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The Association Between Short-Term Nitrogen Dioxide (NO_2) Exposure and Ischemic Stroke or Transient Ischemic Attacks (TIA): A National Study in Israel

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Abstract

Background: Air pollution is an environmental risk factor for stroke, but most studies have focused on fine particulate matter ($PM_{2.5}$), and fewer have investigated the independent association with exposure to nitrogen dioxide (NO_2).

Methods: We conducted a nationwide case-crossover study including all ischemic stroke or transient ischemic attack (TIA) reported in the Israeli National Stroke Registry from 2014 to 2018. We obtained daily NO_2 levels from high-resolution geospatial models and linked to residential addresses. We used distributed lag nonlinear models to assess the cumulative association with NO_2 exposure over a lag of 0–5 days, adjusting for $PM_{2.5}$ and temperature. We further evaluated the modification of the associations by age, sex, urbanicity, and comorbidities (ischemic heart disease, hypertension, diabetes).

Results: We included 85,162 cases, about 54% were males, and the mean age was 71.8. Cumulative NO_2 exposure was associated with increased odds of ischemic stroke or TIA (odd ratio – OR and 95% confidence interval –1.064 [1.041–1.088]), with the strongest effects 3–5 days before the event. The associations were more pronounced in urban areas (1.070[1.038;1.103]) compared to suburban areas (1.054[1.021;1.088]). Although the overall association was similar across ages and sexes, the lag specific associations on lag days 3-5 were more pronounced in younger adults and women.

Conclusion: Short-term exposure to NO_2 is associated with an increased risk of ischemic stroke and TIA, with differential associations across urbanicity, sex and age groups. These results underscore the urgent need for public health initiatives to reduce NO_2 emissions.

Synopsis

Short-term NO_2 exposure increases ischemic stroke and TIA risk, informing air-quality policy to curb traffic emissions and protect vulnerable populations.

Introduction

Stroke is one of the leading causes of death and disability worldwide[1]. Each year, there are over 12 million new stroke cases worldwide, a number that has seen over a 50% increase over the last two decades [2]. Therefore, research in recent decades has focused on identifying modifiable risk factors that can be targeted to reduce the global stroke burden [3]. There is substantial evidence indicating that exposure to air pollution increases the risk of cardiovascular diseases (CVD) beyond traditional CVD risk factors [4]. Given that the vast majority of the global population currently lives in regions where the air pollution levels exceed the World Health Organization's Global Air Quality Guidelines, air pollution represents a critical target for stroke prevention [5,6]. Most existing research has focused on particulate matter smaller than 2.5 microns ($PM_{2.5}$), indicating an increased risk of stroke associated with both long

(1.01 per 10 μg/m^3 CI 1.011-1.012) and short-term exposures (1.06 per 10 μg/m^3 95% CI 1.018–1.105) [6,7]. Although nitrogen dioxide (NO_2) has been studied, the evidence is less extensive than for $PM_{2.5,}$ and important research gaps remain [8,9]. These gaps underscore the need to investigate the health effects independently associated with NO_2 exposure [6].

NO_2 is an anthropogenic air pollutant originating primarily from traffic and industrial sources through the combustion of fossil fuels [10]. Studies suggest that NO_2 may increase stroke risk by triggering oxidative stress, systemic inflammation, and endothelial dysfunction, leading to blood clots and restricted blood flow to the brain [11]. A large meta-analysis in 2023 found that NO_2 exposure is associated with stroke hospitalizations and mortality (1.014 per 10 ppb, CI 1.009-1.019) [6]. However, the analysis concluded that it had insufficient information to establish a causal relationship between exposure to NO_2 and stroke [6].

In this comprehensive national study, we leverage the Israeli National Stroke Registry (INSR) data to investigate the association between short-term NO_2 exposure and ischemic stroke or transient ischemic attacks (TIA). We further investigate differential susceptibility among population groups by urbanicity, demographic, and clinical characteristics. Israel's unique topography, which includes mountains, coastal lowlands, and deserts, offers a diverse environment to investigate NO_2 exposure and cardiovascular health effects in varying climates [12]. These findings may inform policy and interventions aimed at reducing NO_2 exposure levels and stroke burden in the population.

