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Ambient air pollution and the self-perceived and objective health status among the older populations in Germany

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Table of content

List of abbreviations

A list of abbreviations can be helpful to the reader, especially if when you are using numerous and uncommon abbreviations.

AQGs	Air Quality Guidelines
BMI	Body Mass Index
CIs	Confidence Interval
COPD	Chronic Obstructive Pulmonary Disease
CO	Carbon Monoxide
CSRH	Comparative Self-Rated Health
CVDs	Cardiovascular Diseases
df	Degrees of Freedom
EQ-5D	European Quality of Life 5 Dimensions
EQ-5D-5L	Five-Level Versions of the European Quality of Life 5 Dimensions
EQ-VAS	European Quality Visual Analogue Scale
ETEs	Extreme Temperature Events
FH	University of Applied Sciences Augsburg
GAM	Generalized Additive Model
GDP	Gross Domestic Product
HRQoL	Health-Related Quality of Life
ICD-10	10th version of the International Classification of Diseases
INGER	Integrating Gender into Environmental Health Research
IQR	Interquartile Range
KORA-FIT	Cooperative Health Research in the Region of Augsburg study-FIT
LUR	Land-Use Regression
MCS	Mental Component Summaries
mRS	Modified Rankin Scale
NDVI	Normalized Difference Vegetation Index
NIHSS	National Institutes of Health Stroke Scale

NO_2	Nitrogen Dioxide
NOx	Nitrogen Oxide
O_3	Ozone
ORs	Odds Ratios
PLC	Particle Length Concentration
PM	Particulate Matter
$PM_{2.5}$	Fine Particulate
$PM_{2.5abs}$	Fine Particle Absorbances
PM_{10}	Particulate Matter of 10 microns or less in diameter
PM_{coarse}	Coarse Particles
PMC	Particle Mass Concentration
PNC	Particle Number Concentration
PSC	Particle Surface Concentration
R^2	Explained Variance
ROS	Reactive Oxygen Species
SES	Socioeconomic Status
SO_2	Sulfur Dioxide
SRH	Self-Rated Health
TIAs	Transient Ischemic Attacks
UFPs	Ultrafine Particles
WHO	World Health Organization

List of papers included in this dissertation

This dissertation consists of two published papers and a submitted manuscript, which is in the appendix.

Paper I

Liao M, Zhang S, Wolf K, Bolte G, Laxy M, Schwettmann L, Peters A, Schneider A, Kraus U. Long-term associations between ambient air pollution and self-perceived health status: Results from the population-based KORA-Fit study. *Int J Hyg Environ Health*. 2025 Mar: 264:114513. doi: 10.1016/j.ijheh.2024.114513.

Paper II

Liao M, Zhang S, He C, Breitner S, Cyrys J, Naumann M, Braadt L, Traidl-Hoffmann C, Hammel G, Peters A, Ertl M, Schneider A. Air pollution and stroke: short-term exposure's varying effects on stroke subtypes. *Ecotoxicology and Environmental Safety*. 2025 May: 298(2025): 118296. doi: 10.1016/j.ecoenv.2025.118296.

Paper III (Appendix)

Liao M, Zhang S, Schwarz M, He C, Breitner S, Cyrys J, Naumann M, Braadt L, Traidl-Hoffmann C, Hammel G, Peters A, Ertl M, Schneider A. Short-term effects of ultrafine particles on stroke events: An assessment using four different exposure metrics.

Contribution to the publications

I, Minqi Liao, am the first author of three papers that are incorporated into this Ph.D. dissertation. During the time of my Ph.D. journey, I regularly updated my findings and the progression to the Thesis Advisory Committees (TAC) of Ludwig-Maximilians-Universität Munich (LMU Munich) and Helmholtz Graduate School Environmental Health (HELENA). I also presented my work at the Work-In-Progress seminars of the Research Group Environmental Risk (EnRi), the Monday Seminar of the Institute of Epidemiology, Helmholtz Munich (EPI-HMGU), the PhD Journal Clubs of the Institute for Medical Information Processing, Biometry, and Epidemiology (IBE, LMU), as well as international conferences such as the International Society for Environmental Epidemiology Europe Young and Early Career Researchers Conference 2024. I was also invited to give a poster presentation at the Poster Session of the LMU Munich-China Scholarship Council (LMU-CSC) program for Chinese doctoral students. I received an HDR UK-Helmholtz-Travel Award and was invited to give an oral presentation at the 2025 HDR UK and Helmholtz Workshop on Advancing Data-Driven Environmental Health Research.

As the first and corresponding author, I was responsible for managing all included manuscripts' manuscript preparation, submission, revision, and publication processes. This entailed responding to data analyses, manuscript drafting, peer review feedback, implementing the necessary revisions, and supervising the proofreading and post-publication procedures. The individual contributions of each manuscript are presented in the following section.

Contribution to paper I

In the first publication, entitled "Long-term associations between ambient air pollution and self-perceived health status: Results from the population-based KORA-Fit study", we implemented a cross-sectional study using data from the Cooperative Health Research in the Region of Augsburg-FIT (KORA-FIT) and the Integrating Gender into Environmental Health Research (INGER) studies. We found that higher long-term air pollution exposure was associated with declined health-related quality of life (HRQoL), indicated by a lower European Quality of Life 5 Dimensions (EQ-5D) index and the European Quality of Life Visual Analogue Scale (EQ-VAS), and an elevated odds for poor self-rated health. Single-item indicators of self-perceived health status may demonstrate greater efficacy or practicality compared to their multi-dimensional counterparts.

As the first and corresponding author of this publication, I was responsible for conducting comprehensive literature reviews and preliminary data processing, performing the primary data analysis, visualizing the results, preparing supplementary materials, drafting the manuscript, and managing the submission process. I also addressed peer-review feedback, revised the manuscript accordingly, and supervised the proofreading and post-publication processes.

Contribution to paper II

In the second publication, entitled "Air pollution and stroke: short-term exposure's varying effects on stroke subtypes", a case-crossover study design was used to explore the short-term effect of classical ambient air pollutants ($PM_{2.5}$, PM_{10}, PM_{coarse}, O_3, NO_2, and NO) on strokes. We derived data on 19518 stroke cases from the University Hospital Augsburg in Southern Germany. Using conditional logistic regression, we observed that short-term exposure to air pollution may precipitate stroke events, with varying effects depending on the stroke subtype and the severity of pre-existing disability. More attention should be given to climate change due to the enhanced air pollution effect on strokes during warmer seasons.

As the first and corresponding author of this publication, I was responsible for applying for the data, reviewing the current literature on the topic, preparing the statistical analysis plan (SAP), conducting preliminary data procession, performing the primary data analysis, visualizing the results, preparing supplementary materials, drafting the manuscript, and managing the submission process. I also addressed peer-review feedback, revised the manuscript accordingly, and supervised the proofreading and post-publication processes.

Contribution to paper III (Appendix)

In the third publication, entitled "Short-term effects of ultrafine particles on stroke events: An assessment using four different exposure metrics", we continuously utilized stroke data from the University Hospital Augsburg, but focused on the health effects of ultrafine particles (UFPs). Based on the case-crossover study design, we explored the association of different subtypes of strokes with short-term exposures to different size-segregated UFP metrics, including particle number concentration (PNC), mass concentration (PMC), length concentration (PLC), and surface area concentration (PSC). The findings highlighted that an increased occurrence of strokes was consistently triggered by short-term exposure to all four UFP metrics, especially for ischemic strokes. Aside from the defined UFP mode (10-100 nm), special attention might be given to the particles in the Aitken mode (30-100 nm), and the metrics of PLC and PSC might serve as promising alternative indicators of UFPs. Extremely low temperatures may amplify the damaging effects of UFPs.

As the first and corresponding author of this publication, I was responsible for applying for the data, reviewing the current literature on the topic, preparing the SAP, conducting preliminary data processing, performing the primary data analysis, visualizing the results, preparing supplementary materials, drafting the manuscript, and managing the submission process. I also addressed peer-review feedback, revised the manuscript accordingly, and supervised the proofreading and post-publication processes.

1. Background

1.1 Air pollution burden: From health and economic aspects

In recent decades, both regional and global pollution problems have arisen, such as ozone (O_3) depletion, photochemical smog, and haze [1]. Consequently, air pollution continues to negatively impact human health and is emerging as a leading cause of global mortality. The State of Global Air Report 2024 stated that an estimated 8.1 million global deaths were attributable to air pollution in 2021, which was the second leading cause of death worldwide [2]. Specifically, ambient air pollution accounted for 11.9% (95% uncertainty interval [UI]: 10.1%; 13.8%) of the total global deaths, resulting in an age-standardized disability-adjusted life years rate per 100,000 of 3037 (95% UI: 2553; 3549) worldwide [3]. People with persistent noncommunicable diseases are particularly at risk from air pollution, which leads to 48% of global deaths caused by chronic obstructive pulmonary disease (COPD), 28% by ischemic heart disease, 27% by stroke, 19% by lung cancer, and 18% by type 2 diabetes [2].

While policies and technologies have helped improve air quality in many countries, 99% of the global population still lives in places where air quality exceeds the World Health Organization (WHO) air quality guidelines (AQGs) [4], suggesting that nearly everyone on the planet breathes unhealthy air every day [2]. Aside from causing substantial health costs, air pollution also imposes a heavy economic burden by reducing productivity, hindering competitiveness, raising health care expenditures, and overburdening the healthcare system [2]. According to a report from the World Bank Group, the global cost of mortality and morbidity associated with airborne particles with an aerodynamic diameter ≤ 2.5 µm ($PM_{2.5}$) reached $8.1 trillion, accounting for 6.1% of global gross domestic product (GDP) in 2019 [5]. In Europe, data has also shown that, for every unit (1µg/m^3) increase in $PM_{2.5}$, the GDP per capita was supposed to decline by 0.8% [6]. Contrary to this, an annual reduction in air pollution could boost regional GDP growth by 0.16% [6]. This suggests that the improving air quality could exceed the relative costs, and bring health, economic, and social benefits [6, 7].

Recognizing the gravity and urgency of the problem, in 2021, the WHO updated its global guidance based on updated evidence that air pollution affects health in a variety of ways at lower levels than previously thought [8]. However, the updated WHO guidelines only provided recommendations for each air pollutant individually, without recommendations about pollutant mixtures or the combined effects of pollutants. Thus, it is crucial that we prioritize additional research and systematic measurements to safeguard the health of populations worldwide and create a cleaner, safer environment for everyone.

1.1.1 The characteristics of different ambient air pollutants

Air pollutants are typically classified as PMs or gaseous pollutants [9]. Ambient air pollution largely results from the incomplete combustion of fuels and subsequent chemical reactions among atmospheric gases [10].

Key contributors to outdoor pollutant concentrations include high-temperature combustion associated with vehicular traffic, industrial operations, power generation facilities, the resuspension of surface dust, and construction activities [8, 10]. Although the air contains hundreds of measurable chemical compounds, regional and local authorities maintain accessible databases of only a limited subset, with the selected pollutants serving as indicators representing various types of air pollution and their primary emission sources. Several commonly found air pollutants, including $PM_{2.5}$, particles of 10 microns or less in diameter (PM_{10}), nitrogen dioxide (NO_2), ground-level O_3, sulfur dioxide (SO_2), and carbon monoxide (CO), were determined as the criteria pollutants due to their common measurements and certain health damages [2, 8]. Of note, the present dissertation will not address the health effects of SO_2 and CO, as the ambient concentrations of these pollutants are substantially lower in Germany than in many other regions, particularly in less developed countries.

As the proxy indicator for air pollution, PMs refer to a mixture of solid inhalable airborne particles, which are formed through chemical reactions among various atmospheric pollutants, and lipid droplets in the air [9, 11]. There are several sources of airborne PMs, including primary sources like combustion of fuels in vehicles, coal-burning power stations, construction sites, unpaved roads, fields, industrial activities, and waste burning, as well as secondary sources like chemical reactions between gases [2, 10]. The destiny and development of particle size distribution in the atmosphere are influenced by their aerodynamic diameters, which are determined by the physical processes of particle formation [9]. Aside from $PM_{2.5}$ and PM_{10} mentioned above, the coarse particles (PM_{coarse}) refer to particles with diameters from 2.5 µm to 10 µm [9]. The aerodynamic diameter of PMs further determines the extent to which they can penetrate the respiratory system [10]. Small PMs, especially ultrafine particles (UFPs), are generally characterized as particles measuring 100 nanometers or smaller (<100 nm) [12], have higher capabilities of penetrating deep into the lung and entering the bloodstream than larger particles, resulting in an increased production of reactive oxygen species (ROS), damage to DNA and cells, inflammation, endoplasmic reticulum stress, atherosclerosis, and airway remodeling, thereby posing the greatest health risk to cardiovascular, cerebrovascular, and respiratory health [10, 13].

According to the WHO, NO_2, O_3, SO_2, and CO are considered major health-damaging air pollutants [8]. In general, NO_2 is a highly reactive gas classified as an oxide of nitrogen (NOx), and its ambient sources are primarily determined by the high-temperature combustion of fuels and emissions from motor vehicles, industry, and power generation [10, 14]. The inhalation of air containing high concentrations of NO_2 can irritate the respiratory system, leading to higher occurrences of asthma and respiratory symptoms, and higher hospital admissions or emergency visits [14]. When sunlight is present, ground-level O_3 forms through photochemical reactions with other pollutants, such as volatile organic compounds, CO, and NOx [10]. As a major component of smog, excessive exposure to ground-level O_3 can trigger breathing difficulties, asthma, decreased lung function, and lung disease [10]. A major source of SO_2 is combustion without emission control or an uncontrolled metal processing facility, which can damage the respiratory system and is associated with excess mortality [15]. In contrast, CO is generated by the incomplete combustion of gasoline or diesel engines, causing unconsciousness, dizziness, and even death [9, 10, 16].

