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The influence of ambient air pollutants on stroke occurrence: a clinically relevant prospective study

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Abstract

Evidence from prospective studies on heterogeneity in responses to ambient air pollutants across stroke clinical subgroups is limited. We conducted an exploratory, region-wide ecological time-series analysis to estimate lag–response associations, focusing on stroke clinical-phenotype subgroups. Daily stroke admissions (14 February 2024–31 August 2025) were modelled using single-pollutant, log-linear quasi-Poisson generalised additive models with distributed-lag non-linear cross-basis functions (penalised splines), adjusting for potential confounders. Cumulative relative risk (RR) estimates were summarised for two exposure contrasts: the interquartile range (IQR) and the 97.5th versus 2.5th percentiles (adverse-episode), across predefined lag windows (days). Cumulative RRs were estimated for clinical subgroups. Across pollutants, adverse-episode contrasts ($RR_{97.5th}$) generally yielded larger effects than day-to-day contrasts (RR_{IQR}). Nitrogen dioxide (NO_2) showed the largest positive cumulative effect at lag 0–5 days ($RR_{97.5th}$: 1.24). Under the day-to-day contrast, NO_2 showed marginally significant increases in cumulative RRs at lag 0–3 among older adults (≥65 years), male patients, and those with diabetes or hypertension. Week-scale lag effects for NO_2 were statistically significant among patients with macroangiopathy (RR_{IQR}: 1.49; and $RR_{97.5th}$: 3.01). Ozone showed negative associations across lag windows for most clinical subgroups. For particulate matter, elevations were most evident at lag 0–3 and attenuated by lag 0–7. Among female patients, PM_{10}–stroke associations at lag 0–3 were statistically significant under both contrasts (RR_{IQR}: 1.08; and $RR_{97.5th}$: 1.41). Under the day-to-day contrast, PM_{10} showed a statistically significant association among patients undergoing thrombectomy across all lag windows; no significant association was observed under the adverse-episode contrast. This study leverages data from one of the first large, prospective registries of stroke admissions, with detailed clinical phenotyping, to examine pollution–stroke associations by clinical subgroup. Although exploratory, these findings suggest clinically relevant links that warrant validation in multicentre cohorts.

Keywords Stroke Occurrence · Air Pollutants · Stroke Clinical Subgroups · Prospective Study · Distributed lag non-linear model · Macroangiopathy

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Abbreviations

CI	Confidence interval
DLNM	Distributed-lag non-linear model
HT/ICH	Haemorrhagic transformation or intracranial haemorrhage
IQR	Interquartile range
mRS	Modified Rankin Scale
NIHSS	National Institutes of Health Stroke Scale
NO_2	Nitrogen dioxide
O_3	Ozone
$PM_{2.5}$	Particulate matter with an aerodynamic diameter of ≤ 2.5 µm
PM_{10}	Particulate matter with an aerodynamic diameter of ≤ 10 µm
PM_{coarse}	Coarse particulate matter ($PM_{coarse} = PM_{10} - PM_{2.5}$; i.e., particles with an aerodynamic diameter between 2.5 and 10 µm)
RR	Relative risk
STROBE	STrengthening the Reporting of OBservational studies in Epidemiology statement

Background

Population-level research has accumulated evidence that ambient air pollutants are associated with stroke (Shah et al. 2015; Verhoeven et al. 2021). This body of evidence informs high-level stakeholders (e.g., the World Health Organization and regional environmental and health agencies), guides air-quality management to protect health at the population level, and supports public health decision-making at the national and regional levels (European Environment Agency 2023; World Health Organization 2021). However, such population-level associations do not translate directly to healthcare settings, where more clinically nuanced information is required to guide patient- and hospital-level stroke management and to inform service planning (Verhoeven et al. 2021).

Most prior studies examining these associations have relied on retrospective analyses of stroke registries designed to maximise feasibility and comparability across centres (Liao et al. 2025; Vidale et al. 2017). Regional-scale registry analyses typically distinguish only broad stroke subtypes (ischaemic versus haemorrhagic) and report summary measures of severity and disability—such as the National Institutes of Health Stroke Scale (NIHSS) and the modified Rankin Scale (mRS)—rather than detailed clinical phenotypes (Liao et al. 2025; Verhoeven et al. 2021). This limited granularity constrains the identification of clinically meaningful associations between ambient air-pollutant exposure and specific patient characteristics (Maheswaran et al. 2016; Verhoeven et al. 2021).

Conducting clinically detailed, prospective multicentre analyses of associations between ambient air-pollutant exposure and stroke on a regional scale is essential but challenging (Verhoeven et al. 2021). Such work is resource-intensive and often hampered by incomplete and heterogeneous data, variability in diagnostic and coding practices, and the burden of harmonising clinical variables across sites (McCormick et al. 2015). Consequently, a key research gap remains (Verhoeven et al. 2021).

To better inform clinical stroke management at the hospital level in the context of air-pollutant exposures, we conducted an exploratory analysis using prospectively collected data from a region-wide stroke registry. The objectives were: (i) to estimate short-term lag–response associations between ambient air pollutants and stroke occurrence; and (ii) to assess how these associations vary across clinically distinct stroke subgroups. Methodologically, we used distributed lag non-linear models (DLNMs) to flexibly characterise potentially non-linear exposure–response relationships and delayed effects across multiple lag days, rather than relying on single-lag or strictly linear specifications (Gasparrini et al. 2010, 2017; Iñiguez et al. 2022).

Methods

Patients and data source

We established a prospective, single-centre stroke registry at the University Hospital Augsburg. The registry enrolled consecutive patients admitted to the Department of Neurology and Clinical Neurophysiology, with a clinical diagnosis of stroke between 14 February 2024 and 31 August 2025. Two trained study nurses (S.K., M.S.) abstracted patient data from discharge summaries and electronic medical records for all eligible patients, including both survivors and those with in-hospital deaths. Data were entered into the web-based REDCap (Research Electronic Data Capture) system. Two study physicians (L.B., J.W.) verified the entries, performed logic and range checks to ensure internal consistency and completeness, and resolved discrepancies by consensus in research meetings. Any missing, ambiguous, or inconsistent entries were flagged and resolved through re-review of the source records and email communications. This procedure was intended to maximise completeness and reliability of the analytical dataset.

Environmental exposures

We obtained hourly air pollutant concentration data from the regulatory monitoring station "Bourges-Platz" operated by the Bavarian Environment Agency, via the European

Environment Agency's Air Quality Download Service (Bavarian Environment Agency (LfU) 2023; European Environment Agency 2025). The station is located near the city centre of Augsburg and is classified as "urban background".

We analysed nitrogen dioxide (NO_2), ozone (O_3), particulate matter with an aerodynamic diameter of≤10 µm (PM_{10}), with an aerodynamic diameter of≤2.5 µm ($PM_{2.5}$), and coarse particulate matter ($PM_{coarse} = PM_{10} - PM_{2.5}$; i.e., particles with an aerodynamic diameter between 2.5 and 10 µm). Pollutant concentrations were summarised as daily means, except O_3, which was expressed as the daily maximum 8-h average.

Other meteorological covariates included air temperature (daily mean and diurnal amplitude), relative humidity (daily mean), mean sea-level pressure (daily mean), wind speed (daily mean), and cloud cover (daily mean). The meteorological covariates were obtained from the weather station in Augsburg, operated by the German Weather Service. The station is located on the site of the former Augsburg airport (German Meteorological Service 2024).

Missing environmental or meteorological values were rare, affecting three non-consecutive calendar days during the 565-day study period (0.5%). These missing values were imputed using a linearly weighted 5-day moving average based on the two preceding and two following valid daily observations.