Methods

Population and outcome

We used data from the INSR, which includes all permanent residents in Israel admitted to general hospitals with a primary diagnosis of stroke or TIA, reported using the International Classification of Diseases, ninth edition (ICD-9). We included all ischemic stroke (ICD-9:433, 434.x1, 436, or 997.02) and TIA (ICD-9: 435) cases of individuals 18 years and older across Israel between the years 2014 - 2018. The INSR data are retrieved from electronic medical records and include diagnoses and comorbidities coded using ICD-9, encompassing hospitalization diagnoses, chronic conditions, and discharge diagnoses. Sociodemographic information (age, sex, ethnicity, and geocoded address) is retrieved from the Ministry of Interior database and linked to the INSR. Ethnicity was grouped into Jewish versus non-Jewish due to the small percentage of the non-Jewish population (Arab, Druze, or other ethnic groups).

This study was approved by the institutional review boards at Soroka University Medical Center in Beer Sheva, Israel (study 01718-19), and the Icahn School of Medicine at Mount Sinai, New York, USA (study 21-00076). A waiver of informed consent was granted due to the minimal risk nature of the study and the use of de-identified registry data with no direct participant contact. All methods were performed in accordance with the relevant institutional and national guidelines and regulations.

Exposure

We obtained daily 1-km^2 predictions of NO_2 from a hybrid spatiotemporal model we built over Israel from 2004 to 2022[13]. The model, which is based on methodology we used previously for an NO_2 model in Mexico City, incorporates a combination of satellite, land use, and meteorological data and employs machine learning-based methods (random forest and gradient boosting) for prediction[14]. All models were rigorously evaluated using 10-fold cross-validation and demonstrated strong performance[14-17]. The exposures were then linked to each individual based on the proximity of the geocoded residential address to the corresponding 1-km² grid cells of the satellite-based model predictions. We excluded 1,289 individuals without a valid residential address (1.6%).

Covariates

Models were adjusted for temperature averaged over lag days 0-4. In a sensitivity analysis, we further adjusted the model for fine particulate matter ($PM_{2.5}$) exposure. We obtained daily mean $PM_{2.5}$ and temperature estimates from satellite-based spatiotemporal models that apply a hybrid approach and estimate daily mean temperature and $PM_{2.5}$ exposures at a fine resolution [18,19]. Briefly, these models use both extreme gradient boosting and inverse-distance weighting techniques that incorporate aerosol optical depth, meteorology, and land-use variables to generate daily predictions at 1-km resolutions. The models were calibrated daily by applying a mixed-modeling approach using the MODIS-based multiangle implementation of atmospheric correction (MAIAC) aerosol optic depth (AOD) and various spatial and temporal predictors. This resulted in excellent performance with out-of-sample cross-validated R^2 values of 0.82–0.92 for the $PM_{2.5}$ model and 0.96–0.98 for the temperature model.

Statistical analysis

We used distributed lag nonlinear models (DLNMs) in a case crossover design to investigate the associations between NO_2 exposures and ischemic stroke or TIA. This approach accounts for confounders that do not vary within a short period by design and allows the flexible estimation of lag-specific and cumulative associations over time [20]. We defined the admission day as the case day, and matched control days by the day of the week within the same month and year. We defined the exposure window as exposure on lag days 0-5, based on the smallest Bayesian Information Criteria (BIC). We used a linear function for the exposure response association and natural splines with two degrees of freedom (df) to estimate the lag structures, based on the smallest BIC. Then, we used generalized nonlinear models (GNM) with conditional stratification. We adjusted the models for the temperature mean for lags 0-4. We selected the exposure window that yielded the strongest association with the outcome to ensure there is no residual confounding by temperature exposure.