1.1.2 The long-term and short-term health effects of air pollution

Exposure to air pollutants from any source, quantified as long- or short-term exposure, can cause health problems [10]. Temporal variation is a key feature of ambient air pollution because concentrations of pollutants vary with respect to their spatial distribution, and their aggregation (e.g., daily or seasonal), the characteristics and dynamics of pollutants (dispersion, deposition, interaction with other pollutants), and weather conditions [10]. The long-term exposure, typically measured as a mean of one or several years, is used to assess whether chronic air pollution exposures are contributing to the development or progression of chronic health outcomes [10], such as cardiovascular diseases (CVDs: hypertension, atherosclerosis, myocardial infarction, strokes) [17, 18], COPD [19], various cancers [20, 21], metabolic disorders [22], cognitive decline [23], and mental issues (depression and anxiety) [24]. By contrast, by exploring the short-term exposure, ranging from hours to a few days, we can examine whether acute surrogate or intermediate endpoints are linked to time-varying pollutant concentrations [10]. Evidence suggested that short-term air pollution exposure, especially during smog episodes or traffic peaks, could trigger acute health outcomes, including respiratory outcomes (COPD acute exacerbations, asthma) [25, 26] or cardiovascular conditions (heart failure, myocardial infarction, stroke) [17, 18, 27, 28]. Consequently, the distinction in exposure duration is crucial for assessing health outcomes, understanding the underlying biological mechanisms, and determining public health strategies for preventing and mitigating them.

1.1.3 The specific concerns about ultrafine particles

Although the overwhelming majority of evidence on the adverse health effects of $PM_{2.5}$ and PM_{10} is based on studies of human exposures, few studies focus on the adverse health effects of UFPs. The majority of UFPs were emitted from anthropogenic activities, including traffic transportation (vehicles, aviation, and shipping), industrial activities, biomass burning or fuel combustion, and construction [29]. Extremely small size and vast number make them more likely to be inhaled, and enable them to deeply penetrate the lungs and transmigrate into the bloodstream, with their high surface area (total exposed surface area per unit of mass) allowing them to absorb more toxic chemicals, thus making them more threatening than larger particles [12, 29, 30]. However, there is insufficient clear quantitative evidence for the WHO to formulate specific AQGs for ultrafine particles [8], as challenges exist in monitoring atmospheric UFPs and examining their health effects. First, ambient UFP concentrations, which are not routinely monitored in most places, are highly variable spatially and heavily influenced by factors such as location and meteorological indicators. Still, there are no internationally agreed-upon standard technologies or detection limits to quantify ambient UFPs [8, 12, 30]. Second, the UFPs size fractions can also be classified by their formation processes: the nucleation mode (<30 nm) originating from the condensation of hot gaseous molecules in the vehicle tailpipe, the accumulation mode (30-500 nm) originating from condensation and coagulation in the engine, and the Aitken mode (30-100 nm) being associated with the combustion sources [30-32]. Aside from the commonly used measured metrics, particle number concentration (PNC) or mass concentration (PMC), UFPs can be assessed as particle length concentration (PLC) and surface area concentration (PSC) per volume [30]. Notably, the PLC, defined as the product of particle number and diameter, exhibited a strong correlation with

PSC in the lung [33]. This is significant because particles with a larger surface area relative to their mass can adsorb higher amounts of toxic metals and organic pollutants, thereby posing greater health risks [30].

Thus, it is challenging to examine the complex health effects of various metrics of UFPs across different size modes because differences in the chemical composition and physical attributes of UFPs can be related to divergent toxicological profiles. Exposure to UFPs has been reported to contribute to the development of acute and chronic health outcomes, including oxidative stress and the generation of reactive oxygen species [29], neuro-inflammation [34], and further cause diseases in the respiratory, cardiovascular, and nervous systems, as well as metabolic diseases and cancers [29, 35]. Considering the high spatial and temporal variabilities of UFPs, more advanced approaches and technologies assessing population UFP exposure levels are needed to draw firm conclusions on health outcomes in response to UFP exposure.

1.2 Potential effects on self-perceived and objective health outcomes

1.2.1 Air pollution and self-perceived health status

The self-perceived health status is useful in understanding how individuals evaluate their current and future health, taking into consideration physical, psychological, and socioeconomic factors [36, 37]. For clinicians, self-perception of health may represent an underutilized source of information because it can reveal problems that clinical testing may not detect [36]. For instance, people with poor self-perceived health status may have a stronger willingness to seek preventive medical services and a higher likelihood of adopting healthy life behaviors [38]. Self-perceived health status can therefore be used to predict chronic diseases, mortality, recovery from illness, functional decline, and medical utilization [36, 37], especially among older populations [39]. There is a growing trend toward assessing a person's perceived health status by asking a simple question or completing a questionnaire. Health-related quality of life (HRQoL) serves as a suitable indicator of how individuals perceive their own health status [40], encompassing subjective well-being across physical, emotional, and social health dimensions [41]. Based on the definitions of HRQoL above, several preference-based measurement tools could be used to quantify HRQoL effects. A commonly used HRQoL questionnaire developed by the European Quality of Life Group (EuroQol Group) is the five-level version of the European Quality of Life 5 Dimensions (EQ-5D-5L) [42]. It is a short, cognitively simple questionnaire, which is preferred by medical institutions as a tool for measuring HRQoL in adults [43]. There are two sections to the EQ-5D-5L: a short descriptive system measuring from five perspectives, in which five responses are available for each dimension; and a visual analogue scale for measuring European Quality (EQ-VAS), which measures an individual's overall state of health through a vertical visual analogue scale [42]. In order to represent the health status of a country or region, the EQ-5D index values were calculated by using a formula that assigns weights to each level within each dimension according to the preferences of the general population, with a higher score signifying complete health [42]. An additional common measure of general health perception is self-rated health (SRH) / subjective health, which asks respondents to rate their overall health [44]. Rather than focusing on specific dimensions, this general concept allows us to assess objective health information and people's subjective evaluations of it [45]. Besides, the age-comparative SRH has also been developed with questions asking the respondents about their perceptions of health in comparison with other people of their age, considering the health of the community that the individuals belong to, and their perception of it [44]. As an indicator of chronic illness or its treatment, self-perceived health status may be affected by personal characteristics [36, 37] and may be associated with air pollution. A recent study in Europe used the Short Form-36 to measure HRQoL, and it found that higher air pollution levels are related to lower mental health scores (MCS) [46]. SRH has been shown to be negatively affected by prolonged exposure to air pollution in the Netherlands [47], Canada [48], China [49], Belgium [50], Bulgaria [51], Northern Ireland [52], as well as in South Korea [53], in which the HRQoL was measured using the subjective stress, EQ-5D index values, and depression. Nonetheless, it is still uncertain how various self-assessed health indicators are related to prolonged exposure to air pollution, and no comparative studies have been undertaken.

1.2.2 Air pollution and objective health status

An objective health status refers to the presence and number of chronic medical conditions assessed objectively [54]. As a major part of the objective health conditions, CVDs remain the leading cause of premature death around the world [55]. Specifically, ischemic heart disease and strokes emerged as the foremost causes of disability-adjusted life years among individuals aged 50 to 74 and those 75 and older in 2019 [56]. Notably, air pollution has become a significant health issue worldwide, particularly affecting cardiovascular health [17, 57], though its associated risk of CVDs is less than that associated with conventional risk factors like hypertension and hyperlipidemia [58]. A growing body of research indicates an association between exposure to ambient air pollutants and the occurrence of stroke[17, 18, 28, 59]. Although both long- and short-term ambient air pollution exposures have been recognized as risk factors for strokes [17, 18, 60], they likely operate through distinct biological and epidemiological pathways. In general, acute exposures to air pollution may trigger stroke events [59], whereas the underlying vascular pathophysiology (e.g., atherosclerosis progression and enhanced plaque vulnerability) contributing to cerebrovascular events may be more related to chronic exposures [61]. Besides, the short-term effects are particularly critical in individuals of advanced age, who might be more susceptible to the transient spikes in air pollution due to their physiological differences changing as age increases [62], pre-existing diseases, or higher inflammation [63]. Consequently, short-term exposure could be particularly relevant for public health, as its effects are more immediately modifiable through timely interventions, such as public alerts or behavior changes, and isolating its impacts in some vulnerable population enhances our understanding of how transient pollution peaks may trigger acute health outcomes.

2. Aims of the dissertation

Drawing on data from Augsburg, southern Germany, this doctoral dissertation aims to elucidate whether air pollution exposure is related to any adverse health outcomes from the following perspectives:

1. To investigate whether long-term exposure to air pollution may negatively affect self-perceived health—assessed using multiple evaluation tools—and to identify population groups with increased susceptibility.
2. To assess the short-term impact of routinely monitored ambient air pollutants on stroke events, considering differences by stroke subtype, stroke-induced disability, severity, and susceptibility among individuals.
3. To evaluate the association between short-term exposure to four UFP metrics across five size fractions and the occurrence of stroke events; to explore differences by stroke subtype, stroke-induced disability, and stroke severity; and to examine potential effect modification by time-invariant factors (e.g., sex, age), seasonal variation, temporal trends, and the extreme temperature events.

This cumulative dissertation comprises two publications addressing the first two aims. Additionally, a third manuscript—currently under revision—is included in the appendix and corresponds to the third aim.

3. A brief overview of methods

The following section outlines the methodological framework of each study and is organized into two parts. The first part presents research on the association of self-perceived health status with prolonged exposure to air pollution (Paper I), while the second part examines whether strokes are associated with short-term exposure to ambient air pollutants, including analyses of routinely monitored air pollutants (Paper II) and UFPs (Paper III). Further details are provided in the respective manuscript. **Figure 1** illustrates the work-flow of the included papers.

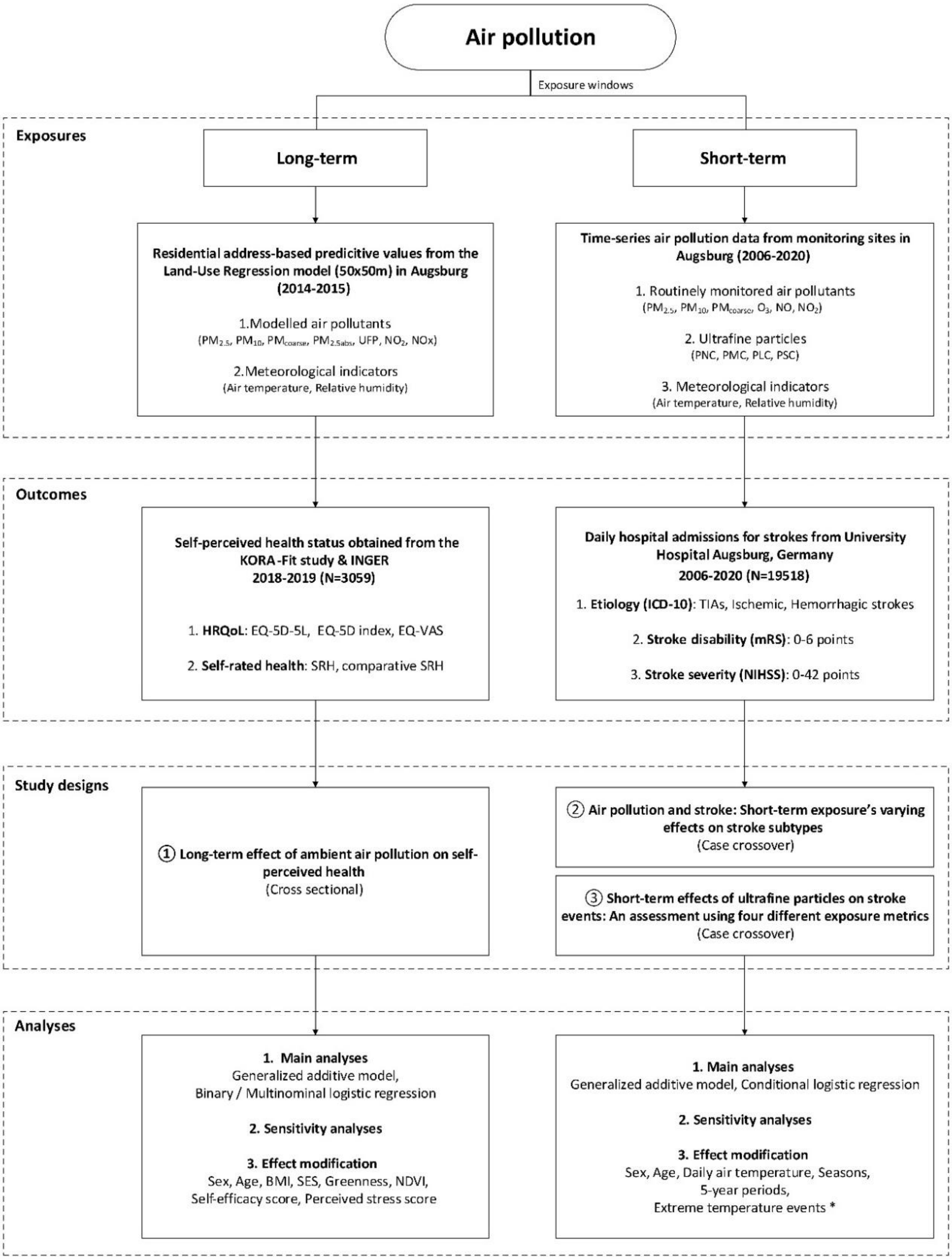

Figure 1. The workflow of the included papers.