Daily stroke counts and clinical-phenotype subgroups

For each calendar day in the study period, the daily stroke count was the number of patients admitted with a recorded stroke diagnosis, irrespective of whether the event was first-ever or recurrent. Dates without stroke admissions were retained and assigned zero counts to preserve the complete time series.

To derive clinical-phenotype subgroups, we identified for each admitted patient whether specific characteristics applied. For each calendar day, these indicators were summed across patients to obtain subgroup-specific daily counts.

Subgroups comprised sex (male, female); age (≥65 years) (Shah et al. 2015); stroke type (ischaemic, haemorrhagic) (Verhoeven et al. 2021); aetiology (macroangiopathy, microangiopathy, cardiogenic) (Adams et al. 1993); acute treatment (intravenous thrombolysis [systemic thrombolysis], thrombectomy) (Powers et al. 2019); functional outcomes (NIHSS: minor [0–3], severe [>3] (Waddell et al. 2023); mRS at discharge: favourable [0–2], unfavourable [3–6]) (Berkhemer et al. 2015); risk factors (arterial hypertension, dyslipidaemia, atrial fibrillation, diabetes mellitus, smoking, and a composite "multiple risk factors" indicator including concurrent dyslipidaemia, arterial hypertension, diabetes mellitus, and reported smoking) (Pedamallu et al. 2023); in-hospital complications (pneumonia; haemorrhagic transformation or intracranial haemorrhage) (Kumar et al. 2025); and time of symptom onset (morning [06:00–11:59], afternoon [12:00–17:59], evening [18:00–23:59], night [00:00–05:59]) (Elliott 1998). We grouped symptom onset time into four clinically interpretable 6-h time-of-day categories (night, morning, afternoon, and evening) to capture circadian and daily activity/exposure cycles, thereby enabling assessment of time-of-day differences in stroke risk. These broad 6-h categories also reduce potential misclassification due to imprecise onset-time recording in routine clinical practice, while preserving sufficient counts for subgroup time-series analyses. All targeted clinical-phenotype indicators were selected based on the published literature and international guidelines.

Study design and research outcome

We conducted a region-wide ecological time-series study, following the study design principles of Iñíguez et al. (Iñiguez et al. 2022). The primary outcome was the cumulative relative risk (RR) for short-term associations between ambient air pollutants and stroke across clinical-phenotype subgroups.

Inclusion and exclusion criteria

All available observations from the study period were included; no exclusion criteria were applied.

Statistical analyses

Distributed-lag non-linear model with penalised splines

We followed the methodological approach of Iñíguez et al. (Iñiguez et al. 2022), as our modelling foundation. Daily stroke counts (treated as the dependent variable) were analysed using log-linear quasi-Poisson models, with each ambient air pollutant treated as the independent variable (i.e., NO_2, O_3, $PM_{2.5}$, PM_{10}, and PM_{coarse}, respectively), with appropriate adjustment for confounders (Iñiguez et al. 2022).

For each single-pollutant, we incorporated a DLNM with penalised splines (Gasparrini et al. 2017), constructed using the `crossbasis` function from the `dlnm` R package. Models were fitted as generalised additive models using the `gam` function from the `mgcv` R package, using a log link, quasi-Poisson variance structure, with smoothing parameters estimated by restricted maximum likelihood. Both the

exposure–response and lag–response functions were specified as penalised splines, each with eight degrees of freedom for the basis dimension (Gasparrini et al. 2017); the effective degrees of freedom were selected automatically by restricted maximum likelihood.

We supplied the DLNM penalty matrix to gam via the paraPen argument to impose quadratic roughness penalties on the cross-basis in both dimensions (Gasparrini et al. 2017). Under this specification, the model maximised a penalised quasi-likelihood, shrinking the cross-basis as needed. This penalisation constrains overfitting of the two-dimensional exposure–lag surface, enhances numerical stability (especially near boundaries), and yields smoother and more reliable cumulative risk estimates.

We evaluated cumulative RRs over three prespecified lag windows: lag 0–3 days (acute response), lag 0–5 days (intermediate response), and lag 0–7 days (one-week timescale response).

Adjustment for temporal and meteorological confounding

To control for temporal confounding, models included a natural spline of time with seven degrees of freedom per year to capture long-term and seasonal patterns (Gasparrini et al. 2010), plus indicators for day of week and public holidays based on the Bavarian holiday calendar.

Meteorological confounding was addressed using natural cubic splines (3 degrees of freedom) of the 3-day moving averages of daily mean temperature, relative humidity, and mean sea-level pressure, as suggested by Zhou et al. (Zhou et al. 2025).

Model equation (conceptual) of the DLNM with penalised splines

$$\log E\left(Y_t\right) = \alpha + s_{time}\left(t\right) + \sum_j s\left(M_{j,t}^{(3d)}\right) + f_{DL}\left(X_t, \ldots, X_{t-L}\right) + DOW_t + Holiday_t$$

where $E\left(Yt\right)$ is the expected daily (or subgroup-specific) stroke count; fDL is the penalised-spline cross-basis for exposure and *lags 0...L*; $s(\cdot)$ denotes smooth functions; Mj,t are meteorological covariates; and $DOWt$ and $Holidayt$ are categorical variables representing the day of the week and the Bavarian public holidays.

Cumulative exposure–response estimates

We estimated cumulative exposure–response associations across the observed concentration range for each single pollutant. We centred the DLNM predictions at the model-predicted minimum cumulative risk to express estimates as excess risk above the nadir and to avoid an arbitrary reference (Iñiguez et al. 2022). For comparability between full series (full-dataset) and rolling-window analyses, we used fixed centring at the global minimum exposure concentration for each pollutant, anchoring the models to the same baseline (Iñiguez et al. 2022).

Effect estimates were interpreted as changes in risk relative to the reference concentration. We reported cumulative RRs with 95% confidence intervals (CIs) for two prespecified contrasts: (i) the interquartile range (IQR) contrast in air-pollutant concentrations (the third quartile relative to first quartile), representing typical day-to-day variability used to characterise exposure–response associations (Liao et al. 2025; Verhoeven et al. 2021); and (ii) the 97.5th versus 2.5th percentile contrast, representing a realistic high-exposure (adverse) scenario rather than an extreme outlier, and approximating the upper bound of real-world risk during pollution episodes (Iñiguez et al. 2022). P values < 0.05 were considered statistically significant, while P values between 0.05 and 0.10 were regarded as marginally significant (Liao et al. 2025).

Furthermore, we examined delayed effects by estimating cumulative RRs over lag 5–7 for each single-pollutant model, using the same penalised quasi-Poisson DLNM for comparison with Liao et al. (Liao et al. 2025).

Rolling time-window analysis

To examine sensitivity of our findings to the analysis period (14 February 2024–31 August 2025), we used a rolling-window approach, with 400 consecutive-day windows advanced by a single-day step. This yielded 166 distinct analysis windows (starting from 14 February 2024 through 28 July 2024). We applied the same methodology as in the full-dataset analysis, fitting a quasi-Poisson DLNM with penalised splines for each single-pollutant under three prespecified lag windows.

We prespecified a 400-day rolling window (approximately 13 months) to ensure that each iteration captured a full seasonal cycle and provided sufficient observations for stable estimation of the penalised quasi-Poisson DLNM, including spline adjustment for seasonality (7 degrees of freedom per year). With 565 study days, this yielded 166 overlapping windows ($565-400+1$), enabling a robust assessment of temporal stability while maintaining model convergence and interpretability.