We conducted an interaction analysis to evaluate whether the cumulative association between NO_2 exposure and ischemic stroke/TIA differed across urbanicity (cities with over 100,000 residents versus smaller cities, towns and villages), comorbidities (diabetes, hypertension, and ischemic heart disease -

IHD), sex, and age. We classified individuals as younger than 55 years versus 55 years and older, a cutoff commonly used to define stroke in young adults [21]. We repeated the models adding an interaction term between the NO_2 cross-basis and each subgroup indicator separately. Because the exposure-response is represented by multiple spline and lag parameters, the interaction produces a set of coefficients rather than a single term. We therefore used the likelihood ratio test (LRT) to assess whether all interaction parameters significantly differ from the null, comparing models with and without the interaction term. A statistically significant LRT p-value reflects evidence of differences in the *shape* or *timing* of the lagged response across groups, which may be present even if the estimated cumulative risks over the full lag period appear similar. For interpretability, we present group-specific cumulative OR and 95% confidence intervals (CI) and provide lag-specific effects among subgroups of statistically significant modifiers.

Sensitivity analyses

We conducted several sensitivity analyses to ensure the robustness of our findings. First, we repeated the main model using alternative definitions of cumulative NO_2 exposure, summing exposure over 3-, 4-, 5-, and 6-day lag windows. Second, we repeated the main models only with ischemic stroke, excluding TIA, to ensure the associations with NO_2 did not differ between the groups. Third, since the baseline stroke risk may differ between first occurrence and repeated stroke events, we repeated the models excluding recurrent events to ensure the association did not change. Finally, we further adjusted the models to $PM_{2.5}$ exposure on the day of the event to ensure that our results are not confounded by $PM_{2.5}$ exposure.

Results

We included 85,162 cases, of whom 69.9% had ischemic stroke and 30.1% had TIA. About 54% were males, 80.9% were Jewish, 50.28% resided in large cities, and the mean age was 71.8 years. Cardiometabolic diseases were highly prevalent in this population, with 45.8% presenting diabetes, about 15% CHF, and 77.9% hypertension. Finally, about 3% of the cases had a history of myocardial infarction, and 13.64% had recurring stroke events (**Table 1**).

Table 1. Population characteristics (n=85,162)

Variable	Mean (SD)/ N (%)
Age	71.7 (13.4)
Sex	
Male	46,014 (54.03)
Female	39,148 (45.97
Ethnicity	
Jewish	68,837 (80.83)
Other	16,325 (19.17)
Residence type	
Urban	42,795 (50.28)
Suburban and rural	42,311 (49.71)
Stroke type	
Ischemic	59,606 (69.9)
TIA	25,556 (30.1)
Diabetes	39,034 (45.83)
Hypertension	66,376 (77.94)
IHD	28,251 (33.17)
Died in the hospital	59,825 (70.24)
Stroke events	
Single	73,466 (86.26)
Recurring	11,696 (13.74)

The largest number of cases was observed in the summer season (33.42%). Overall, the mean NO_2 exposure level during the observation period was 12.34 ppb, with higher levels in large cities (13.62 ppb) compared to suburban and rural areas (11.02 ppb). The mean $PM_{2.5}$ exposure level was 19.04 μg/m^3, with similar levels between large cities (19.28 μg/m^3) and suburban and rural areas (18.79 μg/m^3). The mean temperature during the observation period was 21.40 ºC (**Table 2**). The correlation between the air pollutants and temperature was low, with the highest correlation between NO_2 and temperature (r=-0.2), and NO_2 and $PM_{2.5}$ (r=0.13). A very low correlation was observed between temperature and $PM_{2.5}$ (r=0.05).

