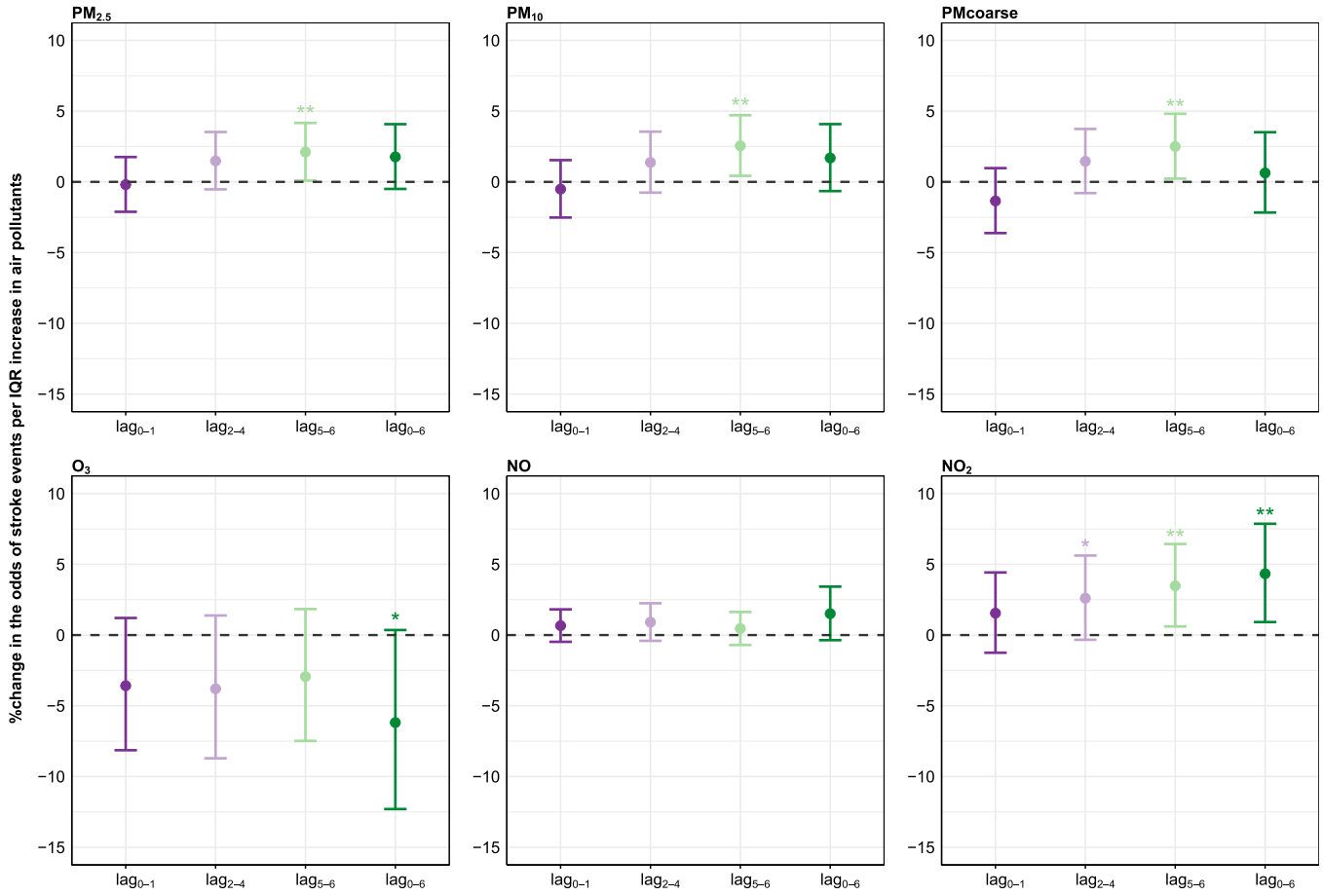

Fig. 2. Percent change (95 % CI) in the odds of overall stroke events in each interquartile range (IQR) increase in moving averaged air pollutants. **Note:** * , $P < 0.10$; * *, $P < 0.05$.

and PM_{coarse} exposure at lag day 5, suggesting that this finding should be interpreted cautiously due to its exclusivity to PM_{coarse} and lack of broader consistency across pollutant types (S.Table 5). Consistent with prior findings, the lagged moving average model demonstrated elevated odds of TIAs associated with NO exposure at lag days 0–6, alongside increased odds of hemorrhagic strokes linked to particulate matter ($PM_{2.5}$ and PM_{10}) and NO_2 at lag days 5–6 (Fig. 3 and S.Table 6).