For visualisation, we overlaid the full-series cumulative exposure–response curve onto the ensemble of rolling-window curves within the same figure for each pollutant and lag span. To reduce visual clutter, 95% CIs were shown only for the full-series curve and omitted for the rolling-window curves. This display enables a direct check of whether the full-series estimate lies within the spread of

the rolling-window results, and it highlights portions of the full-series exposure–response function; marked deviations indicate temporal heterogeneity.

Stroke clinical subgroups analysis

To assess whether associations varied across stroke clinical-phenotype subgroups, we refitted the models using subgroup-specific daily counts as separate outcome series, covering demographic characteristics, stroke type and aetiology, risk factors, stroke-onset time, treatments, and complications.

We treated each subgroup-specific daily count as a dependent variable in a separate model, with a single pollutant as the independent variable. Each model was fitted independently, with no assumed correlation between subgroups. We applied the same methodology as in the main model, fitting single-pollutant penalised quasi-Poisson DLNMs with identical adjustments and fixed centring at the global minimum exposure concentration.

Analyses covered the full study period (14 February 2024–31 August 2025). For each pollutant, we estimated the corresponding effects over three prespecified lag windows. We summarised cumulative RRs with 95% CIs for two prespecified contrasts (the third quartile relative to first quartile; the 97.5th versus 2.5th percentiles).

Ethics

During the preparatory phase, the project proposal was submitted to and assessed by the Data Protection and Information Security Office at the University Hospital Augsburg. In accordance with Article 16(3) of the Bavarian University Hospital Act (BayUniKlinG), de-identified data were transferred to the University of Augsburg; all identifying data remain stored exclusively at the University Hospital Augsburg under special protection. In line with institutional guidance and applicable data protection law, written informed patient consent was not required for this study, and no ethics approval was required.

This study was reported in accordance with the STrengthening the Reporting of OBservational studies in Epidemiology (STROBE) statement (Supplementary Material 1).

Results

Study population

A total of 3,133 stroke cases were recorded at the University Hospital Augsburg from 14 February 2024 to 31 August 2025 (565 days). Daily stroke counts ranged from 0 to 15 (median: 5; IQR: 4–7) and deviated significantly from a normal distribution at the daily level (Supplementary Material 2).

Among consecutive admissions, 54% were male and 77% were aged≥65 years. Ischaemic stroke predominated (95%). Macroangiopathy was the aetiology in 10% of cases. Cardiovascular risk factors were common: 82% of patients had arterial hypertension and 70% had dyslipidaemia. Stroke symptom onset was most often documented in the morning (784 patients, 25%). On admission, more than half of patients had a minor stroke (NIHSS 0–3), and a favourable outcome (mRS 0–2) was documented in 43% of patients. Acute treatments included systemic thrombolysis in 358 patients (11%) and endovascular thrombectomy in 165 (5%). The most frequent in-hospital complication was pneumonia (262; 8%) (Table 1). Figure 1 presents the time series of stroke counts, which appears stable over the study period without pronounced peaks. Supplementary Material 3 shows the time series of all targets ambient air-pollutant concentrations and meteorological data across the study period.

Cumulative relative risk across pollutants and different lag time windows

Overall, effect estimates for the 97.5th versus 2.5th percentile contrast (adverse scenario) in air pollutants concentrations for stroke occurrence were generally larger than those for the IQR contrast (day-to-day contrast) (Fig. 2).

For the IQR contrast, most cumulative $\mathrm{RR_{IQR}}$ estimates were only slightly above 1, showed little variation, and indicated weak associations across pollutants and lag windows. An exception was O_3, which consistently showed negative $\mathrm{RR_{IQR}}$ across all lag windows. None of these estimates reached statistical significance.

For the 97.5th versus 2.5th percentile contrast, distinct patterns emerged across pollutants and lag windows, although none of the estimates was statistically significant. Among gaseous pollutants, NO_2 showed its highest cumulative effect at lag 0–5 ($\mathrm{RR}_{97.5th}$: 1.24; 95% CI: 0.94–1.64, P_{value} = 0.12), exceeding estimates for the acute response (lag 0–3; $\mathrm{RR}_{97.5th}$: 1.20; 95% CI: 0.94–1.52, P_{value} = 0.14) and the one-week response (lag 0–7; $\mathrm{RR}_{97.5th}$: 1.19; 95% CI: 0.88–1.61, P_{value} = 0.26). O_3 again, showed negative cumulative $\mathrm{RR}_{97.5th}$ across all lag windows, and these estimates were more negative association (i.e., farther below 1) than the corresponding O_3 in $\mathrm{RR_{IQR}}$. For particulate pollutants ($PM_{2.5}$, PM_{10}, PM_{coarse}), the overall pattern was similar: elevated cumulative $\mathrm{RR}_{97.5th}$ at lag 0–3 (acute response) with attenuation when the lag time window was extended to lag 0–7. Within particulates, PM_{coarse} at lag 0–3 ($\mathrm{RR}_{97.5th}$: 1.11; 95%CI: 0.90–1.38, P_{value} = 0.325)

Table 1 Basic characteristics of stroke diagnostic cases

Characteristics	N	%
All	3,133	
Sex		
Male	1,680	54%
Female	1,453	46%
Age		
≥65	2,401	77%
<65	732	23%
Type of Stroke		
Ischaemic Stroke	2,961	95%
Haemorrhagic Stroke	172	5%
Aetiology of Stroke		
Macroangiopathy	328	10%
Microangiopathy	310	10%
Cardiogenic	867	28%
Other Aetiology	164	5%
Undetermined Aetiology	1,464	47%
Risk Factor		
Arterial Hypertension	2,572	82%
Obesity	266	8%
Dyslipidaemia	2,191	70%
Smoking	691	22%
Atrial Fibrillation	788	25%
Diabetes Mellitus	764	24%
Patients with Multi-risk	110	4%
Acute Treatment		
Systemic Thrombolysis	358	11%
Thrombectomy	165	5%
Therapy with Both	94	3%
None of Therapies	2,516	80%
Stroke Time Onset		
Morning (06:00–11:59)	784	25%
Afternoon (12:00–17:59)	679	22%
Evening (18:00–23:59)	429	14%
Night (00:00–05:59)	158	5%
Unknown	1,083	35%
Stroke Severity (NIHSS)		
Minor (NIHSS: 0–3)	1,661	53%
Severe (NIHSS: >3)	1,000	32%
Unknown	472	15%
Stroke Severity (mRS)		
Favourable Outcome (mRS 0–2)	1,352	43%
Unfavourable Outcome (mRS 3–6)	1,282	41%
Unknown	499	16%
Key Complications		
Pneumonia	262	8%
Haemorrhagic Transformation or Intracranial Bleeding	127	4%
Intrahospital Mortality		
In-Hospital Mortality	143	5%
Discharge Alive	2,990	95%

All targeted clinical phenotype indicators were selected on the basis of the literature and international guidelines. Counts and percentages for each risk factor reflect its prevalence when considered individually. "Multi-risk" denotes a high-risk cardiovascular profile, defined as the concurrent presence of dyslipidaemia, arterial hypertension, diabetes mellitus, and smoking

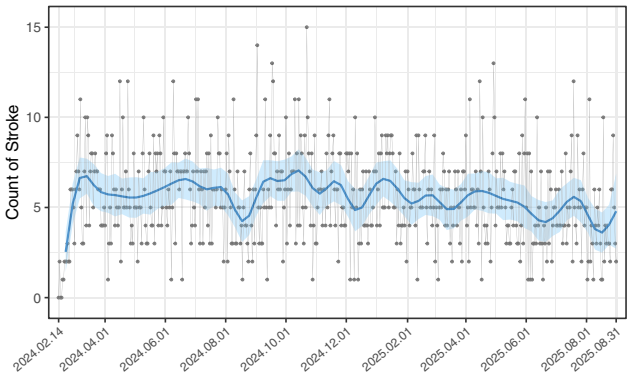


Fig. 1 Time series of daily stroke counts, 14 February 2024–31 August 2025. Note: The time series of stroke counts appears stable over the study period, without any pronounced peaks. The trend estimate, obtained using a B-spline smoother, provides a smooth visualisation of the series

and PM_{10} at lag 0–3 ($RR_{97.5th}$: 1.11; 95%CI: 0.88–1.40, P_{value} = 0.36) were slightly higher risk than for $PM_{2.5}$ at lag 0–3 ($RR_{97.5th}$: 1.08; 95%CI: 0.87–1.34, P_{value} = 0.51) (Fig. 2).