Table 2. Environmental characteristics

	All	Large cities	Suburban and rural
Temperature			
Mean (SD)	21.40 (5.55)	21.40 (5.53)	21.40 (5.56)
Median (IQR)	21.81 (9.79)	21.79 (9.74)	21.82 (9.82)
NO_2			
Mean (SD)	12.32 (8.56)	13.62 (9.09)	11.02 (7.78)
Median (IQR)	10.01 (10.25)	11.40 (11.43)	8.87 (8.75)
$PM_{2.5}$			
Mean (SD)	19.04 (9.92)	19.28 (7.02)	18.79 (9.48)
Median (IQR)	17.25 (6.59)	17.40 (7.02)	17.13 (6.17)

Large cities were defined as those with populations exceeding 100,000 residents. Suburban and rural areas include smaller cities, towns, and villages

The cumulative OR for ischemic stroke or TIA associated with an 8 ppb (standard deviation (SD)) increase in NO_2 exposure, summed over lag days 0–5, was 1.064 (95% confidence interval [CI]: 1.041, 1.088) (**Figure 1.A**). The effects were more pronounced in lag days 3-5. For example, the OR observed on lag 1 was 0.990 (0.980; 1.001) and the OR observed on lag 5 was 1.044 (1.024; 1.065) (**Figure 1.B**). The cumulative ORs remained consistent across the alternative exposure windows, with estimates ranging from 1.050 to 1.061 when using 3- to 6-day cumulative lags (**Supplementary Table 1**).

The associations between NO2 and ischemic stroke/TIA were statistically significantly modified by urbanicity (LRT p value 0.029), sex (LRT p value 0.008), and age (LRT p value 0.037). Overall, the cumulative associations were very similar among younger (1.068, 95% CI 1.036; 1.101) and older adults (1.060, 95% CI 1.027; 1.094), and among men (1.069, 95% CI 1.037; 1.101) and women (1.061, 95% CI 1.027; 1.096). However, as shown in **Figure 2**, the lag specific associations on lag days 3-5 were more pronounced in younger adults and women. For example, on lag day 5, the OR for NO_2 exposure was 1.114 (95% CI: 1.047, 1.184) in younger adults compared with 1.037 (95% CI: 1.016, 1.059) in older adults, and 1.074 (95% CI: 1.044, 1.105) in women compared with 1.019 (95% CI: 0.993, 1.047) in men. Finally, the cumulative OR was larger among people in urban (1.070, 95% CI 1.038; 1.103) versus rural and suburban areas (1.054, 95% CI 1.021; 1.088) with different lag structures between the groups (**Figure 2**).

Table 3. The modification of the associations between NO_2 and ischemic stroke/TIA by patient characteristics.

Subgroup	OR (95% CI)	LRT P value
Residence type		
Rural/suburban	1.054 (1.021; 1.088)	
Urban	1.070 (1.038; 1.103)	0.029
Diabetes		
No	1.047 (1.016; 1.078)	
Yes	1.087 (1.052; 1.123)	0.179
Hypertension		
No	1.076 (1.027; 1.127)	
Yes	1.062 (1.036; 1.088)	0.865
IHD		
No	1.064 (1.036; 1.093)	
Yes	1.067 (1.027; 1.109)	0.89
Sex		
Men	1.069 (1.037; 1.101)	
Women	1.061 (1.027; 1.096)	0.008
Age		
55 and older	1.060 (1.027; 1.094)	
Younger than 55	1.068 (1.036; 1.101)	0.037

We used distributed lag nonlinear models (DLNMs) in a case crossover design to investigate the associations between cumulative NO_2 exposures (lags 0-5) and ischemic stroke or TIA, adjusted for temperature. We repeated the models, adding an interaction term between the NO_2 cross-basis and each subgroup indicator separately. We used the likelihood ratio test (LRT) to assess whether all interaction parameters significantly differ from the null, comparing models with and without the interaction term. A statistically significant LRT p-value reflects evidence of differences in the *shape* or *timing* of the lagged response across groups.

Odds ratios are presented per incremental increase in NO_2 concentration and were estimated using distributed lag nonlinear models adjusted for $PM_{2.5}$ and temperature. Error bars represent 95% confidence intervals.