Stratified analyses by stroke-induced disability further revealed that patients with a severe disability whose stroke occurred at peak lag 5 and 5–6 days were more adversely affected by particulates ($PM_{2.5}$, PM_{10}) and NO_2, whereas those with a slight disability had greater sensitivity to gaseous pollutants (O_3 and NO) at lag 0–6 days (Fig. 4,S.Fig. 4). The effect of O_3 at a lag of 0–6 days seemed to be more evident among those with slight stroke severity (S.Figs. 5 and 6). Numeric data are available in S. Tables 7 and 8.

3.5. *Effect modification and sensitivity analyses*

As shown in S.Table 9, we observed significant effect modification by sex, seasons, and 5-year periods (all *P*-interactions <0.05). Compared to men, women seem to be more susceptible to the effect of PM_{coarse} at lag 5 days (percent change = 5.41 [2.32; 8.60]; *P*-interaction = 0.015) and a 5–6 day lag (percent change = 5.60 [2.29; 9.02]; *P*-interaction=0.041) (S.Fig.7). However, this result needs to be treated with caution because it only exists for PM_{coarse}. As for seasons, the effects of O_3, NO, and NO_2 at a 6-day lag on overall strokes were stronger during the warm seasons (percent changes were −10.79, 8.26, and 12.27, respectively; *P*-interactions < 0.05). A similar pattern of effect modification was found for moving average 5–6 day lags for NO (percent change = 7.42 [0.98; 14.27]; *P*-interaction = 0.031) (S.Fig.8). Regarding 5-year time periods, the effect of $PM_{2.5}$ and PM_{10} on stroke events at a 5-day lag was stronger during 2016–2020 than in prior periods (percent changes were 6.07 and 5.32; both *P*-interactions < 0.05), with similarly stronger effects being also found in the moving 5–6 day average (percent changes were 6.01 and 5.70; both *P*-interactions < 0.05) (S.Fig.9). However, we did not observe any effect modification by age and air temperatures across air pollutants in different exposure windows.

Findings from the two-pollutant models suggest that the associations between air pollution and elevated overall stroke risk in the single-day lagged and lagged moving average models remained mainly stable after further adjustment for other air pollutants (S.Tables 10 and 11). We did not capture substantial deviation from linearity in the exposure-response functions between most air pollutants and stroke events at the lag of 5–6 days (all *P* for likelihood ratio test > 0.05) (sFig. 10).

4. Discussion

Our findings suggest that short-term exposure to air pollution, particularly PM and NO_2, is linked to stroke events, with the strongest effects occurring five to six days after exposure. TIAs and hemorrhagic strokes increased following short-term exposure in this timeframe. Strokes that caused severe disabilities were associated with particulate pollutants, whereas strokes that caused milder disabilities could be attributed to gaseous pollutants. Seasonal and temporal factors also played a role, with air pollution effects appearing stronger during warmer months and in the 2016–2020 timeframe.

Consistent with our findings, growing evidence supports the link between short-term air pollution exposure and stroke risk (de Bont et al.,