Abbreviations: BMI, body mass index; EQ-5D-5L, Five-level dimensions of the European Quality of Life 5 Dimensions questionnaire; EQ-VAS, European Quality of Life Visual Analogue Scale; ICD-10, 10th version of the International Classification of Diseases; INGER, Integrating Gender into Environmental Health Research; KORA, Cooperative Health Research in the Region of Augsburg study; mRS, Modified Rankin Scale; NDVI, normalized difference vegetation index; NIHSS, National Institutes of Health Stroke Scale; NO, Nitric oxide; NO_2, nitrogen dioxide; NOx, nitrogen oxide; PLC, particle length concentration; PM_{coarse}, coarse particles; $PM_{2.5}$, airborne particles under 2.5 µm in size; $PM_{2.5abs}$, fine particle absorbances; PM_{10}, airborne particles under 10 µm in size; PMC, particle mass concentration; PNC, particle number concentration; PSC, particle surface area concentration; SES, socioeconomic status; SRH, self-rated health; TIAs, transient ischemic attacks; UFP, ultrafine particle.

* The modifying effect of extreme temperature events was only explored in Paper III.

3.1 Air pollution and self-perceived health status (Paper I)

3.1.1 Study design and population

Paper I is a cross-sectional analysis based on data from the Cooperative Health Research in the Region of Augsburg study (KORA), launched in 1984 in Augsburg and its two neighboring districts [64]. Four baseline surveys were implemented at 5-year intervals: S1-S4 (1984-2001) [64]. As a follow-up examination, the KORA-FIT study was conducted in 2018/2019, with 3,059 alive participants born in 1945-1964 being regarded as eligible participants [65]. A subgroup of KORA-FIT respondents also participating in the Integrating Gender into Environmental Health Research (INGER) study was included in the analysis to explore the potential influence of gender/sex or residential greenness [66]. After excluding ineligible individuals, a final sample of 2,610 participants remained for Paper I. A concise outline of the studies included in this paper is shown in **Figure 2**.

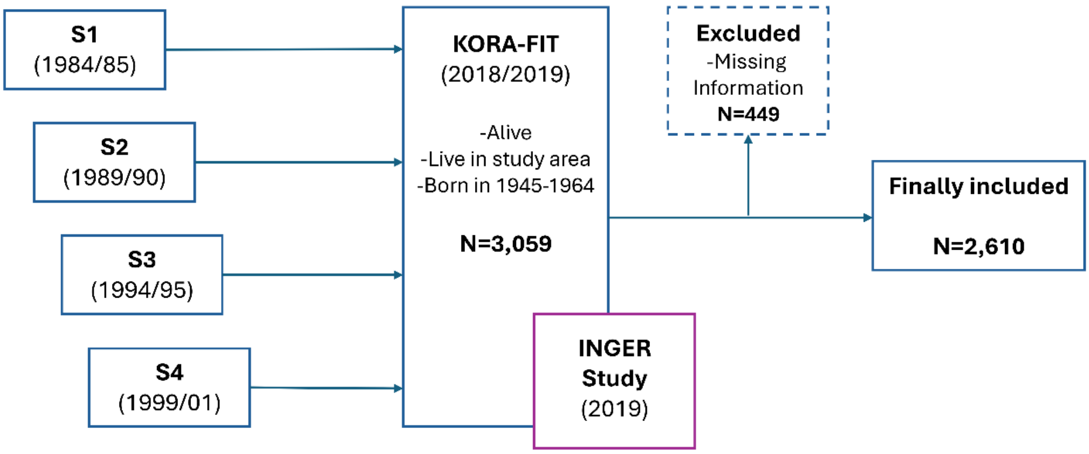

Figure 2. Overview of study populations.

Abbreviations: KORA, Cooperative Health Research in the Region of Augsburg study; INGER, Integrating Gender into Environmental Health Research study.

3.1.2 Outcome assessment

Self-perceived health status was captured using a multidimensional concept of HRQoL and the general concept of subjective health/self-rated health. HRQoL was assessed using the EQ-5D-5L, which contains a descriptive system and the EQ-VAS [67]. Within the descriptive system of EQ-5D-5L, for each of the five dimensions (mobility; self-care; usual activities; pain/discomfort; anxiety/depression), there were five levels to describe the severity, namely *having no problems, slight problems, moderate problems, severe problems, and extreme problems* [67]. Participants were instructed to select the option that most accurately reflected their current health status in each dimension [67]. Responses on the EQ-5D-5L five-level scale were dichotomized, with each dimension being converted into a binary variable indicating the presence of *no problems* versus any level of reported *problems*. Furthermore, according to the preferences of the general population of Germany developed by Ludwig, *et al.* [68], the five-digit codes for five dimensions were converted into the EQ-5D index value by attaching weights to each of the levels in each dimension, which yielded an index between -0,13 and 1.00, with the score below 0 indicating a health status worse than death, a score of 0 being equivalent to death, and a score of 1 being optimal or full.

Due to the variation in definitions and phrasing used to evaluate SRH across different studies, the overall notion of SRH in Paper I was evaluated through multiple instruments. The EQ-VAS, which is a component of the EQ-5D-5L, spans from '*the best health you can envision*' to '*the worst health you can envision*,' representing the person's overall perception of their health [67]. The SRH concept was evaluated based on the answer to this question: "How do you evaluate your present physical health?" [69]. The original answers were labeled as *very good*, *good*, *less good*, and *poor*. We categorized the responses into good SRH and poor SRH to streamline the analysis. Additionally, the comparative self-rated health (CSRH) was assessed by asking the question, "How do you perceive your health in relation to others of your age?", with the responses being limited to three choices: *better*, *equal,* or *worse*. **Figure 3** illustrates the components and interrelationships of various self-perceived health indicators.

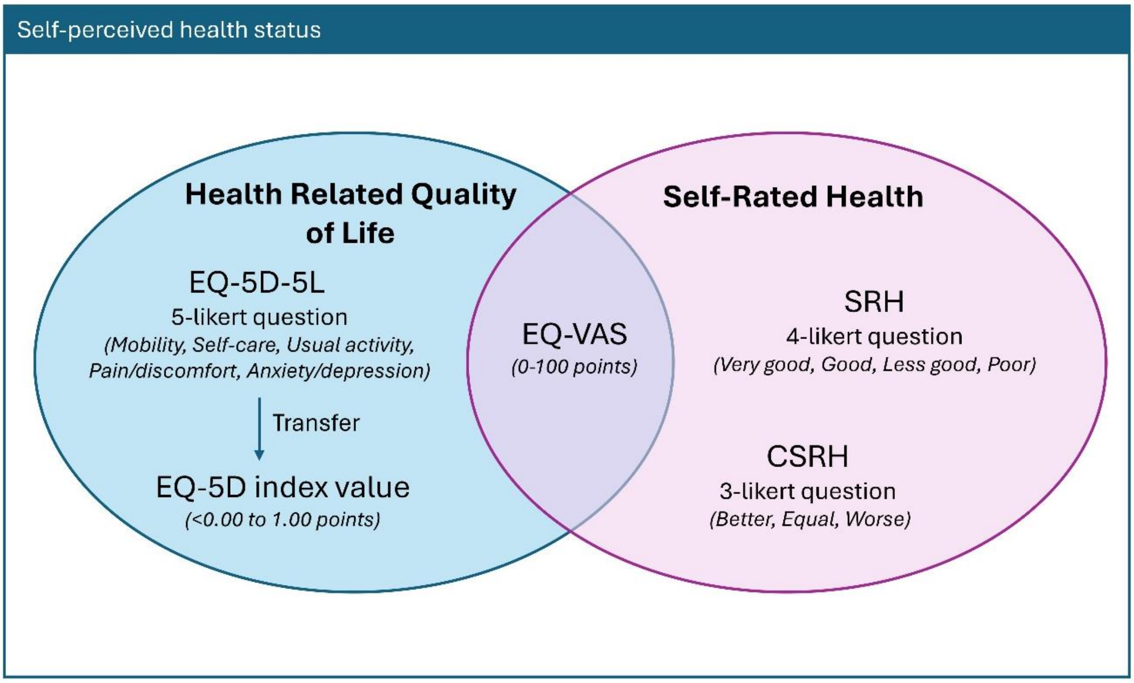

Figure 3. Overview of the indicators used to assess self-perceived health status.

Abbreviations: CSRH, comparative self-rated health; EQ-5D-5L, five-level version of the European Quality of Life 5 Dimensions questionnaire; EQ-VAS, European Quality of Life Visual Analogue Scale; SRH, self-rated health.

3.1.3 Exposure assessment

A land-use regression (LUR) model with a spatial resolution of 50 m × 50 m was employed to assess personal exposure to outdoor air pollutants, utilizing data collected from three bi-weekly measurements at 20 locations within the KORA study area during the years 2014 and 2015 [70]. Paper I employed standardized protocols for the European Study of Cohorts for Air Pollutant Effects to estimate the annual mean concentrations of residential air pollutants, including PNC (as a surrogate for UFP), $PM_{2.5}$, the absorbances of $PM_{2.5}$ ($PM_{2.5abs}$, representing a proxy of black carbon and soot), PM_{coarse}, PM_{10}, O_3, NO_2, and NO_X, using participants' home addresses and spatial predictors derived from geographic information systems [71, 72]. The suitability of the LUR model was demonstrated by the adjusted model-explained variance (R^2) values that varied from 68% to 94%, as well as the adjusted leave-one-out cross-validation R^2, which ranged from 55% to 89%[73]. More details about the methods can be found in Paper I [74].

3.1.4 Statistical analyses

Various analytical models were employed to evaluate the relationship between chronic exposure to air pollution and individuals' self-reported health status. Continuous outcomes (EQ-5D index values and EQ-VAS scores) were analyzed with a Generalized Additive Model (GAM) using fixed effects; binary outcomes (SRH and the five dimensions of EQ-5D) were assessed using binary logistic regression; and CSRH was evaluated with multinomial logistic regression. We implemented four models to adjust for potential confounding, with the main model controlling for sex, age, individual socioeconomic status (SES), living with a partner, body mass index (BMI), smoking, and physical activity. In parallel, potential effect modification was examined across sex, age, BMI, SES, self-perception of residential greenness, normalized difference vegetation index (NDVI), self-efficacy, and perceived stress. Finally, we conducted a series of sensitivity analyses to evaluate the robustness of our findings, including another main model adjusted for covariates selected by a Directed Acyclic Graph, the heteroscedasticity testing, linearity of the exposure-response relationship, the two-pollutant model, and additional adjustment for residential duration.

3.2 Air pollution and objective health: strokes (Papers II & III)

3.2.1 Study population and outcome assessment

Daily stroke records spanning 15 years (April 2006 to August 2020) were collected from the Medical Informatics Department of University Hospital Augsburg [75]. Daily hospital admissions for stroke were routinely and anonymously compiled in official analyses, and ethical approval was waived in line with the Bavarian Hospital Act.

Daily hospital admissions for stroke subtypes were defined as transient ischemic attacks (TIAs, G45), hemorrhagic strokes (I60–I62), and ischemic strokes (I63), using the 10th revision of the International Classification of Diseases (ICD-10). Data on stroke-related functional independence, assessed using the Modified Rankin Scale (mRS), and stroke severity, measured by the National Institutes of Health Stroke Scale (NIHSS), were also collected. The analysis was restricted to first-occurrence, non-fatal stroke cases, excluding cases with undefined diagnoses and repeated hospitalizations.

3.2.2 Exposure assessment

For the study period (2006-2020), daily average concentrations of ambient air pollutants and meteorological indicators were collected from different measurement sites in the study areas of Augsburg, Germany. For the routinely measured air pollutants (PM_{10}, $PM_{2.5}$, PM_{coarse}, O_3, NO_2, and NO) of interest in Paper II, the monitoring sites were selected according to data availability and the adjusted model-explained variance (R^2) of the regression [70]. In Paper III, four size-segregated UFP metrics (PNC, PMC, PLC, and PSC) were measured at a representative measurement site (FH, University of Applied Sciences Augsburg) [76, 77], with detailed information regarding the measurement instruments, calibration processes, and data management being available in the supplementary materials of Paper III. The primary size range of UFP metrics of interest was the ultrafine range (10-100 nm). Additional analyses were conducted for three different UFP sub-fractions, including the nucleation mode (10-30 nm), Aitken mode (30-100 nm), accumulation mode (100-500 nm), and the total measured range (10-500 nm). The impacts of extreme temperature events (ETEs), including cold spells and heat waves, were analyzed in Paper III. We first calculated the specific cutoffs using the daily 24-hour average ambient temperature (°C). A heat wave was defined as an intense period lasting 2, 4, or even 6 consecutive days when daily air temperatures soar above the critical thresholds of the 95.0th and 97.5th percentiles, while a cold spell was defined as 2, 4, or 6 consecutive days with temperatures below the 2.5th and 5.0th percentiles—indicating subnormal conditions relative to the average temperatures in the study areas [78, 79].