Stroke clinical subgroups analysis

Table 2 summarises all ambient air pollutants exposures that show marginally and statistically significant associations with stroke clinical-phenotype subgroups across both contrasts and lag-windows.

Gaseous-pollutant exposures

For the IQR contrast, NO_2 exposure (lag 0–3) was associated with a marginally significant positive cumulative RR among stroke patients aged≥65 years (RR_{IQR}: 1.10, 95%CI: 1.00–1.22, P_{value} = 0.051) and among male patients (RR_{IQR}: 1.16, 95%CI: 0.98–1.36, P_{value} = 0.083) (Supplementary Material 4). NO_2 also showed a marginally positive cumulative RR at lag 0–3 in patients with comorbid diabetes mellitus (RR_{IQR}: 1.18, 95%CI: 0.97–1.44, P_{value} = 0.095) or arterial hypertension (RR_{IQR}: 1.11, 95%CI: 0.99–1.24, P_{value} = 0.065). For patients with haemorrhagic transformation or intracranial haemorrhage, NO_2 associations were directionally similar at lags 0–3 across both contrasts (Table 2).

Compared with the acute response, NO_2 exposure at lag 0–7 showed statistically significant positive cumulative RR associations for stroke patients with aetiology categorised as macroangiopathy (RR_{IQR}: 1.49, 95%CI: 1.04–2.12, P_{value} = 0.027) and microangiopathy (RR_{IQR}: 1.47, 95%CI: 1.02–2.11, P_{value} = 0.039) (Fig. 3 and Supplementary Material 4). For the 97.5th versus 2.5th percentile contrast (adverse episode), NO_2 was only significantly associated with increased

cumulative risk in patients with macroangiopathy at the one-week window ($RR_{97.5th}$: 3.01, 95% CI: 1.13–8.05, P_{value} = 0.027) (Supplementary Material 5).

By contrast, O_3 associations were generally non-significant and tended to be negative or weak in most stroke clinical subgroups, across contrasts and lag windows. Notably, among patients with comorbid diabetes mellitus, O_3 showed a statistically significant inverse (negative) effect across both contrasts and lag-windows. We also observed that O_3 showed marginally negative associations among patients with evening-onset stroke at lag 0–3 under both RR_{IQR} and $RR_{97.5th}$, and statistically significant negative associations at lags 0–5 and 0–7 under both contrasts (Table 2).

Particulate-matter exposures

For the acute response (lag 0–3), female stroke patients appeared more vulnerable to particulate-matter exposures, with positive cumulative risk across both contrasts. Unlike NO_2, particulate matter did not show a statistically significant positive cumulative risk for patients with macroangiopathy; the only marginally positive associations were for $PM_{2.5}$ under the adverse-episode contrast at lag 0–3 ($RR_{97.5th}$: 2.12, 95% CI: 0.96–4.69, P_{value} = 0.063) and at lag 0–5 ($RR_{97.5th}$: 2.03, 95% CI: 0.95–4.34, P_{value} = 0.069) (Fig. 3 and Supplementary Material 5).

Notably, PM_{10} showed significant positive cumulative RR among patients undergoing thrombectomy under day-to-day contrast, with the highest estimate at lag 0–7 (RR_{IQR}: 1.85; 95%CI: 1.10–3.11, P_{value} = 0.020) (Fig. 3), but this pattern was not observed under the adverse-episode contrast. Furthermore, PM_{10} also showed marginally positive cumulative risk for patients with evening-onset stroke at lags 0–5 and 0–7 under both contrasts (Table 2). Associations for particulate pollutants were generally weak and non-significant, irrespective of lag window or contrast, across strata defined by NIHSS on admission, mRS at discharge, and risk factors.

Discussion

Clinically focused prospective studies investigating the effects of air pollutant exposures on stroke risk remain scarce. To address this research gap, we used a large, prospective, hospital-based registry to examine these associations, with a particular focus on clinical subgroup analyses. Our findings provide risk estimates to inform frontline clinical decision-making under different exposure conditions and to guide hospital resource allocation.

Nitrogen dioxide exposures

NO_2 Exposure showed the strongest overall signal, with higher cumulative RR for stroke occurrence than for particulate-matter exposures, consistent with Shah et al. (Shah et al. 2015). By contrast, Liao et al. (Liao et al. 2025), reported a significant positive cumulative odds ratio at lag 5–6; however, in our data, the cumulative RR for NO_2 at lag 5–7 was weak and not statistically significant for both exposure contrasts (Supplementary Material 6). Beyond overall effects, NO_2 was linked to several stroke clinical-phenotype subgroups that reached statistical or marginal significance (Table 2). We observed marginally significant associations for older stroke adults (≥65 years) across both exposure contrasts and across three lag windows, consistent with age-related susceptibility reported by Shah et al. (Shah et al. 2015).

Importantly, NO_2 exhibited statistically significant cumulative RR_{IQR} and $RR_{97.5th}$ for patients with macroangiopathy at lag 0–7 (Table 2), indicating a pronounced week-scale exposure–response. A plausible explanation is the heightened vulnerability of large-artery plaques to traffic-related air pollutant over a multi-day timeframe. NO_2—often used as a proxy for traffic-related mixtures—can impair endothelial function and promote platelet activation and thrombosis (Mills et al. 2007), thereby plausibly destabilising carotid or other large-artery plaques over several days, consistent with the observed cumulative effect at lag 0–7. A delayed week-scale response may reflect cumulative vascular pathways, whereby repeated exposure to traffic-related pollutants sustains oxidative stress and systemic inflammation. These processes can shift haemostasis towards a prothrombotic state and impair fibrinolysis, requiring several days to culminate in endothelial dysfunction and plaque destabilisation, and thromboembolism in large-artery atherosclerosis. This mechanism is supported by Newby et al. (Newby et al. 2015), providing biological plausibility for the observed lag 0–7 pattern in the macroangiopathy subgroup. Our finding is consistent with Johnson et al. (Johnson et al. 2020), who reported that long-term outdoor NO_2 exposure was positively associated with total carotid plaque area (3.4 mm^2 per ppb increase in NO_2), a direct measure of large-artery atherosclerosis.

Patients with comorbid cardiovascular risk factors may respond over a different timeframe. Beyond its role as a major vascular risk factor, dyslipidaemia may itself be influenced by environmental exposures, as shown for example in studies of microcystins and lipid dysregulation (Feng et al. 2023). Under the IQR (day-to-day) contrast, NO_2 showed marginally significant positive cumulative RR_{IQR} associations for stroke patients with comorbid diabetes mellitus or

arterial hypertension in the acute response; whereas no associations were detected in the week-scale window (Table 2). Our finding for comorbid diabetes is consistent with Oudin et al. (Oudin et al. 2011), and a possible clinical explanation is that pre-existing vascular dysfunction in these comorbid conditions heightens sensitivity to day-to-day increases in NO_2, precipitating short-term vascular responses that trigger stroke. Conversely, effects were not apparent under the high-exposure contrast, possibly because high NO_2 days were rare in our data (Supplementary Material 3).