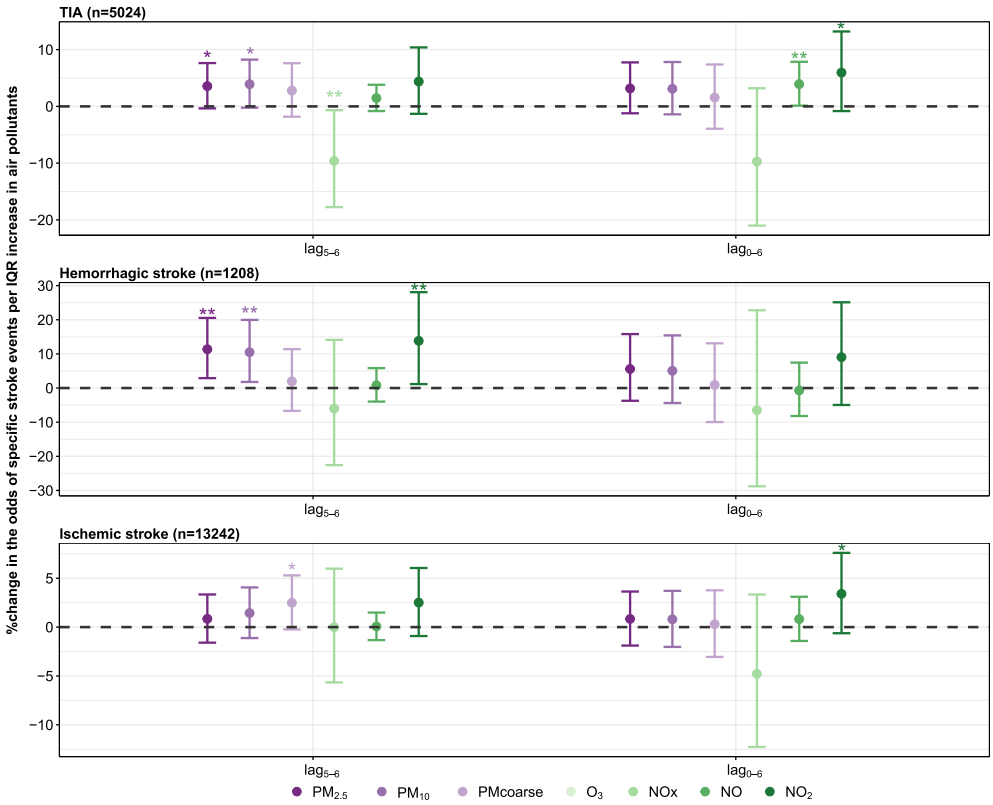

Fig. 3. Subgroup percent change (95 % CI) in the odds of stroke events in each interquartile range (IQR) increase in moving averaged air pollutants (over lag 5–6 and lag 0–6 days) by three subtypes. **Note**: Different scaling on the y-axis for better visibility. * , $P < 0.10$; * *, $P < 0.05$.

2022; Lin et al., 2023; Kulick et al., 2023). A nationwide study in China showed a 13.1 % increase in stroke risk with a 10 μg/m^3 increase in same-day NO_2 levels (Jiang et al., 2024). Similar studies in Beijing and Chengdu found stroke admissions increased by 0.82 % and 0.60 % per 10 μg/m^3 increase in same-day NO_2 and $PM_{2.5}$, respectively (Huang et al., 2017; Zeng et al., 2018), with similar positive associations being also found per 10 μg/m^3 increase in 0–3 days of $PM_{2.5}$, NO_2, and O_3, in Shenzhen (Guo et al., 2020) and hourly exposures to $PM_{2.5}$, PM_{10}, NO_2 in Zhejiang and Shanghai, China (Lv et al., 2023; Fang et al., 2024). However, a study in Thailand found no significant impact of $PM_{2.5}$ on stroke-related emergency visits, possibly due to limited sample size and duration of data collection (Surit et al., 2023). Most existing studies have focused on Asian populations, leaving a gap in the evidence for Caucasian populations (Humphrey et al., 2023; Lisabeth et al., 2008; Villeneuve et al., 2012; Wing et al., 2017; Gutiérrez-Avila et al., 2023; Vivanco-Hidalgo et al., 2018; Maheswaran et al., 2012; Butland et al., 2017). Furthermore, the adverse health effects observed in China and South Asia may be more pronounced because these areas are commonly known to experience higher levels of outdoor air pollution (Health Effects Institute, 2024). The present study utilized data from Augsburg, Germany, where daily air pollution levels exceeded WHO guidelines for less than one-third of the year. This point is extremely important because it shows that the associated risk of stroke is already significantly increased in regions with moderate particulate matter pollution overall.

The results of studies on the effect of air pollution on specific stroke subtypes have been inconsistent. Most existing studies have focused on ischemic strokes, with strong evidence of a link to air pollution in Asia, including China (Liu et al., 2017; Li et al., 2023; Lv et al., 2023; Fang et al., 2024; Liu et al., 2023; Tian et al., 2018; Zhao et al., 2022; Chen et al., 2021; Guo et al., 2017), Japan (Hasegawa et al., 2022), South Korea (Kim et al., 2022), and Singapore (Ho et al., 2018). However, in our study, we found no significant association between air pollution and ischemic strokes in a European Caucasian population, similar to findings in Spain (Vivanco-Hidalgo et al., 2018), Thailand (Surit et al., 2023), and the U.S (Wing et al., 2017). This suggests that ethnic differences, pollution measurement, or distribution variations may affect outcomes, highlighting the need for diverse research on this topic.