As a sensitivity analysis, we repeated the main model excluding repeated events. The cumulative OR of ischemic stroke or TIA, associated with an 8-ppb increase in NO_2 exposure, summed over lag days 0-5,

remained very similar (1.061, 95% CI 1.036, 1.086). Additionally, the results remained similar after adjusting for $PM_{2.5}$ exposure on the day of the event (1.065, 95% CI 1.042; 1.089), and no association was observed with $PM_{2.5}$ (OR 0.997, 95%CI 0.993; 1.001 per 10 mg/m^3 increase). Finally, we repeated the model only among ischemic stroke cases, excluding TIA, and the results remained similar (1.042, 95% CI 1.015, 1.070).

Discussion

In this nationwide study encompassing diverse populations and climate regions, we observed increased odds of ischemic stroke or TIA associated with short-term NO_2 exposure. The associations were strongest at lags 3-5 days and were marginally stronger among residents of large cities, women, and adults <55 years, while remaining broadly similar across cardiometabolic subgroups.

Previous studies have demonstrated associations between short-term NO_2 exposure and an increased risk of ischemic stroke, supporting our findings [9,22]. A 2023 meta-analysis, for example, reported a 1.4% increase in stroke mortality and hospitalizations per 10 ppb rise in NO_2[6] . A recent multi-country analysis of 7.4 million deaths reported stronger short-term associations among older adults[23]. That study focuses on fatal outcomes, while our study examines incident ischemic stroke and TIA; differences in (mortality vs incidence), age cut-points, exposure profiles, and healthcare systems may explain why age-related susceptibility is different between studies. Compared with prior studies, the effects observed in our analysis are similar in direction and magnitude and may appear larger in part because of differences in exposure assessment, spatial resolution, or population susceptibility.

Most existing research on air pollution and stroke has focused on $PM_{2.5,}$ which can originate from various sources, including natural atmospheric reactions in the atmosphere[24]. In a recent study conducted in Israel using the same data source of stroke cases between 2014-2018, researchers found elevated ischemic stroke risks associated with $PM_{2.5}$ exposure lower than the national threshold[25]. Our findings indicate that the NO_2 and Stroke association was independent of $PM_{2.5}$ and temperature, suggesting that NO_2 may contribute to distinct health risks beyond $PM_{2.5}$. Nevertheless, NO_2 can be a marker for a broader mixture of traffic emissions, and residual confounding by unmeasured pollutants cannot be completely excluded.

A key finding of our study is the differential susceptibility observed across population groups. We found evidence of effect modification by urbanicity, sex, and age, with somewhat stronger cumulative associations among residents of large cities, women, and younger adults. These patterns are consistent with existing epidemiological studies showing that individuals in certain sociodemographic groups may be more susceptible to the adverse effects of air pollution[23,26,27]. Urbanicity may reflect differences in exposure intensity, co-exposures (heat, noise), as well as socioeconomic and environmental factors that may amplify NO_2 effects [28,29].

The sex- and age-specific patterns were notable, with stronger and delayed associations between NO_2 exposure and ischemic stroke/TIA observed among women and younger adults. Lag-specific analyses indicated that the risk increased among women, particularly at lags of 3–5 days, compared with men. Although men often have higher age-specific stroke incidence, women experience a greater lifetime stroke burden and may be more vulnerable to vascular risk factors[30-32]. In addition, women are exposed to sex hormone–related risk factors for stroke, including age at menarche, menopause, pregnancy-related complications, and hormonal therapies[31]. The stronger associations we observed among younger adults were consistent with a previous study from Israel reporting disproportionately stronger short-term associations between ambient air pollution and ischemic stroke among younger adults, despite their lower baseline stroke risk[33]. In that study, the authors suggested that air pollution–related vascular injury may exert greater relative effects in younger individuals with fewer competing risk factors, potentially mediated through endothelial dysfunction, inflammatory responses, and prothrombotic pathways[33]. This proposed mechanism aligns with our observed delayed effects at lags of 3–5 days and supports heightened susceptibility among women and younger adults.