In addition, among hospitalised stroke patients with macroangiopathy and coexisting vascular risk factors, NO_2 exposure was associated with an elevated cumulative risk of in-hospital haemorrhagic transformation or intracranial haemorrhage as complications, at lag 0–3 under both exposure contrasts. Given the wide 95% CIs and the potential for treatment confounding, this finding should be regarded as hypothesis-generating and interpreted with caution. Nevertheless, clinicians should remain vigilant for clinical deterioration, possibly even more so following NO_2 exposure.

Ozone exposures

Unlike prior systematic reviews (Shah et al. 2015; Verhoeven et al. 2021), there appears to be an "O_3 paradox" in our cohort. O_3 showed generally inverse (negative) associations for both cumulative RR_{IQR} and $RR_{97.5th}$ across all lag windows for stroke occurrence (Fig. 2). This pattern is broadly consistent with Liao et al. (Liao et al. 2025), who reported negative associations at both individual and cumulative lags. In contrast to NO_2, the main-model O_3 estimate consistently lay near the lower envelope of the rolling-window-specific distribution (Fig. 2 and Supplementary Material 7), even though the main model was adjusted for both temporal and meteorological confounders to minimise bias (Zhou et al. 2025). That said, we refrain from attributing these findings solely to an "O_3 paradox" at this stage. This is because, in the rolling time-window analysis, many window-specific cumulative RR estimates exceeded 1, indicating possible temporal heterogeneity and data-driven variability in the O_3 exposure–response. Additionally, in multi-pollutant models adjusting for NO_2, $PM_{2.5}$, and meteorological confounders, O_3 exposure showed little change in cumulative risk estimates compared with single-pollutant models (Fig. 4 and Supplementary Material 8).

Notably, in contrast to NO_2 in the acute response, O_3 exposure was associated with statistically significant inverse effects for both RR_{IQR} and $RR_{97.5th}$ among stroke patients with diabetes mellitus at lag 0–3. We caution against interpreting these findings as "protective". From an atmospheric-chemistry perspective, O_3 is a secondary photochemical pollutant whose formation depends on nitrogen oxides and volatile organic compounds. In traffic-dominated urban settings, freshly emitted nitric oxide can rapidly consume O_3 through ozone titration, producing nitrogen dioxide and contributing to an inverse relationship between O_3 and traffic-related nitrogen oxides (Sillman 1999). Therefore, higher ambient O_3 may sometimes reflect a different pollutant-mixture regime, with lower fresh traffic-related co-pollutants, rather than a protective exposure; this mechanism can yield apparent inverse O_3–stroke associations in single-pollutant time-series models.

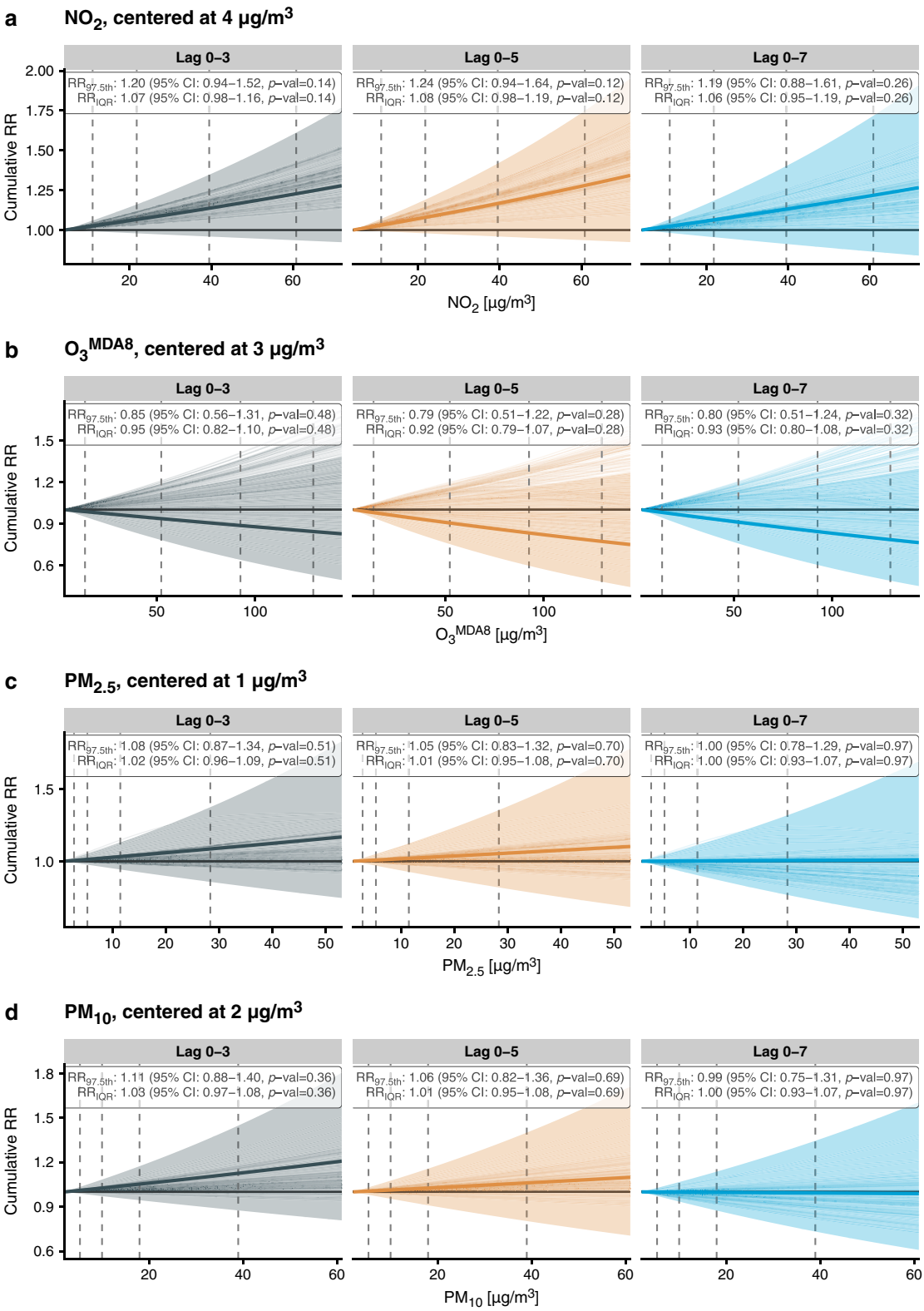
Exposure measurement may further contribute to this pattern. O_3 is highly reactive, and indoor concentrations are typically substantially lower than outdoor concentrations; fixed-site ambient O_3 may therefore be a weaker proxy for personal exposure than less reactive pollutants, especially when time spent indoors and building ventilation vary across individuals (Nazaroff and Weschler 2022).

Mechanistically, O_3-related cardiovascular responses may also be heterogeneous rather than uniformly adverse in direction. Human panel data indicate that short-term O_3 exposure can alter autonomic function, systemic inflammation, oxidative stress, and fibrinolytic pathways (Song et al. 2020). Whereas experimental work in metabolically susceptible rats showed cardiovascular depression and delayed adaptation after O_3 or O_3/particulate matter exposure (Wagner et al. 2014). Taken together, these mixture-, exposure-surrogate-, and autonomic-response mechanisms provide a more biologically plausible explanation for relative risks below one and reinforce that the inverse O_3 estimates should not be interpreted as protective.