There is limited evidence on TIAs, partly due to inconsistent definitions, which make the diagnosis complicated. TIAs are typically defined by symptoms resolving within 24 hours or by magnetic resonance imaging (MRI) results showing no infarction (Perry et al., 2022). Despite challenges in defining TIAs, studies from China (Zhang et al., 2021), Israel (Gaines et al., 2023), and the U.S (Lisabeth et al., 2008). have reported the association between air pollution and TIA hospitalizations, while a Canadian study found no such effect (Villeneuve et al., 2012). Despite that, we found an association between TIAs and increased air pollution exposure; larger population-based studies are needed to better reveal the adverse health effects of air pollution on TIAs.

In line with our findings, short-term exposure to NO_2 was found to be associated with hemorrhagic strokes in both China (Liu et al., 2017) and the U.S (Sun et al., 2019). in previous studies. PM_{10}, NO_2, and NO exposures were also associated with hemorrhagic strokes in the UK (Butland et al., 2017; Czernych et al., 2024) and South Korea (Kim et al., 2022), as well as $PM_{2.5}$ in China (Wang et al., 2023a). There are also a few reports that have explored this relationship in comparison to those for ischemic strokes, possibly due to hemorrhagic strokes being less common and their mechanisms being less influenced by air pollution (Estol, 2019). In line with a Chinese study (Chen et al., 2020), we noticed an inverse association of strokes with O_3. This inverse association may reflect confounding by co-pollutants and photochemical processes. O_3 could be titrated by NO in high-traffic environments, which might be related to the photochemical reaction between them (Sillman, 1999). Also, adjustments for temperature and relative humidity did not fully attenuate this association, and the association was not robust in the two-pollutant model, suggesting residual confounding by unmeasured factors tied to pollution mixtures. Thus, the observed association may