3.2.3 Statistical analyses

In papers II and III, a time-stratified case crossover design was utilized to control for any potential confounding from long-term trends, seasonal variations, day-of-week effects, and time-invariant factors such as sex and age by comparing the exposure levels on case days and those on control days [80]. We examined the effects of air pollutants on strokes at single-day lags from lag0 (current day of strokes) to lag6 (6 days before strokes), at lagged moving averages lag0-1, lag2-4, lag5-6, and at cumulative lag0-6 (7-day moving average) by conditional logistic regression. We controlled the same lagged days of ambient air temperature and relative humidity by incorporating a natural cubic spline with three degrees of freedom (df) in the model. Stratified analyses were conducted by stroke subtypes, stroke-induced disability, and stroke severity to assess differences in susceptibility. Several sensitivity analyses were carried out to evaluate the robustness of the findings. Additionally, the interaction model was used to examine potential effect modification by sex, age, season, 5-year admission periods, and ETEs (assessed only in Paper III).

4. Key findings

This section summarizes the main results from the two published papers and the submitted manuscript included in this dissertation. Aligned with the structure of the methodological section, the results are organized as follows: first, the study examining the long-term impacts of air pollution on self-perceived health status (Paper I) is evaluated, followed by the studies investigating the associations of strokes with the short-term exposures to routinely monitored air pollutants (Paper II) and UFPs (Paper III).

4.1 Long-term effects of air pollution on self-perceived health status

This analysis of self-perceived health status addresses the first specific aim of this dissertation: to investigate whether elevated exposure to air pollution was related to poorer self-perceived health status, assessed through various instruments.

Increased annual air pollution exposures were associated with decreased EQ-5D index values and EQ-VAS. An interquartile range (IQR) increase in O_3 concentration was related to a reduction in the EQ-5D index value (percent change [95% confidence interval, CI]: −0.91% [−1.76%; −0.06%]). Likewise, the EQ-VAS decreased in response to elevated annual concentrations of air pollutants, including PM_{10} (−1.38% [−2.37%; −0.38%]), PM_{coarse} (−1.25% [−2.28%; −0.23%]), $PM_{2.5abs}$ (-1.57% [-2.69%; -0.45%]), PNC (−0.89% [−1.68%; −0.10%]), NO_2 (−1.30% [−2.36%; −0.23%]), and NOx (−0.96% [−1.83%; −0.10%]). Participants with a lower BMI and higher self-perceived stress appeared more vulnerable to the impact of air pollution on EQ-VAS scores.

Individuals exposed to higher levels of air pollution were more likely to report poor SRH and unfavorable CSRH. For each IQR increase in air pollutant concentrations, the odds ratios (ORs [95% CIs]) of poor SRH were 2.67 (1.07; 6.67) for PM_{10}, 1.70 (1.14; 2.54) for PM_{coarse}, 1.42 (1.01; 1.99) for PNC, and 1.36 (1.04; 1.79) for NO_X. A similar trend was also found for worse CSRH in response to elevated concentration of $PM_{2.5abs}$ (OR=2.59 [1.12; 5.99]). All the above associations were proved to be robust in a series of sensitivity analyses. Particularly, single-item indicators (EQ-VAS and SRH) may have better performance in assessing self-perceived health than multi-dimensional measurements (EQ-5D index value) due to their more intuitive and straightforward characteristics.

4.2 Short-term effects of routinely measured air pollutants on strokes

This analysis of strokes addresses the second specific aim of this dissertation: to assess the short-term impact of classical air pollutant exposures on stroke occurrence.

Our study found the association between elevated short-term air pollution exposure and a higher likelihood of stroke occurrence. The delayed effects were primarily observed about 5- or 6-days following exposure to increased levels of $PM_{2.5}$, PM_{10}, PM_{coarse}, O_3, and NO_2. The lagged moving average model yielded similar trends. Stroke risk increased by 2.11% (0.09%; 4.17%) for $PM_{2.5}$, 2.55% (0.43%; 4.71%) for PM_{10}, 2.50% (0.23%; 4.82%) for PM_{coarse}, and 3.48% (0.61%; 6.44%) for NO_2 at lag 5–6 days per IQR rise in pollutant levels. For O_3, a negative association with strokes was found at lag 6 and the moving average lag 0-6 days.

Patients with TIAs and hemorrhagic strokes were disproportionately impacted by air pollution. Severe stroke cases with higher stroke-induced disability were more likely to be affected by particles, whereas milder cases with lower stroke-induced disability were more affected by gaseous pollutants. The relationship between air pollution and stroke risk was more pronounced during the warmer months and in the 2016–2020 period. Further sensitivity analyses confirmed the robustness of these findings.

4.3 Short-term effects of UFP metrics on strokes

This analysis addresses the third specific aim of this dissertation: to evaluate the association between short-term exposure to four size-segregated UFP metrics and stroke events.

Comparable adverse impacts on stroke events were observed for short-term exposure to four distinct UFP metrics. Consistent delayed effects were observed across the four UFP metrics for both single-day lags of 3 or 4 days and moving average lags of 2–4 days, with the strongest effects appearing at the cumulative lag of 0–6 days. Each IQR increase in PNC, PMC, PLC, and PSC in the specific ultrafine fraction (10-100 nm) was associated with an elevated risk of stroke events of 4.76% (1.06%; 8.60%), 3.99% (0.93%; 7.13%), 4.52% (1.11%; 8.05%), and 4.14% (1.00%; 7.38%), respectively, at the cumulative lag 0-6 days. This suggests that, in addition to PNC, the metrics of PLS and PSC may have promising alternative roles in measuring UFPs. Notably, the effect of PMC warrants further validation in other size ranges, as a substantial portion of PMC lies outside the 10–100 nm range typically measured.

When examining potential variations in effects across UFP size fractions, we found that, within the size range of 10–100 nm, the effects of all four UFP metrics appeared stronger in the Aitken mode (30–100 nm) than in the nucleation mode (10–30 nm). Larger particles in the accumulation mode (100–500 nm) may exert more immediate adverse health effects. Furthermore, UFP metrics in the total measured range (10–500 nm) appeared to have a more consistent effect with the Aitken mode, apart from the PMC, which may be more related to the accumulation mode.

The effect of UFP metrics was more likely to be seen for ischemic strokes than for the other two subtypes. Besides, a more pronounced UFP effect was found among milder stroke patients with a low stroke-related disability or stroke severity. Finally, we noticed that the UFP effect on strokes may be amplified by cold spells with extremely low air temperature in cold seasons.

5. Discussion

This section provides a brief summary of the overall findings, the susceptible groups or effect modifiers, and their potential biological mechanisms, as presented in the three papers. Detailed discussions and information can be found in each paper.

5.1 Air pollution and self-perceived health status

In Paper I, higher annual air pollution levels were found to be associated with reduced HRQoL and poor SRH. More and more studies corroborate this finding, despite the use of different instruments across studies to assess the general subjective health status. For instance, HRQoL, as measured by both the Short Form-36 MCS and the EQ-5D related questionnaires, declined with increasing annual mean concentrations of air pollutants [46, 53, 81]. Similarly, the association with poor SRH has also been found in China [49, 82, 83], Netherlands [47], Canada [48], Belgium [50], Bulgaria [51], Northern Ireland [52], Chile [84], and in the United States [85]. Previous studies assessed self-perceived health status using a single indicator, highlighting the need for validation through multiple measurement tools. Our study is the first to concurrently employ various self-rated health measures, revealing that single-dimensional instruments (EQ-VAS and SRH) may have higher sensitivity to air pollution exposure than multidimensional tools (EQ-5D-5L or EQ-5D index value). Researchers can draw new insights from this discovery to inform their choice of subjective health-related indicators. Of note, inconsistent evidence also exists in studies from Mongolia [86] and China [87] , as well as a study in the United Kingdom [88]. Multiple factors could account for the inconsistent results regarding the impact of air pollution on self-perceived health, including spatial and temporal variations in air pollution concentrations, differing subjective health status measurements, or different socioeconomic levels across studies.

The exact biological mechanisms underlying these associations remain unclear. Typically, the negative effects of prolonged exposure to air pollution on self-perceived health can be attributed to its consequences for the cardiovascular, respiratory, and immune systems [89, 90], which can contribute to worse physical health conditions that negatively influence perceived health. Specifically, individuals with higher exposure to air pollution may be more prone to developing respiratory symptoms (e.g., cough, breathlessness, wheezing, phlegm), which can limit daily activities, increase health-related anxiety [91, 92], and potentially contribute to mental health issues and poorer self-perceived health.

The results of this paper indicated that participants with a lower BMI or higher stress perception were more susceptible to air pollution's detrimental effects on self-perceived health. Air pollutants may have synergistic effects with psychosocial stress in increasing individuals' inflammatory response and inducing oxidative stress [93]. BMI modification might reflect the obesity paradox, which suggests a better prognosis for chronic diseases for those with higher BMI because of persistent low-grade inflammation [94]. Additional research is required to validate these findings.

5.2 Routinely monitored air pollutants and strokes

In Paper II, short-term exposure to commonly regulated air pollutants, particularly $PM_{2.5}$, PM_{10}, PM_{coarse}, and NO_2, was associated with an increased stroke risk among older adults in Augsburg, Germany. This finding is in line with epidemiological evidence from recent reviews or meta-analyses [17, 18, 95]. Aside from that, our study employed daily average levels of air pollution in Augsburg, located in southern Germany. In this less polluted area, air pollution levels meet the WHO air guidelines for two-thirds of the year. The stroke risk remains adversely correlated with air pollution in areas with lower levels of pollution, underscoring the need for further actions to improve air quality and reduce stroke rates worldwide.

The detrimental effects of air pollution varied by stroke etiology, with the estimates being more pronounced among patients with TIAs and hemorrhagic strokes. In general, hemorrhagic stroke hospitalization is less commonly associated with short-term air pollution exposure than ischemic stroke hospitalization [28]. This could be due to the lower frequency of hemorrhagic strokes and the less likely influence of transient air pollution on their pathogenic mechanisms [96]. Notably, with limited supporting evidence, the results of TIAs need to be confirmed due to the difficulties in diagnosing them, as the symptoms resolve within 24 hours, and an obvious lack of an infarction on magnetic resonance imaging [97]. Furthermore, stroke cases associated with PM caused more severe disability, whereas strokes associated with gaseous pollutants caused less severe disability. It may be due to differences in physicochemical composition and exposure specificities among air pollutants [98], calling for more attention to physicochemical properties and related advanced measurement tools.

Multiple mechanisms may underlie the link between air pollution and acute physiological responses in the neurovascular system, including local and pro-inflammatory responses, production of ROS, endothelium dysfunction, acceleration of atherosclerosis, and formation of immune-thrombosis [18, 98]. Additionally, pollutants may activate receptors of the lung and may thereby interfere with the autonomic nervous system, causing vasoconstriction and altering cardiac rhythms, leading to hemorrhagic or ischemic strokes [18].

The potentially amplified adverse effects of air pollution during warmer seasons may be attributed to increased personal exposure from greater outdoor activity [99], enhanced solubility and bioavailability of pollutants [100], the synergistic interactions between contaminants [101], and reduced detoxification capacity at higher temperatures [102]. Besides, we hypothesize that temporal variations in air pollution–related health effects between the previous five-year periods (2006-2010, 2011-2015) and the most recent period (2016-2020) may be related to changes in pollutant sources and composition, advances in engine technology and fossil fuel use, potential shifts in population susceptibility and socioeconomic conditions, and improvements in disease detection and treatment technologies. There is a need for more research to elucidate the changes in air pollution's health impacts over time.

5.3 Different UFP metrics and strokes

Using stroke admission data, we further unveiled the comparable detrimental effects of four size-segregated UFP metrics (PNC, PMC, PLC, and PSC) on strokes, which indicated that, aside from the commonly used number and mass concentrations, the physical properties of UFPs need to be further considered. So far, the evidence from epidemiology has been sparse to clarify the relationship between acute exposure to UFP and strokes. Additionally, the use of different UFP exposure metrics [103, 104] and size fractions [103, 105-107] may further add complexity to the conclusions. Measuring UFP using the PNC metric, a prior study in Finland observed an adverse association between short-term UFP exposure and strokes, but the effect estimates did not reach statistical significance [108]. Similarly, a related study conducted in Denmark discovered a higher likelihood of strokes associated with short-term exposure to UFPs [109]. The comparable effects across different UFP metrics modes in our research suggest that the particles' chemical composition might be an additional important factor. However, the strong correlations among the four UFP metrics limited our ability to discern the distinct characteristics of each, and the absence of data on particle chemical composition further constrained our investigation into differences in toxicity and underlying mechanisms linking UFPs to stroke. Specifically, we noted the largest estimate in the ultrafine defined modes (10-100 nm), while particles in the Aitken mode (30-100 nm) might have a more consistent effect than particles in the nucleation mode (10-30 nm). The observed variations in UFP effects across different size fractions may be attributed to their aerodynamic properties, particularly the diffusion losses of smaller particles (<30 nm) during measurement, as well as variations in particle-size distributions [33]. Given the daily fluctuations in particle concentrations driven by traffic peaks and variability in emission sources across regions, it would be highly beneficial to expand the coverage of real-time UFP monitoring stations to improve spatial and temporal resolution and to develop advanced prediction models with enhanced accuracy to better capture fine-scale variability in UFP concentrations.