Furthermore, seasonal patterns, residual confounding by temperature, and case-mix differences may further contribute to the observed inverse estimates, but we consider the atmospheric-chemistry and exposure-measurement mechanisms to be the more mechanistically grounded explanations in an urban time-series setting.

Fig. 2 Cumulative Relative Risk of Air Pollutants Associated with Stroke Occurrence. Note: We reported cumulative relative risks with 95% confidence intervals for two prespecified contrasts: (i) the interquartile-range contrast (the third quartile relative to first quartile), representing typical day-to-day variability; and (ii) the 97.5th versus 2.5th percentile contrast, representing a realistic high-exposure (adverse) scenario. For the sensitivity analysis, we used a rolling-window approach, with 400 consecutive-day windows advanced by a single-day step. This yielded 166 distinct analysis windows (starting from 14 February 2024 to 28 July 2024), covering the entire study period. For visualisation, each panel overlays the full-series cumulative exposure–response curve, with 95% confidence intervals, on the ensemble of rolling-window curves for the same pollutant and lag window. To minimise visual clutter, the 95% confidence interval is shown only for the full-series curve. Supplementary Material 7 summarises relative risk estimates for both exposure contrasts as box plots and marks the full-series estimate to show where it lies within the rolling-window distribution. Information on PM_{coarse} is provided in Supplementary Materials 4 and 5

Cumulative RR of Stroke (All) with varying lags



Dashed vertical lines indicate, from left to right, the 2.5th, 25th, 75th, and 97.5th percentiles of the exposure distribution.

Table 2 Summary of ambient air-pollutant exposures showing marginally significant or statistically significant associations with stroke clinical subgroups

		Interquartile-range contrast in relative risk			97.5th versus 2.5th percentile contrast in relative risk		
	Pollutants	Lag 0–3 days	Lag 0–5 days	Lag 0–7 days	Lag 0–3 days	Lag 0–5 days	Lag 0–7 days
Positive cumulative risk	NO_2	+Age 65plus +Male +Arterial Hypertension +Diabetes Mellitus +HT/ICH	+Age 65plus +Microangiopathy +Macroangiopathy +Arterial Hypertension	+Age 65plus **+Microangiopathy*** **+Macroangiopathy***	+Age 65plus +HT/ICH	+Age 65plus +Macroangiopathy	+Age 65plus +Microangiopathy **+Macroangiopathy***
	O_3	N/A	N/A	N/A	N/A	N/A	N/A
	$PM_{2.5}$	+Female +Evening onset	+Evening onset +Thrombectomy	+Thrombectomy	+Female +Macroangiopathy	+Evening onset +Macroangiopathy	N/A
	PM_{10}	**+Female*** **+Thrombectomy***	+Evening onset **+Thrombectomy***	+Evening onset **+Thrombectomy***	**+Female***	+Evening onset	+Evening onset
	PM_{coarse}	+Female +Thrombectomy	N/A	+Pneumonia	+Female +Thrombectomy	N/A	N/A
Negative cumulative risk	NO_2	- Patients Multi Risk	N/A	N/A	- Patients Multi Risk	**- Patients Multi Risk***	**- Patients Multi Risk***
	O_3	**- Diabetes Mellitus*** - Evening onset	- Cardiac Embolism **- Diabetes Mellitus*** - Patients Multi Risk **- Evening onset***	**- Diabetes Mellitus*** - Patients Multi Risk **- Evening onset***	**- Diabetes Mellitus*** - Patients Multi Risk - Evening onset	- Cardiac Embolism **- Diabetes Mellitus*** - Patients Multi Risk **- Evening onset***	**- Diabetes Mellitus*** - Patients Multi Risk **- Evening onset***
	$PM_{2.5}$	N/A	N/A	N/A	N/A	N/A	N/A
	PM_{10}	N/A	N/A	N/A	N/A	N/A	N/A
	PM_{coarse}	N/A	N/A	- Diabetes Mellitus	N/A	N/A	- Diabetes Mellitus

HT/ICH Haemorrhagic Transformation or Intracranial Bleeding, *N/A* Not applicable. Patients Multi Risk: denotes a high-risk cardiovascular profile, defined as the concurrent presence of dyslipidaemia, arterial hypertension, diabetes mellitus, and smoking

Indicators with P values <0.05 are marked with an asterisk (*), and the corresponding indicators are also shown in bold

Indicators with positive cumulative estimates (relative risk >1) and negative cumulative estimates (relative risk <1) are marked with '+' and '−', respectively

Supplementary Material 4 presents all subgroup-specific relative risks, 95% confidence intervals and P values for the interquartile-range contrast. Supplementary Material 5 presents the corresponding results for the 97.5th versus 2.5th percentile contrast