We also observed slightly higher odds among individuals with diabetes compared to those without, although the test for interaction was not statistically significant. This is consistent with previous studies suggesting that underlying cardiometabolic dysfunction, with diabetes, may intensify the effects of NO_2 exposure, adding to greater cardiovascular risk from air pollution [34,35].

In addition to the cumulative association, we observed that the risk of ischemic stroke and TIA peaked 3-5 days after NO_2 exposure, with particularly pronounced delayed effects among women and younger adults. This pattern is consistent with studies that suggest exposure to air pollution can trigger pulmonary and systemic inflammation, pro-coagulant changes, and vascular dysfunction, which typically evolve over hours to several days after exposure[36]. Several mechanisms could explain these patterns. While our data cannot directly account for all the pathways, the observed heterogeneity by sex and age suggests that short-term NO_2 effects disproportionately affect specific demographic groups. These highlight the importance of considering sex and age groups in air pollution and stroke research.

Strengths of our study include high spatiotemporally resolved exposure assessment, population-based setup, rich outcome, and covariate data. The case-crossover design inherently accounts for confounders that do not vary within a short period. However, some limitations remain. Although numerous confounders were accounted for by design, residual confounding from simultaneous environmental exposures is still possible. Considering this, we adjusted the models for $PM_{2.5}$ and temperature. We observed no significant change in the results, reaffirming that NO_2 is independently associated with stroke. Another key limitation is that NO_2 exposure levels were only linked to residential addresses, not accounting for daily mobility. Since the NO_2 exposure levels may differ at their workplaces or other locations, this could lead to exposure misclassification[40]. Nevertheless, this would be considered a non-

differential misclassification, resulting in bias towards the null, likely underestimating the true association between NO_2 exposure and stroke[41].

In conclusion, we found an increased risk of ischemic stroke and TIA associated with higher NO_2 exposure. The peak effects were observed 3-5 days after exposure, and there was evidence of stronger effects in urban residents, women, and younger adults. The findings support NO_2 as an acute, modifiable risk factor for ischemic stroke/TIA, suggesting the need to develop public health interventions to reduce NO_2 exposure at the population level.

Abbreviations

NO_2	Nitrogen Dioxide
TIA	Transient Ischemic Attack
$PM_{2.5}$	Particulate Matter less than 2.5 microns
DLNM	Distributed Lag Nonlinear Model
IHD	Ischemic Heart Disease
CVD	Cardiovascular Disease
INSR	Israeli National Stroke Registry
AOD	Aerosol Optical Depth
MAIAC	Multiangle Implementation of Atmospheric Correction
ICD-9	International Classification of Diseases, Ninth Revision
OR	Odds Ratio
CI	Confidence Interval
SD	Standard Deviation
IQR	Interquartile Range

Declarations

This study was approved by the institutional review boards at Soroka University Medical Center in Beer Sheva, Israel (study 01718-19), and the Icahn School of Medicine at Mount Sinai, New York, USA (study 21-00076). A waiver of informed consent was granted due to the minimal risk nature of the study and the use of de-identified registry data with no direct participant contact. All methods were performed in accordance with the relevant institutional and national guidelines and regulations.