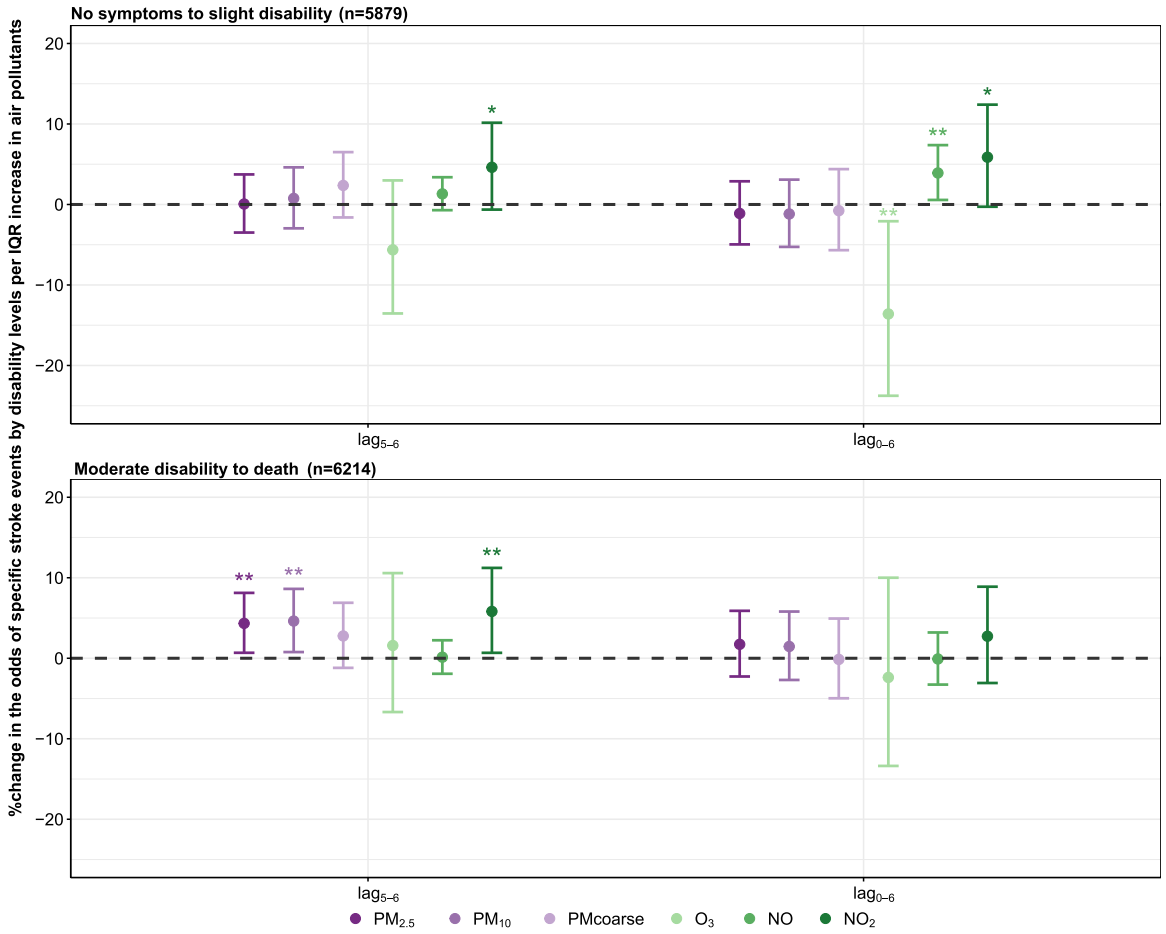

Fig. 4. Stratified percent change (95 % CI) in the odds of overall stroke events in each interquartile range (IQR) increase in moving averaged air pollutants (over lag 5–6 and lag 0–6 days) by disability levels. **Note**: * , $P < 0.10$; * *, $P < 0.05$.

reflect competing sources rather than a "protective" effect, as O_3 remains harmful in contexts where it is the dominant oxidant. All of the evidence from previous studies is summarized in the S.Table 12.

The mechanisms underlying air pollution and stroke are still unclear. Vascular endothelial dysfunction, increased cerebrovascular resistance, and reduced cerebral blood flow have been discussed as possible factors (Toubasi and Al-Sayegh, 2023; Münzel et al., 2020; Wellenius et al., 2013). Air pollution may also cause oxidative stress and inflammation, which can damage blood vessels and the brain (Alhussaini et al., 2023; Wellenius et al., 2013; Peters et al., 1997). IIt's possible also that air pollution changes cerebrovascular hemodynamics, such as by increasing cerebrovascular resistance, lowering cerebral blood flow velocity (Toubasi and Al-Sayegh, 2023; Wellenius et al., 2013), increasing plasma viscosity (Peters et al., 1997), increasing sympathetic tone, causing acutely constricting arteries (Brook et al., 2002), and thereby contributing to elevated blood pressure, ischemia, and thrombosis risks (Toubasi and Al-Sayegh, 2023; Louis et al., 2023).

Gaseous pollutants are known to trigger respiratory inflammation (Glencross et al., 2020). Redox imbalance related to the decreased activity of nitric oxide, and the existence of reactive oxygen species (ROS) could directly damage the vasodilatory, antithrombotic, antioxidant, and anti-inflammatory effects in an intact endothelium (Hahad et al., 2020). After being inhaled, small particles can cause blood-brain barrier impairment by passing through the nose-brain barrier (Hahad et al., 2020) and entering the brain parenchyma (Kafa et al., 2015), thus inducing mitochondrial dysfunctions (Ku et al., 2016), contributing to increased monocyte infiltration, activation of microglia, and ROS production, finally triggering neuroinflammation in the brain (Arias-Pérez et al., 2020). Additionally, due to their complex composition, PMs have been thought to be more important in causing disease because they contain metals, carbon, sulfates, and nitrates, compared with gaseous pollutants (Glencross et al., 2020). This could explain the fact that strokes with different severities may be differently related to ambient air pollutants, with more disabling strokes occurring mainly in relation to PM exposure.

Effect modifications by seasonal and temporal trends were found, with stronger adverse health effects of gaseous pollutants being observed during warm seasons, as well as the effect of particles between 2016 and 2020. The observed effect modification by season may be explained by the amount of time spent outdoors or the fact that windows may be opened for ventilation with more frequency and longer duration during warm season as compared to cold season, which results in higher personal exposure to ambient air pollutants (Turner et al., 2012), despite the fact that based on daily monitoring data, PMs, NO, and NO_2 levels were lower during the warm seasons than in cold seasons in our study areas. The activated thermoregulatory mechanisms caused by increases in exercise in warm weather also elevate inhalation rates, enhancing pollutant uptake into the airways (Gordon, 2003; Rai et al., 2023). Though we did not capture a direct effect modification by temperature in our study, heat stress has been shown to increase stroke risk as an additional factor (He et al., 2024). Higher ambient temperature could increase the solubility and bioavailability of contaminants, thus exaggerating the toxicokinetic characteristics of contaminants (Wang et al., 2023b), whereas the related ability of the body to detoxify chemicals may be reduced by increased thermoregulatory responses to heat stress (Gordon, 2003; Rai et al., 2023). Furthermore, in warm seasons, higher levels of sunlight and air temperature can drive photochemical reactions between nitrogen oxides and volatile organic compounds, forming