Being inconsistent with the more pronounced effects of routinely monitored air pollutants on TIAs and hemorrhagic strokes observed in Paper I, the subgroups of patients with ischemic strokes were prone to be impacted by UFP exposures. This might be explained by that UFPs can deeply penetrate the lungs, enter the bloodstream, and promote atherosclerosis by triggering vascular inflammation owing to their small size and large surface area [18]. Compared to $PM_{2.5}$, UFPs can thus trigger stronger and broader neuroinflammation, involving greater activations of immune markers, inflammasome components, cytokines, and chemokines, and especially cause mitochondrial dysfunction and lipid metabolism impairment [34]. Additionally, their distinctive small size allows them to traverse alveolar epithelial barriers and directly access the central nervous system through the olfactory bulb, leading to neuroinflammation [18, 110].

The greater vulnerability to UFPs in less severe stroke cases may reflect a ceiling effect in advanced disease and the preferential targeting of early inflammatory and endothelial pathways by UFPs during early-stage atherosclerosis [111, 112]. Additionally, the amplified detrimental health effects of UFPs may be related to higher vehicle emissions [113], enhanced particle formation[114], and limited atmospheric dispersion on days with low air temperatures [115], especially at night when stable air layers trap pollutants near their sources. These findings underscore the importance of considering disease stages and air temperatures when evaluating the health impacts of UFP exposure.

5.4 Strengths and limitations

The following section briefly summarizes some of the major strengths and their respective limitations. There is a detailed discussion of the strengths and limitations in each paper.

There are several key strengths of these three papers. Paper I utilized the standardized and comprehensive data from the well-established KORA-Fit cohort study. Utilizing various self-assessed health tools enabled a thorough and multi-dimensional evaluation of the impact of air pollution on both physical and psychosocial health aspects. In papers II and III, the validated stroke hospital admission data from the University Hospital Augsburg over 15 years enhanced the reliability of our findings. Moreover, the time-stratified case-crossover study design automatically adjusted for fixed individual-level factors and minimized the bias from seasonal and temporal time trends. Additionally, including both routinely monitored air pollutants and UFPs allowed for evaluation of potential variations in pollutant sources and aerosol characteristics. Specifically, there has been no study examining the effects of four UFP metrics in four size fractions on stroke events until Paper III.

However, certain limitations across the three publications need to be acknowledged. In Paper I, the validation of spatial variations in pollutant exposure was not feasible due to the temporal mismatch between the exposure (2014–2015) and the outcome (2018–2019) assessments. In papers II and III, reliance on fixed-station air pollution data restricted the capacity to consider the spatial variability within the city and individual movement patterns. As well, misclassification of stroke cases was unavoidable, and the less reliable diagnosis of TIAs may have attenuated the observed associations. Finally, the generalizability of this dissertation was limited by the single-center observational design (cross-sectional or case-crossover study).

6. Conclusions and Outlook

In summary, this dissertation provides evidence that elevated ambient air pollution could exert detrimental effects on self-perceived health and objectively diagnosed stroke events. Prolonged exposure to outdoor air pollution can influence how a person views their health and overall quality of life, which can be captured using various instruments from functional, psychological, and social viewpoints. Specifically, EQ-VAS and SRH may be more sensitive in assessing early or subtle effects of air pollution on general health status. Notably, individuals with a lower BMI and those who perceive stress as high may have a poorer self-perception of health when exposed to long-term air pollution. These results provided an understanding of the disease burden related to the cumulative exposure to air pollution from the viewpoint of the patient, and emphasized the additional importance of subjective health assessments alongside objective clinical results.

This dissertation also demonstrates the association between short-term exposure to routinely monitored ambient air pollution with elevated stroke risk, with greater susceptibility observed among patients with TIAs and hemorrhagic strokes. Stroke cases linked to PM exposure tended to result in more severe disabilities, whereas those associated with gaseous pollutants were more likely to present with milder impairments. The adverse association between air pollution and stroke risk appeared to be intensified during warmer seasons and in the most recent five-year period. These findings highlighted the need for more individualized prevention strategies, enhanced air quality monitoring, and climate-adaptive health policies within stroke prevention frameworks.

The four distinct UFP metrics were first found to exhibit comparable detrimental associations with stroke risk, with more consistent effect estimates observed in the 10–100 nm and 30–100 nm size ranges. Ischemic stroke patients and those experiencing minor strokes with a lower severity appeared more vulnerable to transient UFP exposure. Besides, extremely low air temperatures and cold spells may exacerbate the adverse health effects of UFPs. This means that expanding size-segregated real-time UFP monitoring and adopting stricter regulatory policies across different UFP metrics may help in alleviating the stroke burden, especially among more vulnerable individuals with pre-existing risk factors of ischemic strokes and during cold spells with extremely low air temperatures.

We have to acknowledge that the observational study data (cross-sectional and case crossover) from the exclusively German-based participants and the fixed monitoring air pollution data will limit the generalizability of our findings. Therefore, we suggest that additional research utilizing data from multiple centers, which encompass diverse study populations and various sources of air pollutants, should be conducted to further validate the harmful effects of air pollution on both subjective and objective health outcomes. Furthermore, this dissertation observed the temporal trend that the detrimental health effects of air pollution exposure have not decreased but have even increased, despite the air pollution levels having substantially declined across years. We suggested that stricter air quality regulations and focused policy measures are essential to alleviate the health impact associated with air pollution. Finally, the WHO has not yet established specific AQGs for UFPs because of a lack of clear evidence owing to their variations in particle metrics, size fractions, chemical compositions, and even exposure settings. It is therefore urgent to implement the “Good Practice Statements” for UFPs across the world, such as improving quantification, expanding monitoring networks, differentiating concentration levels, and developing standardized assessment methods, particularly in urban areas with substantial vehicle/traffic emissions, thereby providing more consolidated evidence for the re-evaluation and establishment of international limits of UFPs.

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Paper I

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Long-term associations between ambient air pollution and self-perceived health status: Results from the population-based KORA-Fit study

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A R T I C L E I N F O

Keywords:
Ambient air pollution
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A B S T R A C T

Background: Little is known about the association between air pollution and self-perceived health (including both health-related quality of life [HRQoL] and self-rated health [SRH]). The aim of this study was therefore to explore whether long-term air pollution exposure is associated with worse self-perceived health, as measured by different tools.

Methods: We used a land-use regression model to determine the annual average levels of particulate matter with a diameter <10 μm (PM_{10}), coarse particles (PM_{coarse}), fine particles ($PM_{2.5}$), fine particle absorbances ($PM_{2.5abs}$), particle number concentration (PNC), ozone (O_3), nitrogen dioxide (NO_2), and nitrogen oxide (NO_X) for geo-coded residential addresses (2014–2015). Questionnaires and face-to-face interviews were used to collect HRQoL (measured using the European Quality of Life 5 Dimensions [EQ-5D] index and the European Quality of Life Visual Analogue Scale [EQ-VAS]) and SRH indicators (measured through two survey questions) (2018–2019) from participants of the Cooperative Health Research in the Region of Augsburg (KORA)-Fit study in Germany. We explored associations via generalized additive models, multinomial logistic regression, and logistic regression.

Results: We included 2610 participants with a mean age of 64.0 years in this cross-sectional study, of which 1428 (54.7%) were female. Each interquartile range (IQR) increase in O_3 was associated with a reduced EQ-5D index value (% change of mean points and 95% confidence interval: -0.91% [-1.76; -0.06]). The average EQ-VAS score declined between -1.57% and -0.96% with each IQR increase in PM_{10}, PM_{coarse}, $PM_{2.5abs}$, PNC, NO_2, and NO_X. These pollutants were associated with increased occurrence of poor SRH, with odds ratios ranging from 1.24 to 2.67. $PM_{2.5abs}$ was linked to a higher likelihood of reporting a worse comparative SRH (2.59 [1.12; 5.99]). Body mass index and self-perceived stress modified these associations.

Conclusions: Long-term air pollution exposure was associated with poor self-perceived health, presenting as lower HRQoL and higher odds of poor SRH. Single-item indicators measuring self-perceived health status may work better than multi-dimensional indicators.

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1. Introduction

Increasing epidemiological evidence suggests that exposure to airborne particulate matter (PM) or gaseous air pollutants affects nearly all human body organ systems (Thurston et al., 2017). Exposure to ambient PM pollution was one of the top three risk factors accounting for more than 1% of global disability-adjusted life-years in 2019 (GBD, 2019), and between 1990 and 2019, the number of global deaths and disability-adjusted life-years attributable to exposure to ambient PM with a diameter <2.5 μm ($PM_{2.5}$) have increased by 102.3% and 67.7%, respectively (Sang et al., 2022). According to the State of Global Air (2024), air pollution accounted for 8.1 million premature deaths worldwide in 2021, including 48% of global deaths from chronic obstructive pulmonary disease, 28% from ischemic heart disease, and 27% from stroke (Health Effects Institute, 2024). Air pollution, however, may also affect health without directly manifesting as morbidity or mortality, instead resulting in feelings of malaise and a lower self-perceived health status. Within the body, air pollution may adversely affect health due to oxidative stress, inflammation, dysregulation of the nervous system, and direct particle transfer into organ systems (de Bont et al., 2022). When exposed to air pollution, people may perceive an increase in headaches, dizziness, nausea, feeling ill, and higher perceived psychological stress (Trushna et al., 2021; Zhao et al., 2018). Even though there is a growing body of evidence supporting the adverse health effects of air pollution, most studies are focused on "objective" measures of health status, leaving a gap in the research using "subjective" measures.

"Self-perceived health status" may include a wide range of constructs representing different aspects of subjective overall health. Both health-related quality of life (HRQoL) and the general concept of self-rated health (SRH) are useful as they can capture a comprehensive summary of health problems that may not be detected by standard medical screening procedures (Anillo Arrieta et al., 2021; Ko and Boo, 2016; Phyo et al., 2021). HRQoL is a multidimensional concept that focuses on subjective overall well-being in the physical, mental, and social domains of life (EuroQol-Group, 2023). One of the most commonly used measures of HRQoL is the standardized European Quality of Life 5 Dimensions questionnaire (EQ-5D), which is appropriate for evaluating quality of life among the general population (EuroQol-Group, 2023) and among patients in healthcare settings (AlSaeed et al., 2022; Chase et al., 2022; Guillaumier et al., 2022; Mueller et al., 2021; Munyombwe et al., 2021). HRQoL can also be assessed as "health utility," defined as a person's preference for their overall health state, by transferring the EQ-5D into an index value (EuroQol-Group, 2023). SRH can be assessed using the European Quality of Life Visual Analogue Scale (EQ-VAS), and a general assessment of SRH and age-comparative SRH (CSRH) which are gathered using categorical questions (Huohvanainen et al., 2016). SRH and CSRH are well-established predictors of mortality (Jylhä, 2009) and chronic or severe diseases and can be used to provide a subjective assessment of individual current physical and mental health (Huohvanainen et al., 2016; van de Weijer et al., 2022).

A growing number of epidemiological studies have linked air pollution to worse self-perceived health status. Air pollution effects on HRQoL and/or SRH have been reported in China (Tan et al., 2023), Korea (Shin et al., 2018), Japan (Yamazaki et al., 2005), Netherlands (Klompmaker et al., 2019), Belgium (Hautekiet et al., 2022), Spain (Moitra et al., 2022), and across Europe (Boudier et al., 2022). In most of these studies, however, the constructs of self-perceived health status varied across studies, and only one or two specific outcomes were generally evaluated in each study. Furthermore, no literature exists on the association between air pollution exposure and SRH measured using the EQ-VAS. Without a study that collects HRQoL, SRH, and CSRH at the same time, it is difficult to identify the most relevant self-perceived health measure for analyzing the effect of air pollution effects on general health status.

Previous studies have demonstrated that air pollution effects on health are modified by various biological or social dimensions such as age, sex/gender, and socioeconomic position (Hooper and Kaufman, 2018). The modification of air pollution on self-perceived health remains inconclusive as one study found more pronounced effect estimates in those with a higher socioeconomic level (educational background, income level, and neighborhood) (Tan et al., 2023), while another study indicated that air pollution exerted a larger effect on poor SRH in participants who had lower education, who were experiencing financial difficulties, or who lived in lower-income areas (Dzhambov et al., 2023). Moreover, a previous study suggested that the effects of air pollution on quality of life or SRH were stronger for men or those younger than 65 years (Shin et al., 2018). The effect of air pollution on poor SRH was found to be modified by residential surrounding greenness in Netherlands (Klompmaker et al., 2019). Aside from the objective measures of air quality, neighborhood reputation, the level of individual knowledge and prior experiences suffering from air pollution are unobserved latent variables that affect health risk perception, the psychosocial determinants of health (Borbet et al., 2018; Cori et al., 2020; King, 2015).

Using various measurement tools, our study's objective was to explore the associations between long-term air pollution and self-perceived health status and identify which population groups are most susceptible to the effects of air pollution.

2. Materials and methods

2.1. Study design and population

This study used data from the Cooperative Health Research in the Region of Augsburg (KORA) cohort, implemented in Augsburg and two adjacent districts in southern Germany since 1984 (Holle et al., 2005). Since the start of the study, four cross-sectional surveys have been conducted at 5-year intervals: S1 (1984–1985), S2 (1989/1990), S3 (1994–1995), and S4 (1999–2000). In 2018/2019, the follow-up study KORA-Fit took place, for which all participants of the four surveys aged 54–75 years were invited to participate. After excluding those who were unable to participate, 3059 participants (64.6% of the net sample) finished a standardized interview and completed a questionnaire in the study centre. For the present analysis, we only analyzed KORA-Fit participants who were also participants in another subgroup study, Integrating Gender into Environmental Health Research (INGER). In the INGER project, sex/gender themes were integrated into environmental health research through a newly developed questionnaire, which combined biological and social information about gender/sex, as well as environmental information about green spaces (Kraus et al., 2023). All study methods were approved by the ethics board of the Bavarian Chamber of Physicians (KORA-Fit EC No.17040) in adherence to the declaration of Helsinki. All study participants gave written informed consent before the survey.