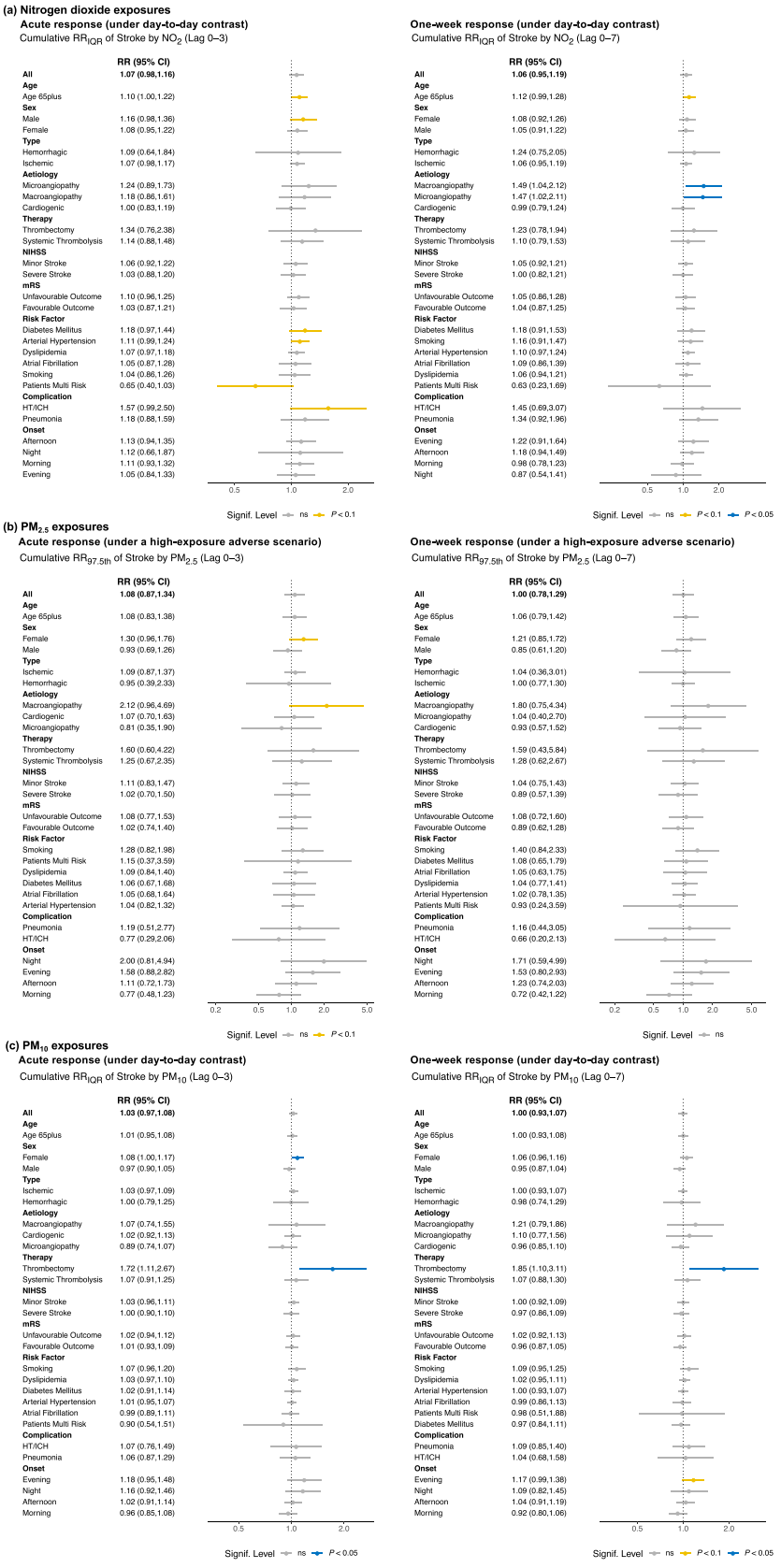


Fig. 3 Forest plots of clinical subgroup analyses for nitrogen dioxide, $PM_{2.5}$, and PM_{10} exposures. **Note:** HT/ICH: Haemorrhagic Transformation or Intracranial Bleeding. Patients Multi Risk: denotes a high cardiovascular-risk profile, defined as the concurrent presence of dyslipidaemia, arterial hypertension, diabetes mellitus, and active smoking. Forest plots present the key results of the clinical analyses for nitrogen dioxide and PM_{10} exposure at the one-week response under day-to-day contrast, and for $PM_{2.5}$ exposure at the acute response under a high-exposure (adverse) scenario. We treated each subgroup-specific daily count as an individual dependent variable in each single model, with each single pollutant as the independent variable. Each model was fitted independently, with no assumed correlation within subgroups. Supplementary Material 4 presents all subgroup-specific relative risks, 95% confidence intervals and *P* values for the interquartile-range contrast. Supplementary Material 5 presents the corresponding results for the 97.5th versus 2.5th percentile contrast

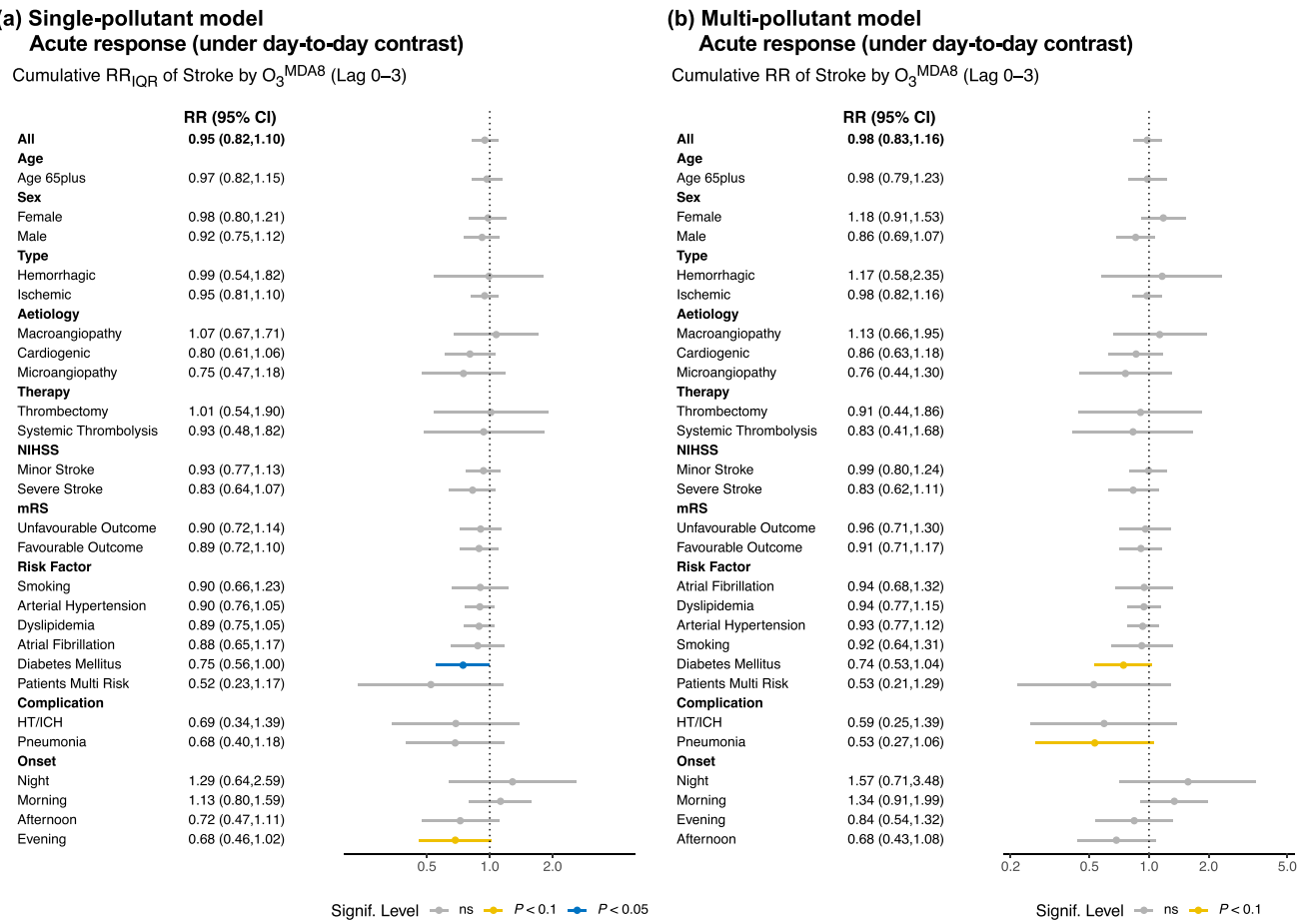


Fig. 4 Cumulative ozone effects in single- and multi-pollutant models. **Note:** In multi-pollutant models adjusting for NO_2, $PM_{2.5}$, and meteorological confounders, O_3 exposure showed little change in cumulative risk estimates compared with single-pollutant models. Supplementary Material 8 presents detailed subgroup analyses of cumulative ozone effects in single- and multi-pollutant models

Particulate-matter exposures

Female stroke patients appeared vulnerable to particulate matter, particularly under the high-exposure contrast at lag 0–3. PM_{10} exposure showed a statistically significant association among female patients in the acute response. This is consistent with Shah et al. (Shah et al. 2015), who reported more pronounced adverse effects of larger particles. In view of Saharan dust intrusions (Cuevas-Agulló et al. 2024) that elevate PM_{10} levels across Bavaria (including Augsburg), seasonal alerts and targeted protective advice may be warranted.

Under the high-exposure contrast at lag 0–3, $PM_{2.5}$ showed a marginally significant positive cumulative $RR_{97.5th}$ for macroangiopathy, and PM_{10} showed an elevated but non-significant $RR_{97.5th}$ for macroangiopathy. For large-artery disease, the mechanisms relevant to NO_2 and particulate matter likely overlap but differ in emphasis; this may explain the week-scale (lag 0–7) cumulative RR_{IQR} (day-to-day variability) observed for NO_2 in macroangiopathy, in contrast to the short-lag (lag 0–3) elevations in cumulative $RR_{97.5th}$ during concurrent $PM_{2.5}$ /PM_{10} increases (e.g., dust episodes) (Table 2).