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Figures

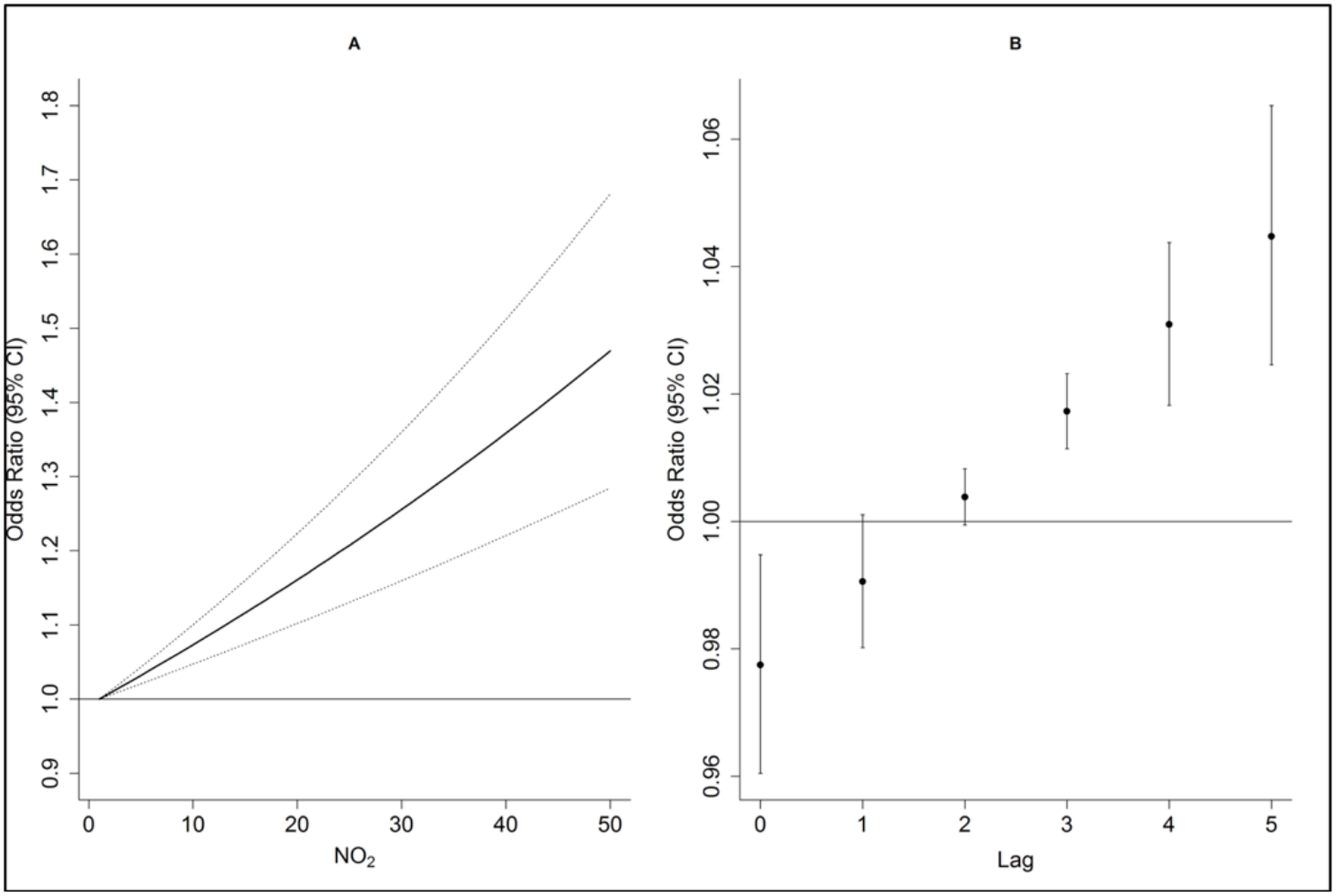

Figure 1

The association between NO_2 exposure in lag days 0-5 and ischemic stroke or TIA.

Panel A shows the cumulative NO_2–stroke/TIA association (solid line) with 95% CIs (dashed). Panel B shows lag-specific odds ratios (lags 0–5 days) with 95% CIs. Estimates were derived from distributed lag nonlinear models adjusted for $PM_{2.5}$ and temperature; the horizontal line indicates OR = 1.0.