2.2. Assessment of outcomes, exposures, and covariates

2.2.1. Health-related quality of life

HRQoL is often measured using standardized questionnaires (Karimi and Brazier, 2016). Being one of the most widely used generic questionnaires, the EQ-5D includes two parts: the descriptive system covers the five domains of mobility, self-care, usual activities, pain/discomfort, and anxiety/depression, and the visual analogue scale, EQ-VAS (EuroQol-Office, 2023). We used the five-level version of EQ-5D (EQ-5D-5L) to determine the current HRQoL of individuals who participated in KORA-Fit in 2018–2019. Each dimension has five response levels (1–5 points), which were labeled "1 = no problems", "2 = slight problems", "3 = moderate problems", "4 = severe problems", and "5 = unable or extreme problems".

The EQ-5D can be transformed into an index value (EQ-5D index value) using the aggregated German preferences developed by Ludwig et al. (Ludwig et al., 2018). Because these preferences emerged from composite time-trade-off and discrete choice experimental data from a population-based German adult sample, the score could also be seen as an economic concept "health utility" and can therefore differ between countries/regions (EuroQol-Office, 2023). In our study, the EQ-5D index values ranged from -0.13 to 1.00, with a value below 0 equivalent to a health state "worse than death", a value of 0 equalling death, and a value of 1 corresponding to perfect or full health. We also dichotomized the 5-point scales of each EQ-5D dimension as a binary variable by considering the original response 1 as "0 = have no problems" and combining responses 2–5 as "1 = any problems".

2.2.2. Self-rated health

The general concept of SRH was measured via the EQ-VAS as part of the EQ-5D (EuroQol-Office, 2023). It is a vertical analogue scale with a range from 0 (the worst health you can imagine) to 100 (the best health you can imagine) and was used to directly assess participants' current overall health status on the day of questionnaire completion. We also evaluated the general concept of self-rated health by asking the question, "How would you rate your current physical condition?". Answers were given on a 4-point Likert scale (1 = very good, 2 = good, 3 = less good, 4 = poor), and then these variables were dichotomized as "good SRH" (including the responses "very good" and "good") and "poor SRH" (including the responses "less good" and "poor"). When we use the abbreviation term "SRH" below to refer to our outcome, we are referring to this binary variable. CSRH was measured by asking the question, "How would you rate your health compared to other people of your age?", with the three answer possibilities being "better", "equal", and "worse". An overview of the recoding of outcome variables can be found in the supplementary data (Table S1).

2.2.3. Air pollution

Air pollutants at the residential addresses of participants were estimated via land-use regression models with 50 × 50 m spatial resolution from March 2014 and April 2015, mainly following the standardized approach developed by the European Study of Cohorts for Air Pollution Effects (ESCAPE) project (Beelen et al., 2013; Eeftens et al., 2012). The details of the process have been previously reported (Wolf et al., 2017). Briefly, three bi-weekly measurements were taken in different seasons (warm, cold, and intermediate seasons) at 20 sites within the KORA study area, involving twelve sites located within the city of Augsburg and eight in the two adjacent districts of Augsburg and Aichach-Friedberg. Throughout the whole study period, measurements were additionally carried out at an urban background site as a reference to adjust for temporal variations. Linear regression models were used to calculate the annual mean concentration at the monitoring stations using potential spatial predictor variables, including local land use, traffic network, altitude, population, building density, and household density. Based on participants' home addresses, we calculated the residential annual average concentrations of air pollutants including particle number concentration (PNC) as an indicator for ultrafine particles (UFP), PM in aerodynamic diameter <10 μm (PM_{10}), <2.5 μm ($PM_{2.5}$), between 2.5 μm and 10 μm (PM_{coarse}), soot ($PM_{2.5absorbance}$; a proxy of elemental carbon related to traffic exhaust), ozone (O_3), nitrogen dioxide (NO_2) and nitrogen oxides (NO_X). The performance of the land-use regression model was validated by leave-one-out cross-validation and the adjusted model explained variance (R^2) ranged from 0.68 to 0.94, suggesting a good model fit (Wolf et al., 2017).

2.2.4. Covariates

For our analysis, we operationalized sex dichotomously with the categories "female" and "male" without further distinguishing between biological sex and socially constructed gender identity. Participants indicated their sex through self-report. Other demographic and social characteristics (age, living with a partner, pension, individual socioeconomic status [SES], self-perception of residential greenness) were obtained via a face-to-face interview. SES was calculated based on a system developed by Mielck A (Mielck, 2000) from the three characteristics, including the level of education, employment status, and individual income, with higher values indicating a higher socioeconomic level. We also collected data about lifestyle-related behavior, including physical activity, alcohol consumption, and smoking status. Self-efficacy, or one's ability to plan and execute actions effectively and successfully, was assessed using the general self-efficacy short scale via a self-administered questionnaire (Beierlein et al., 2013). Participants were also invited to complete the 10-item perceived stress scale, which aimed to rate their subjective perception of stress, with a higher score indicating greater perceived stress (Cohen et al., 1983).

Physical examinations were carried out to obtain anthropometric data, including height, weight, waist circumstance, and hip circumstance. These measurements were used to calculate body mass index (BMI, kg/m^2) and waist-to-hip ratio. Residential greenness was assessed using two variables related to greenness: self-perception of residential greenness and normalized difference vegetation index (NDVI). Self-perception of residential greenness was estimated by asking participants how green their neighborhood is in terms of every type of green space (from green strips along the street to gardens and parks). Answers included "very green", "a little green", "hardly green", and "not green at all". Due to the small sample size, the last three answers were combined and grouped under "hardly green". According to our previous study, the NDVI within a 300m buffer of participant residential addresses was calculated using the cloud-free Sentinel-2 satellite images, with a resolution of 10 m (Niedermayer et al., 2024). Each NDVI map of the Augsburg area was built with two pictures, and the negative pixels of the NDVI map were excluded before assignment to home addresses (Niedermayer et al., 2024). We used the mean NDVI data between the years 2018 and 2019 to match the KORA-Fit data.

2.3. Statistical analyses

2.3.1. Regression models

Participants with missing data on any outcome variable were excluded from analysis. Generalized additive models with fixed effects were used to test for associations between each individual air pollutant and EQ-5D index values and EQ-VAS scores. Binary logistic regression was used to assess whether each individual air pollutant was associated with the odds of reporting poor SRH as compared to good SRH. Multinomial logistic regression was used to measure whether each individual air pollutant was associated with the likelihood of reporting equal or worse CSRH, as compared to better CRSH. We also examined the associations between air pollution exposures and the five dichotomized dimensions of EQ-5D using binary logistic regression. We were able to generate reliable coefficient estimations using maximum likelihood estimation based on the asymptotic properties of logistic regression with a large sample size. By doing this, small-sample biases are alleviated, and robust results are ensured.

Potential covariates were identified based on the disjunctive cause criterion (VanderWeele, 2019) and the guidance of the World Health Organization (WHO, 2020). Starting with the full list of potential covariates, we used a stepwise forward regression method reducing the Bayesian Information Criterion to select our final list of covariates separately for each outcome variable. First, we included sex and age in the minimum model. Next, we included SES, additional socioeconomic variables, lifestyle variables, and BMI for selection. Based on the results of this selection process, we included all confounders separately selected for each outcome variable into one main model containing age, sex, SES, living with a partner, BMI, physical activity, and smoking status. Apart from the covariates in the main model, extended model 1 was further adjusted for the percentage of households with low income (<1250 euro) and degree of urbanization, and extended model 2 for self-efficacy and perceived stress, to control potential confounding.

Effect estimates are expressed as the percentage changes (% change) of the mean of continuous outcomes (EQ-5D index value and EQ-VAS) or the absolute change of EQ-VAS only, and odds ratios (ORs) for categorical outcomes (SRH, CSRH, and five dichotomized dimensions of EQ-5D) together with their 95% confidence intervals (CIs) per interquartile range (IQR) increase in air pollutant concentration. A positive "% change" indicates that a participant perceives their health status to be better, whereas a higher OR value means a person perceives their health status to be worse.

2.3.2. Sensitivity analyses and effect modification

As sensitivity analysis, in order to further identify the potential bias introduced by confounders and colliders, we firstly drew the Directed Acyclic Graphs (DAGs) using the web-version of program "DAGitty" (http://www.dagitty.net/) (Niedermayer et al., 2024). We developed another main adjustment model to test the robustness of our results. Secondly, regarding the continuous outcomes (EQ-5D index value and EQ-VAS), we tested the regression models for potential heteroscedasticity using the "glam" R package including a single global test to assess the linear model assumptions, and the results indicated that the assumptions of homoscedasticity were acceptable. Thirdly, we tested the linearity of the exposure-response relationship for these two continuous outcomes by including air pollutant concentrations as penalized splines into generalized additive models using the "mgcv" R package. In testing for multicollinearity, we found that all models had variance inflation factors less than 2. Fourthly, we further tested the robustness of our results by conducting two-pollutant models for all pollutant pairs for which Spearman's correlation coefficient was less than 0.7, the threshold for high correlation (U.S. EPA, 2019). Finally, we additionally included the "residential duration" in the adjustment model to account for the potential movement of addresses.

By adding an interaction term to the main model, we then investigated the effect modification of variables that have been categorized: sex (female, male), age (<65.0 years, ≥65.0 years), BMI (<30.0 kg/m^2, ≥30.0 kg/m^2), self-perception of residential greenness (very green, hardly green), SES tertiles (1.0–12.0 points, ≥12.0–16.5 points, ≥16.5 points), and three continuous variables, including NDVI (<0.43, ≥0.43), self-efficacy score (<4.02, ≥4.02) and perceived stress scale score (<13.59, ≥13.59), which were dichotomized using their mean values as the threshold. All statistical analyses were performed using R software (version 3.6.2), with a two-tailed *P*-value of <0.05 being considered statistically significant.

3. Results

3.1. Baseline characteristics

Of 3743 eligible participants of both the KORA-Fit and INGER studies, we included 2610 subjects who completed the standardized interview and the questionnaire (Fig. S1). As shown in Table 1, participants had a mean age of 64.0 years at the time of the survey and 1428 (54.7%) were females. 2066 (79.8%) participants lived with a partner. The mean values of BMI and SES at study entry were 28.0 kg/m^2 and 14.9 points, respectively. The baseline characteristics of participants varied widely across EQ-5D index value and SRH groups. In general, participants with a higher EQ-5D index value or who reported good SRH were younger, were more likely to be male, be non-smokers, be physically active, live in a very green environment, have a higher level of SES, have higher self-efficacy, consume more alcohol, have a lower BMI, and have lower perceived stress than participants with a lower EQ-5D index value or with poor SRH.

3.2. Outcomes and exposures

Table 2 shows that the mean levels for the EQ-5D index value and EQ-VAS were 0.9 ± 0.1 and 79.2 ± 14.7, respectively. Most participants reported having at least slight problems in the dimension of pain/discomfort (62.0%). 16.7% of participants reported poor SRH and 8.3% reported worse CSRH. A moderate positive correlation was found between the EQ-5D index value and the EQ-VAS (Spearman correlation coefficient *rho* = 0.5), and a weak positive correlation was found between SRH and CSRH (Kendall correlation coefficient *tau* = 0.3). As higher SRH and CSRH values were coded as meaning worse health, we observed a moderate negative correlation between SRH and both the EQ-5D index value and the EQ-VAS (both *rho* and *tau* were -0.4) and a weak negative correlation between CSRH with HRQoL measures (coefficients were -0.3 and -0.4). As for different dimensions of EQ-5D-5L, both the EQ-5D index value and the EQ-VAS score had weak to moderate negative correlations with the five EQ-5D dimensions, aside from a strong negative correlation between EQ-5D index value and "pain/discomfort" (*tau* = -0.7). SRH and CSRH only had weak positive correlations with the five dimensions since higher codes indicate having problems in the five dimensions (Table 2).

Descriptive statistics of average annual air pollution concentrations are displayed in Table 3. During the study period, the annual average levels of $PM_{2.5}$, PM_{10}, and NO_2 were within the European Union air quality standard limits ($PM_{2.5}$: 25 μg/m^3; PM_{10} and NO_2: 40 μg/m^3) but exceeded the air quality guidelines set by the WHO ($PM_{2.5}$: 5 μg/m^3; PM_{10} and NO_2: 10 μg/m^3). Most air pollutants were moderately to strongly positively correlated with each other, with the highest correlation being found for NOx and PNC (*rho* = 0.9). O_3 was weakly positively correlated with PM_{10} (*rho* = 0.1) and PM_{coarse} (*rho* = 0.2), but negatively correlated with $PM_{2.5}$, $PM_{2.5abs}$, PNC, NO_2, and NOx (*rho* ranged from -0.2 to -0.1).