secondary pollutants, which might be more biologically reactive and damaging than primary pollutants (NO/NO_2) (Pinto et al., 2010). The temporal trends we identified indicating stronger adverse health effect of PMs during the 2016–2020 timeframe were contradictory to a study on intracerebral hemorrhage which compared an earlier study period (2014–2017) to 2018–2021 (Wang et al., 2023a). However, in a recent multicenter study, increased cardiovascular mortality has been observed as a result of exposure to $PM_{2.5}$, despite a declining trend of $PM_{2.5}$ exposure concentrations (Schwarz et al., 2024). The temporal increase in the effect of PMs may be related to the following two points: i) the composition of particles and aerosol mixtures may have changed over time due to changes in vehicle fleets, fossil fuel types, and combustion technologies used for heating and industrial processes in recent years, thus causing different patterns of pollutants' effect on strokes across time; ii) we cannot completely elucidate the potential deviation from linearity, despite finding no evidence of non-linear exposure-response relationships. There may exist a supralinear concentration-response relationship, characterized by steeper slopes at low concentrations and either flat or continuously gradual slopes at high concentrations. This pattern may indicate a significant change, particularly in low-concentration contexts (Weichenthal et al., 2022). Furthermore, the temporal variation in the toxicity may partly be ascribed to the changes in socioeconomic factors, population distribution, and susceptibility (Schwarz et al., 2024). More studies are needed to clarify the time trend of the health impacts of air pollution.

This study has several strengths. Firstly, this study was conducted based on the validated registration of stroke events by the University Hospital Augsburg, with the time of stroke events being obtained from the medical records. Second, the design of a case-crossover study enables us to control long-term time trends, seasonality, the effects of days of week, and time-invariant individual-level confounders. Conversely, there were some limitations to our study. First, we cannot account for intra-city spatial variability or personal mobility because the air pollution data was collected from fixed monitoring stations. Future studies incorporating individual-level exposure models or satellite-based estimates could shed further light on this topic. Second, potential misclassification is inevitable in our study. Nevertheless, the stroke data used in our study comes from the University Hospital Augsburg, one of Germany's largest stroke centers serving approximately 750,000 residents in the region (Ertl et al., 2019). Consequently, non-differential misclassification could only cause Berkson bias, which may not have much effect on the associations (Zeger et al., 2000; Armstrong, 1998). Third, the diagnosis for TIAs may be less reliable due to their symptoms and signs usually being resolved by the time of assessment. However, this would only reduce the precision of association rather than blur the effect of air pollution on stroke risk, as the misclassification is less likely to be related to air pollution. Fourth, the relatively older age of our study population may limit the generalizability of the findings to younger or more diverse demographic groups. Finally, the inference of causality from our findings could be questionable because of our observational study design.

5. Conclusions

In summary, our 15-year time-stratified case-crossover study found that short-term exposure to air pollution (mainly PM_{10}, $PM_{2.5}$, PM_{coarse}, and NO_2) was associated with higher odds of stroke events, particularly TIAs and hemorrhagic strokes, with the events mainly occurring after the fifth to sixth day post-exposure. Stroke severity also seems to be related to specific types of air pollutants. Hospitalizations of patients with stroke, triggered by higher air pollution exposure, were mainly increased during warmer seasons and within the period of 2016–2020.

CRediT authorship contribution statement

Naumann Markus: Writing – review & editing. **Cyrys Josef:** Writing – review & editing. **Hammel Gertrud:** Writing – review & editing. **He Cheng:** Visualization, Software, Formal analysis. **Breitner Susanne:** Writing – review & editing. **Schneider Alexandra:** Supervision, Methodology, Conceptualization. **Liao Minqi:** Writing – original draft, Visualization, Formal analysis. **Zhang Siqi:** Visualization, Software, Formal analysis. **Peters Annette:** Writing – review & editing, Supervision. **Ertl Michael:** Methodology, Conceptualization. **Braadt Lino:** Writing – review & editing. **Traidl-Hoffmann Claudia:** Writing – review & editing.

Ethics statement

The research was conducted following guidelines set out in the Declaration of Helsinki and the STROBE guidelines. The ethical approval was waived in the present study according to the Bavarian Hospital Act.

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Declaration of Competing Interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

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Appendix A. Supporting information

Supplementary data associated with this article can be found in the online version at doi:10.1016/j.ecoenv.2025.118296.

Data availability

Data will be made available on request.

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