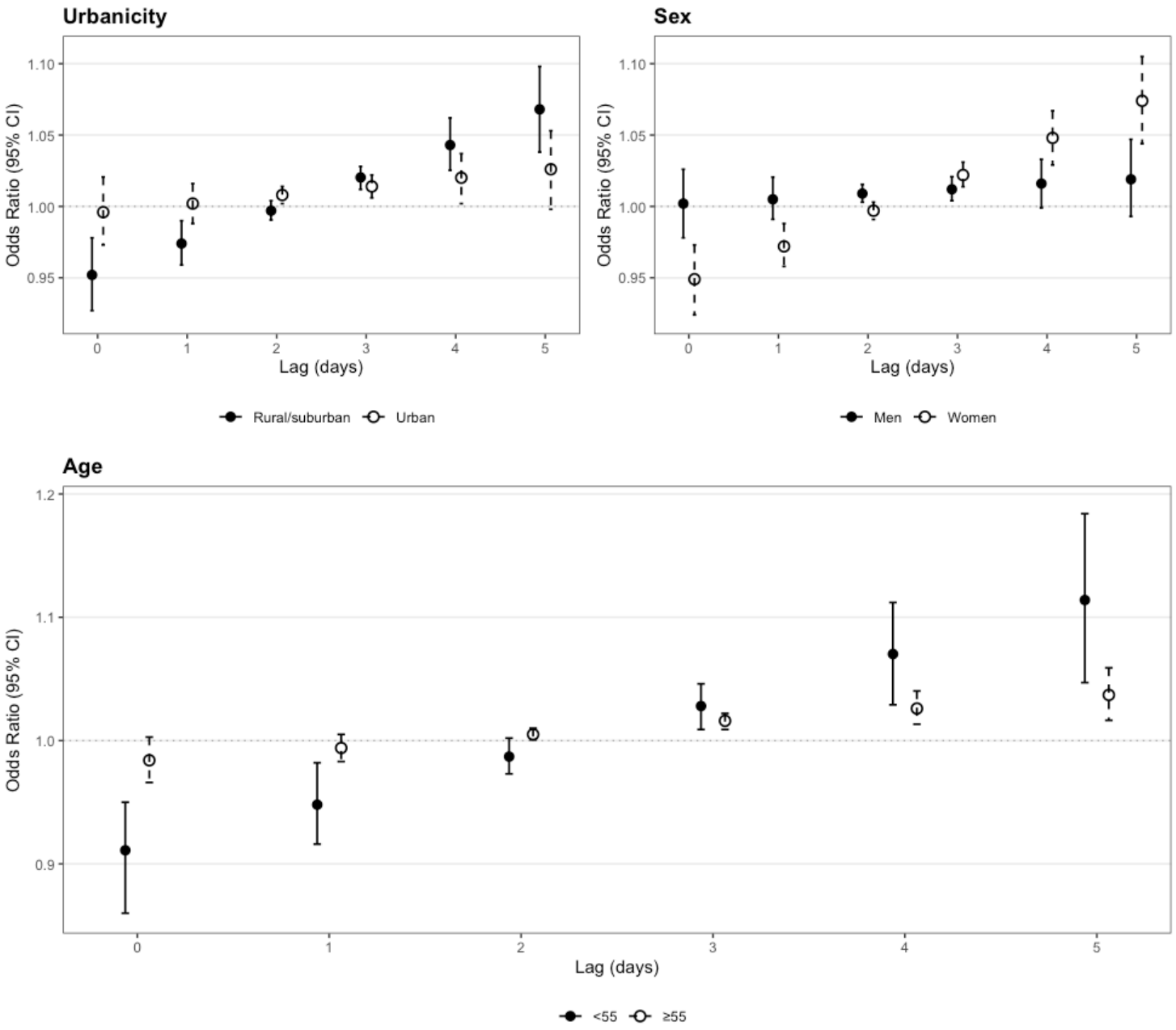

Figure 2

Lag-specific associations between short-term NO_2 exposure and ischemic stroke or TIA, stratified by urbanicity, sex, and age.

Supplementary Files

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- TableS1.docx