Under the day-to-day contrast, PM_{10} was associated with significant effects at both lag 0–3 and lag 0–7 for stroke patients undergoing thrombectomy, although the 95% CIs were wide (Supplementary Material 4). This finding suggests that particulate-matter exposure may be linked to severe occlusive events or large-vessel occlusion pathways. Given the exploratory nature of this analysis and the limited sample size, this finding may have operational implications. Although our study remains exploratory, monitoring thrombectomy counts alongside air-quality alerts, particularly particulate matter alerts, could provide preliminary support for thrombectomy service planning, including staffing, angiography suite availability, and inter-hospital transfer coordination. This may be especially relevant during acute particulate matter elevations that could coincide with severe occlusive presentations.

Furthermore, timing patterns of stroke onset are clinically important. Evening-onset strokes predominated, and $PM_{2.5}$ exposure showed a higher, marginally significant, positive cumulative RR_{IQR}, exceeding the corresponding non-significant RR_{IQR} estimates for PM_{coarse} and PM_{10} at lag 0–3. Clinically, $PM_{2.5}$ penetrates deep into the lungs, and a small fraction may translocate into the systemic circulation, thereby rapidly triggering systemic inflammation and prothrombotic responses; daytime accumulation may push vulnerable patients over a threshold by evening. This is consistent with Wellenius et al. (Wellenius et al. 2012), who reported that the increase in stroke risk was greatest within 12–14 h of exposure to $PM_{2.5}$, potentially reflecting evening onset following daytime exposure.

Strengths and limitations

The strengths of the study include the prospective inclusion of consecutive stroke admissions within a defined catchment area; and a large, clinically phenotyped sample across the full hospitalisation pathway—an aspect rarely examined in depth in the literature (Shah et al. 2015; Verhoeven et al. 2021). We explicitly evaluated biologically plausible lag windows. Our dual-contrast analytical strategy distinguishes everyday exposure from short-term pollution spikes, with operational implications.

Despite the scientific rigour of our analyses and study design, we acknowledge several limitations. First, this was a single-centre study; generalisability is therefore largely limited to Bavarian Swabia. Nevertheless, although the data were derived from an urban region, Augsburg's meteorological and air-pollution patterns are broadly representative of central-southern Germany, supporting external validity. Second, several subgroup analyses involved sparse counts, including days with zero events, which may reduce model stability and precision. Third, our analyses focused only on stroke occurrence rather than on mechanistic endpoints at the cellular level (e.g., endothelial dysfunction or platelet activation) (Gabet and Puy 2025) or detailed neuroimaging phenotypes (vessel status or infarct patterns) (Wu et al. 2021). For example, in patients with ischaemic stroke complicated by pulmonary infection, inflammatory and nutritional indices such as the systemic immune–inflammation index and the C-reactive protein–albumin–lymphocyte index have been shown to have prognostic utility, highlighting the value of integrating biomarker information (Chen et al. 2025). Integrating pollution exposures with imaging biomarkers and cellular-level readouts could improve inferences about stroke onset and recurrence risk (Raza et al. 2021), and should be a priority for future research. Fourth, our exposure data are based on regulatory, ground-based measurements from an urban-background monitoring station in Augsburg, which cannot fully characterise intra-urban spatial heterogeneity (compared with spatially resolved exposure estimates) (Cetin 2019); however, given our ecological time-series study design, this is the most appropriate option. Fifth, we acknowledge that exposure assessment based on a single urban-background outdoor monitoring station cannot capture individual-level variability arising from indoor air quality, building infiltration, time spent indoors versus outdoors, commuting patterns, and personal mobility across microenvironments. These factors can introduce exposure misclassification, particularly in an ecological time-series framework, and may attenuate or distort observed associations. Future multicentre studies with higher-resolution exposure assessment, such as personal monitoring, mobility-informed models, or validated spatially resolved estimates, would help reduce misclassification and strengthen inference where such data are available.

Public-health and clinical-practice implications

From a public-health and clinical perspective, our findings translate routine environmental data into clinically actionable risk stratification. Rather than predicting individual stroke events, our results suggest that pollutant-specific patterns can help identify periods of elevated risk for vulnerable populations. At the healthcare-system level, these findings support the concept of integrating air-quality indicators into hospital surveillance and preparedness frameworks to optimize emergency stroke pathways and resource allocation. Ultimately, these associations, as preliminary signals, provide a rationale for operational forecasting models that use environmental and lagged predictors to anticipate daily stroke presentations and improve hospital service planning.

Conclusions

Our study supports a pragmatic, risk-stratified, patient- and hospital-level alert-based approach for stroke management. Signals for NO_2 were most informative among patients with macroangiopathy and those with comorbid cardiovascular risk factors, suggesting targeted counselling and monitoring in these high-risk groups. For particulate matter, risks require attention during the acute window, with greater vulnerability observed in older women and in those with macroangiopathy; heightened evening-onset vigilance is warranted. Recommended measures include reinforcing adherence to the treatment of cardiovascular risk factors, limiting strenuous outdoor activity at times of peak air pollution, avoiding hotspots such as busy streets, and supporting self-management through early recognition and timely activation of emergency medical services. Although

exploratory, our findings highlight clinically relevant air-pollution–stroke links that warrant validation. More broadly, pollution transfer across regions and the evolution of inter-regional pollution networks may contribute to environmental-health risks beyond local emissions, reinforcing the importance of regional-scale evidence for public-health and clinical decision-making (Hu et al. 2026). Future multicentre studies integrating air-pollution exposure with imaging biomarkers and cellular-level readouts are needed to strengthen mechanistic inference and confirm generalisability, and multi-source integration of exposure data may be a further direction for future work, particularly for individual-level exposure assessment and forecasting applications.

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Author contributions Conception and study design: BZ, LB, JW, MN, CK, and ME. Data management: BZ, LB, JW, SK, MS, MN, CK, and ME. Analysis of data: BZ, JW, and CK. Interpretation of data: BZ, LB, JW, MN, CK, and ME. Drafting the manuscript: BZ, LB, JW, SK, MS, MN, CK, and ME. Critical revision for important intellectual content and approval for submission: BZ, LB, JW, SK, MS, MN, CK, and ME.

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Data availability Due to data protection laws in Germany, the datasets generated and/or analyzed during the current study are not publicly available. The German law prohibits the use of this data for purposes other than research. Access to the data is granted to qualified research institutions upon request at the Forschungsdatenzentrum (FDZ) in accordance with §§ 303a, 303f of Sozialgesetzbuch (SGB) V.
Details on the application process to obtain data access can be found on the website of the FDZ (in German) (https://www.forschungsdatenzentrum-gesundheit.de/das-fdz). Additionally, relevant laws pertaining to this matter are available on the website (in German) (https://www.gesetze-im-internet.de/sgb_5/BJNR024820988.html#BJNR024820988BJNG008700308).

Declarations

Ethics approval During the preparatory phase, the project proposal was submitted to and assessed by the Data Protection and Information Security Office at the University Hospital Augsburg. In accordance with Article 16(3) of the Bavarian University Hospital Act (BayUniKlinG), de-identified data were transferred to the University of Augsburg; all identifying data remain stored exclusively at the University Hospital Augsburg under special protection. In line with institutional guidance and applicable data protection law, written informed patient consent was not required for this study, and no ethics approval was required.

Consent to participate Not applicable.

Consent to publication Not applicable.

Competing interests All the authors declare that they have no conflict of interest relevant to this study.

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