3.3. Regression results

3.3.1. Health-related quality of life

Regression results for the EQ-5D index value and EQ-VAS are shown in Fig. 1 and Table S2 (supplementary materials). In the main model, we found adverse associations between the EQ-5D index value and most air pollutants, particularly for O_3 (% change: -0.91% [95% CI: -1.76; -0.06]). After adjustment for additional covariates, associations were strengthened for O_3 in extended model 1 and for $PM_{2.5abs}$ in extended model 2 (Fig. S2). We found that each IQR increase in air pollutant concentration was associated with decreased EQ-VAS for PM_{10} (-1.38% [-2.37; -0.38]), PM_{coarse} (-1.25% [-2.28; -0.23]), $PM_{2.5abs}$ (-1.57% [-2.69; -0.45]), PNC (-0.89% [-1.68; -0.10]), NO_2 (-1.30% [-2.36; -0.23]), and NO_X (-0.96% [-1.83; -0.10]). Most of these associations were attenuated in extended model 1 but remained robust in extended model 2 (Fig. S2). Details of the absolute changes in EQ-VAS are available in Table S3.

In our analysis of dichotomized EQ-5D-5L dimensions, the dimension "usual activities" had the strongest associations with increasing air pollution, though not all associations were statistically significant (Table S4, Fig. S3). Participants had higher odds of reporting difficulties in their usual activities when exposed to higher concentrations of PM_{10} (OR: 3.46 [95% CI: 1.32; 9.10]), $PM_{2.5abs}$ (1.65 [0.96; 2.84], PNC (1.53 [1.07; 2.19]), and NO_X (1.31 [0.98; 1.75]). Those exposed to higher levels of $PM_{2.5abs}$ had higher odds of reporting pain/discomfort, and those exposed to higher levels of $PM_{2.5}$ had higher odds of reporting difficulties with self-care. For the other two dimensions, we observed only some null tendencies towards increased odds of having problems.

3.3.2. Self-rated health

The long-term effects of air pollution on poor SRH are presented in Fig. 2 and Table S5. In the main model, we consistently observed increased odds of reporting poor SRH with increased exposure to PM_{10} (2.67 [1.07; 6.67]), PM_{coarse} (1.70 [1.14; 2.54]), $PM_{2.5abs}$ (1.60 [0.96; 2.67]), PNC (1.42 [1.01; 1.99]), NO_2 (1.24 [0.98; 1.58]) and NO_X (1.36 [1.04; 1.79]). Aside from PM_{coarse} and O_3, most of these associations slightly decreased in the extended model 1, with the extended model 2 similarly leading to lower estimates (Fig. S4).

Table 1
Descriptive analysis of KORA-Fit & INGER studies (N = 2610).

	Missing (%)	Overall	EQ-5D index value[a]			SRH[b]		
			Low (n = 806)	High (n = 1804)	*P*-value[c]	Poor (n = 437)	Good (n = 2173)	*P*-value[c]
			Mean ± SD/No. (%)	Mean ± SD/No. (%)		Mean ± SD/No. (%)	Mean ± SD/No. (%)	
Age, years	0 (0.0)	64.0 ± 5.4	64.3 ± 5.4	63.8 ± 5.5	**0.047**	63.9 ± 5.4	64.0 ± 5.5	0.881
	0 (0.0)				**<0.001**			**0.002**
Sex								
Female		1428 (54.7)	508 (63.0)	920 (51.0)		269 (61.6)	1159 (53.3)	
Male		1182 (45.3)	298 (37.0)	884 (49.0)		168 (38.4)	1014 (46.7)	
Living with a partner	0 (0.0)				**<0.001**			**<0.001**
Yes		2066 (79.2)	576 (71.5)	1490 (82.6)		311 (71.2)	1755 (80.8)	
No		544 (20.8)	230 (28.5)	314 (17.4)		126 (28.8)	418 (19.2)	
Pension	1 (0.0)				**<0.001**			**<0.001**
Yes		136 (5.2)	85 (10.6)	51 (2.8)		54 (12.4)	82 (3.8)	
No		2473 (94.8)	720 (89.4)	1753 (97.2)		383 (87.6)	2090 (96.2)	
Residential durations, years	0 (0.0)	19.1 ± 9.7	19.0 ± 9.8	19.1 ± 9.7	0.746	19.1 ± 9.7	19.1 ± 9.7	0.997
	9 (0.3)	14.9 ± 5.0	13.9 ± 4.7	15.3 ± 5.1	**<0.001**	13.7 ± 4.7	15.1 ± 5.0	**<0.001**
SES								
	9 (0.3)				**<0.001**			**0.001**
SES (tertiles)								
1.0–12.0		664 (25.5)	248 (31.0)	416 (23.1)		139 (32.0)	525 (24.2)	
≥12.0–16.5		1048 (40.3)	344 (43.0)	704 (39.1)		178 (40.9)	870 (40.2)	
≥16.5		889 (34.2)	209 (26.1)	680 (37.8)		118 (27.1)	771 (35.6)	
Self-perception of residential greenness	0 (0.0)				**<0.001**			**0.001**
Very green		2062 (79.5)	598 (74.7)	1464 (81.7)		320 (73.6)	1742 (80.7)	
Hardly green		532 (20.5)	203 (25.3)	329 (18.4)		115 (26.4)	417 (19.3)	
NDVI	1 (0.0)	0.4 ± 0.1	0.4 ± 0.1	0.4 ± 0.1	**0.022**	0.4 ± 0.1	0.4 ± 0.1	0.055
	0 (0.0)				**<0.001**			**<0.001**
Physical activity								
Very active		1017 (39.0)	256 (31.8)	761 (42.2)		105 (24.0)	912 (42.0)	
Moderately active		885 (33.9)	271 (33.6)	614 (34.0)		143 (32.7)	742 (34.2)	
Little active		320 (12.3)	115 (14.3)	205 (11.4)		70 (16.0)	250 (11.5)	
Inactive		388 (14.9)	164 (20.4)	224 (12.4)		119 (27.2)	269 (12.4)	
Alcohol consumption, g/day	1 (0.0)	14.8 ± 19.6	12.9 ± 19.0	15.6 ± 19.8	**0.001**	12.9 ± 20.0	15.1 ± 19.5	**0.030**
	1 (0.0)				**<0.001**			**0.003**
Alcohol consumption (category, g/day)								
None		675 (25.9)	258 (32.1)	417 (23.1)		141 (32.3)	534 (24.6)	
≥0-40		1261 (48.3)	463 (57.5)	1158 (64.2)		254 (58.1)	1367 (62.9)	
≥40-80		280 (10.7)	73 (9.1)	207 (11.5)		34 (7.8)	246 (11.3)	
≥80		33 (1.3)	11 (1.4)	22 (1.2)		8 (1.8)	25 (1.2)	
Smoking status	4 (0.2)				0.057			**0.007**
Non-smoker		1186 (45.4)	349 (43.5)	837 (46.4)		175 (40.1)	1011 (46.6)	
Ex-smokers		1075 (41.2)	329 (41.0)	746 (41.4)		186 (42.7)	889 (41.0)	
Current smokers		345 (13.2)	125 (15.6)	220 (12.2)		75 (17.2)	270 (12.4)	
BMI, kg/m^2	0 (0.0)	28.0 ± 5.2	29.2 ± 6.1	27.5 ± 4.7	**<0.001**	30.0 ± 6.3	27.6 ± 4.9	**<0.001**
	0 (0.0)	0.9 ± 0.1	0.9 ± 0.1	0.9 ± 0.1	0.861	0.9 ± 0.1	0.9 ± 0.1	**0.012**
Waist-Hip-Ratio								
	75 (2.9)	4.0 ± 0.6	3.9 ± 0.6	4.1 ± 0.5	**<0.001**	3.86 ± 0.7	4.1 ± 0.6	**<0.001**
Self-efficacy								
	124 (4.8)	14.3 ± 5.6	17.0 ± 5.8	13.1 ± 5.0	**<0.001**	18.0 ± 6.0	13.5 ± 5.2	**<0.001**
Perceived stress								

Abbreviations: EQ-5D-5L, European Quality of Life 5-dimensional questionnaire; EQ-5D index, index of EQ-5D-5L questionnaire; EQ-VAS, EuroQol group's visual analog scale; SRH, self-rated health; CSRH, comparative self-rated health; NDVI, normalized difference vegetation index; BMI, body mass index; SES, socioeconomic status; Self-efficacy, General Self-Efficacy Short Scale; Perceived stress, Perceived stress scale.
Note: Continuous variables are presented as means ± standard deviations (SDs), as well as their ranges (minimum, maximal), and categorical variables are presented as total numbers (percentages).
[a] Population was divided into groups according to the mean value of the EQ-5D index value (cutoff value = 0.90).
[b] Population was divided into groups according to the recorded SRH (poor/good).
[c] *P*-value was calculated by using the Kruskal-Wallis test or the Chi-square test.

Table 2
Results of correlation analysis for outcomes of interest.

	Missing (%)	Mean (SD)/n (%)	Correlation coefficients			
			EQ-5D index value	EQ-VAS	SRH	CSRH
EQ-5D index value	0 (0.0)	0.9 ± 0.1	1.0	–	–	–
EQ-VAS	0 (0.0)	79.2 ± 14.7	0.5[a,d]	1.0	–	–
SRH	0 (0.0)	–	−0.4[b,d]	−0.4[b,d]	1.0	–
Good	–	2173 (83.3)	–	–	–	–
Poor	–	437 (16.7)	–	–	–	–
CSRH	42 (1.6)	–	−0.3[b,d]	−0.4[b,d]	0.3[b,d]	1.0
Better	–	1287 (50.1)	–	–	–	–
Equal	–	1069 (41.6)	–	–	–	–
Worse	–	212 (8.3)	–	–	–	–
EQ-5D-5L Dimension (dichotomized)	0 (0.0)	–	–	–	–	–
Mobility, yes%	–	727 (27.9)	−0.5[b,d]	−0.3[b,c]	0.4[b,d]	0.3[b,d]
Self-care, yes%	–	85 (3.3)	−0.2[b]	−0.2[b]	0.3[b,d]	0.2[b]
Usual activities, yes%	–	366 (14.0)	−0.5[b]	−0.3[b]	0.4[b,d]	0.3[b]
Pain/ discomfort, yes %	–	1617 (62.0)	−0.7[b,d]	−0.4[b,d]	0.3[b,c]	0.2[b,c]
Anxiety/ depression, yes %	–	709 (27.2)	−0.4[b,c]	−0.3[b]	0.3[b,c]	0.2[b]

Abbreviations: SD, standard deviation; EQ-5D index value, the index of European Quality of Life 5-dimensional questionnaire; EQ-VAS, EuroQol group's visual analog scale; SRH, self-rated health; CSRH, comparative self-rated health.
Note.
[a] The correlation coefficients (*rho*) were calculated by Spearman correlation analysis.
[b] The correlation coefficients (*tau*) were calculated by Kendall correlation analysis.
[c] $P < 0.10$.
[d] $P < 0.05$.

In the case of CSRH, we found a tendency for decreased odds of equal CSRH when compared with better CSRH with increasing exposure to air pollution (Fig. 3, Fig. S5, Table S6). We also generally found increasing odds of worse CSRH compared to better CSRH with increasing exposure to air pollution, but there was no consistent pattern across pollutants. Each IQR increase in $PM_{2.5abs}$ was associated with increased odds of reporting worse CSRH (2.59 [1.12; 5.99]), with similar trends being found for PM_{coarse}, $PM_{2.5}$, and NO_2. All these effects were attenuated in the two extended models (Figs. S6–S7).

3.4. *Sensitivity analyses*

Given that the DAG plot (Fig. S8) shows that BMI and physical activity might be theoretical mediators in the causal pathway, we updated the main adjustment model excluding these two variables. However, as it is shown in Table S7 and Figs S9 – S12, the exclusion did not greatly alter the estimated effects. This supports the robustness of our findings regardless of the inclusion of physical activity and BMI, reducing concerns about over-adjustment. Figs. S13 and S14 show the exposure-response relationships of two continuous outcomes (EQ-5D index value and EQ-VAS) with the different air pollutants. Overall, most associations exhibited a generally linear trend, though associations between $PM_{2.5}$ and O_3 and the EQ-5D index showed several fluctuations. In two-pollutant models, most associations were consistent with those of the main analysis (Table S8). Further adjustments to the residential duration did not cause great changes in our results (Table S9).

3.5. *Effect modification*

Effect modification was solely performed for EQ-VAS because this outcome had the strongest association with air pollution in the main analysis. Results presented in Fig. 4 show that BMI and perceived stress modified the association between air pollution and EQ-VAS. Participants with a BMI below 30.0 kg/m^2 exhibited a stronger association between air pollution and EQ-VAS as compared to those with a BMI at or above 30.0 kg/m^2. Furthermore, participants with higher perceived stress (scale score ≥13.59) showed stronger effects compared to those with lower stress. We did not observe any considerable modification for other covariates (sex, age, self-perception of residential greenness, NDVI, and self-efficacy) (Table S10).

4. Discussion

Our cross-sectional study found that higher long-term exposure to air pollution was associated with worse HRQoL and worse SRH in German adults aged 54 and over. Additionally, effect modification was observed for BMI and perceived stress level. We found that the one-item measurements of self-perceived health status (EQ-VAS and SRH) may show higher sensitivity to air pollution compared to the multi-dimensional

Table 3
Distribution of ambient air pollutant concentrations.

	Mean (SD)	Min	P25	Median	P75	Max	IQR	Spearman correlation coefficients							
								PM_{10}	PM_{coarse}	$PM_{2.5}$	$PM_{2.5abs}$	PNC	O_3	NO_2	NO_X
PM_{10} (μg/m^3)	16.4 (1.4)	13.2	15.2	16.1	17.2	22.3	2.0	1.0							
PM_{coarse} (μg/m^3)	4.8 (1.0)	2.5	4.1	4.7	5.5	8.3	1.4	0.8	1.0						
$PM_{2.5}$ (μg/m^3)	11.7 (1.0)	8.3	11.1	11.8	12.4	14.3	1.4	0.5	0.5	1.0					
$PM_{2.5abs}$ (10^{-5}/m)	1.2 (0.2)	0.8	1.0	1.2	1.3	1.9	0.3	0.8[a]	0.8[b]	0.6	1.0				
PNC (10^3/cm^3)	7.1 (1.8)	3.2	6.1	7.1	8.0	14.6	1.9	0.8[a]	0.7	0.6	0.8	1.0			
O_3 (μg/m^3)	39.1 (2.4)	32.1	37.3	39.2	40.9	46.0	3.5	0.1	0.2	−0.2[b]	−0.1	0.0	1.0		
NO_2 (μg/m^3)	13.6 (4.2)	6.9	10.3	12.9	16.5	28.9	6.2	0.7	0.8[b]	0.7	0.9[b]	0.8	−0.1	1.0	
NO_X (μg/m^3)	21.3 (7.0)	3.8	17.0	22.0	25.5	47.2	8.4	0.7	0.7	0.8[b]	0.7	0.9[b]	−0.1[a]	0.8	1.0

Abbreviations: SD, standard deviation; P25, 25th percentile; P75, 75th percentile; IQR, Inter-quartile range; PM_{10}, particulate matter (PM) with an aerodynamic diameter <10 μm (μg/m^3); PM_{coarse}, coarse particulate matter; $PM_{2.5}$, PM < 2.5 μm (μg/m^3); $PM_{2.5abs}$, the absorbance of $PM_{2.5}$; PNC, particle number concentration; O_3, Ozone (μg/m^3); NO_2, Nitrogen dioxide (μg/m^3); NO_X, Nitrogen oxide (μg/m^3).
Note.
The correlation coefficients (*rho*) were calculated by Spearman correlation analysis.
[a] $P < 0.10$.
[b] $P < 0.05$.

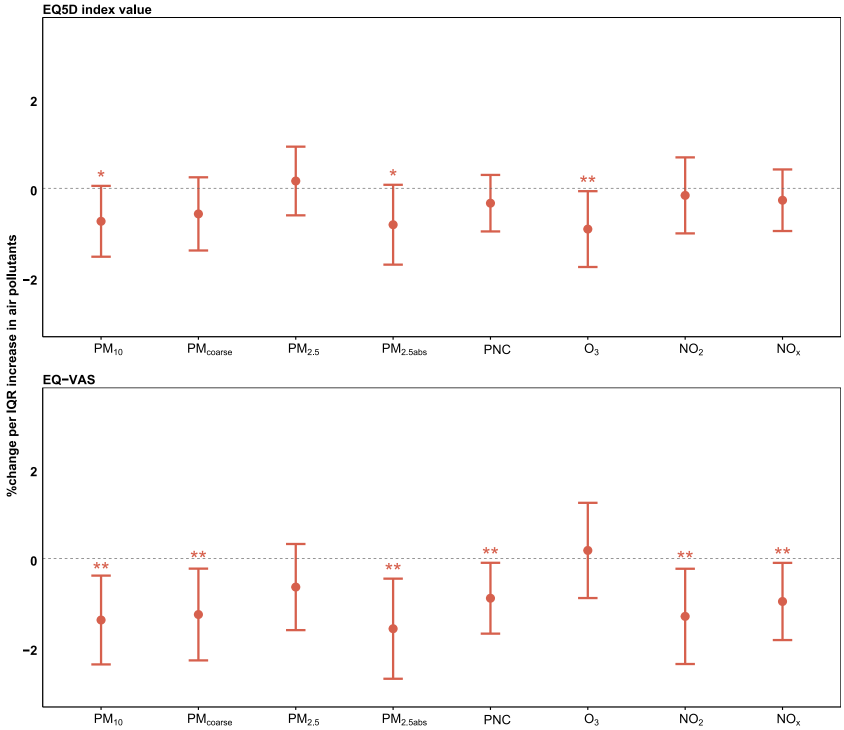

Fig. 1. Results of the main model of linear regression for the associations between air pollutants and EQ-5D index value and EQ-VAS.
Abbreviations: EQ-5D index value, the index of European Quality of Life 5-dimensional questionnaire; EQ-VAS, EQ visual analogue scale; IQR, interquartile range; PM_{10}, particulate matter (PM) with an aerodynamic diameter <10 μm (μg/m^3); PM_{coarse}, coarse particulate matter; $PM_{2.5}$, PM < 2.5 μm (μg/m^3); $PM_{2.5abs}$, the absorbance of $PM_{2.5}$; PNC, particle number concentration; O_3, Ozone (μg/m^3); NO_2, Nitrogen dioxide (μg/m^3); NO_X, Nitrogen oxide (μg/m^3). **Note:** Estimates represented as the percentage changes in EQ-5D index value/EQ-VAS mean for IQR increase in annual exposures to air pollutants (1.95 μg/m^2 for PM_{10}, 1.40 μg/m^2 for PM_{coarse}, 1.39 μg/m^2 for $PM_{2.5}$, 0.28 [10^{-5}/m] for $PM_{2.5abs}$, 1.92 [10^3/cm^3] for PNC, 3.54 μg/m^2 for O_3, 6.20 μg/m^2 for NO_2 and 8.41 μg/m^2 for NO_X).
The plots were developed based on the main model, which was adjusted for age at the survey, sex, socioeconomic status (SES), living with a partner, physical activity, and smoking status.

measure (EQ-5D index value).

There is an increasing number of studies on the long-term health effects of air pollution. However, only two identified studies to date have assessed HRQoL using the EQ-5D (Shin et al., 2018; Tan et al., 2023). Measuring HRQoL with the three-level version of the EQ-5D (EQ-5D-3L), Tan et al. found that per 1 μg/m^3 increase in long-term exposures to $PM_{2.5}$ and PM_{10}, the EQ-5D-3L index value among their study population in Shandong decreased by 0.002 and 0.001, respectively (Tan et al., 2023). In a study in South Korea, Shin et al. dichotomized the EQ-5D-3L index values based on a fourth quartile cut-off, defining participants above the fourth quartile as having poor quality of life. They found that poor quality of life was associated with increased exposures to PM_{10} and NO_2, particularly in younger people (<65.0 years) (Shin et al., 2018). Another study used the Short Form-36 Health Survey (SF-36) Physical and Mental Component Summary scores to assess HRQoL (Boudier et al., 2022). This European population-based study reported that higher $PM_{2.5}$, PM_{10}, and NO_2 concentrations were associated with lower Mental Component Summary scores, but no consistent association was found for Physical Component Summary scores (Boudier et al., 2022).

In terms of the general SRH, there is sparse evidence regarding the long-term effect of air pollution on EQ-VAS. In China, Li et al. found a positive association between annual air pollution (PM_{10}, NO_2, and O_3) and worse SRH among 5172 individuals aged >60.0 years from 123 Chinese cities (Li et al., 2023). Another study in China consistently observed that a higher air pollution index was associated with a greater likelihood of having poor SRH among 7358 residents aged ≥65 years from 171 Chinese cities (Sun and Gu, 2008). Supporting evidence has also been found in European populations, including a cross-sectional study of 16,455 participants aged ≥15 years in Belgium (Hautekiet et al., 2022), a study including 354,827 Dutch citizens aged ≥19 years (Klompmaker et al., 2019), and an analysis of over 500,000 residents aged 37–73 years from the UK Biobank (Mutz et al., 2021). In general, these studies observed the detrimental effect of air pollution on self-perceived health status, in agreement with our results. Until now, however, there has been no evidence linking long-term air pollution with CSRH.

Several biological mechanisms may explain our findings. Self-perceived health is a measurement of both overall subjective physical and mental well-being (EuroQol-Group, 2023). Within the body, long-term air pollution exposure is connected to a variety of diseases (de Bont et al., 2022; Hansel et al., 2016) by producing reactive oxygen species and causing endothelial dysfunction, which may be related to worse HRQoL (Akor et al., 2020; Phyo et al., 2021), poor SRH (Farkas et al., 2009; Ko and Boo, 2016), and worse CSRH (Dong et al., 2018; Verhoeven et al., 2021). Air pollution toxicity can also damage the central nervous system or cause neurodegenerative diseases by altering miRNAs, telomeres, gene expression, and signaling pathways (Costa et al., 2020; van der Meulen et al., 2018). These neurodegenerative diseases may further worsen HRQoL. Air pollution also affects the subjective experience of physical and mental health. For example, people living in areas with higher chronic air pollution exposure may be more stressed and fearful of getting sick (Zhu and Lu, 2023). This high subjective stress in response to ambient air pollution may be related to the abnormal secretion of hormones (e.g., dopamine) (Pereyra-Muñoz et al., 2006), metabolism of neurotransmitters (e.g., serotonin) (Zhao et al., 2018), and stimulation of hippocampal pro-inflammatory cytokine

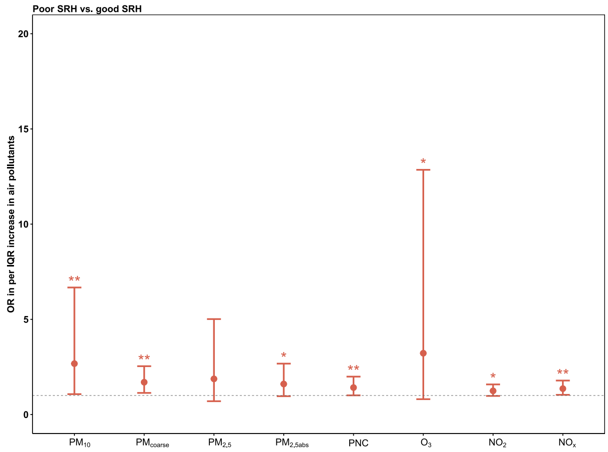

Fig. 2. Results of the main model of logistic regression for the association between air pollutants and the odds of reporting poor SRH.
Abbreviations: SRH, self-rated health; IQR, interquartile range; OR, odds ratio; 95% CI, 95% confidence interval; PM_{10}, particulate matter (PM) with an aerodynamic diameter <10 μm (μg/m^3); PM $_{coarse}$, coarse particulate matter; $PM_{2.5}$, PM < 2.5 μm (μg/m^3); $PM_{2.5abs}$, the absorbance of $PM_{2.5}$; PNC, particle number concentration; O_3, Ozone (μg/m^3); NO_2, Nitrogen dioxide (μg/m^3); NO_X, Nitrogen oxide (μg/m^3). **Note:** With those reported "good SRH" as reference group, estimates represented as ORs (with 95% CIs) of poor SRH for IQR increase in annual exposures to air pollutants (1.95 μg/m^2 for PM_{10}, 1.40 μg/m^2 for PM_{coarse}, 1.39 μg/m^2 for $PM_{2.5}$, 0.28 [10^{-5}/m] for $PM_{2.5abs}$, 1.92 [10^3/cm^3] for PNC, 3.54 μg/m^2 for O_3, 6.20 μg/m^2 for NO_2 and 8.41 μg/m^2 for NO_X).
The plot was developed based on the main model, which was adjusted for age at the survey, sex, socioeconomic status (SES), living with a partner, physical activity, and smoking status.

production (Fonken et al., 2011). Moreover, individuals exposed to higher air pollution are more likely to experience headaches, dizziness, nausea, and feelings of ill health, ultimately affecting their mental well-being (Zhao et al., 2018). Other symptoms related to air pollution exposure (shortness of breath, cough, wheezing, and phlegm) are also likely to interrupt the performance of daily activities and work (D'Oliveira et al., 2023), while also resulting in lower physical capacity and worse self-perceived health (Lopez-Campos et al., 2013). In addition, health risk perception is the psychosocial determinant of health and could also be affected by personal perceptions of air quality (Borbet et al., 2018), neighborhood stigma (King, 2015), and individual's knowledge of air pollution (Cori et al., 2020). As there are fewer studies of the clear specific mechanisms linking air pollution to self-reported health status, more research is needed to validate our findings due to the complex etiology of mental and subjective health outcomes.

Our results related to the association between various sizes of PM and self-perceived health status were somewhat unclear in comparison to other air pollutants. First, the associations between worse self-perceived health status and PM_{10}, $PM_{coarse,}$ and $PM_{2.5}$ gradually disappeared as their particle sizes decreased. This may be because the size fraction of PM plays a significant role in determining its health effects because PM deposits in different parts of the respiratory system and enters the circulatory system depending on its aerodynamic diameters (Zhang et al., 2022). Larger particles lodge in the upper airways, which may cause more obvious symptoms that affect self-perceived health more significantly. Smaller particle sizes and deeper deposit locations are less likely to result in immediate and noticeable symptoms, which may explain why we did not find an association between $PM_{2.5}$ and self-perceived health. Second, PNC contributes most to UFP, which, due to their small size, can diffuse into the most distal lung regions and additionally penetrate all organ systems including the central nervous system (Calderón-Garcidueñas and Ayala, 2022; Oberdörster et al., 2007). This is unlikely to be the scenario for ambient $PM_{2.5}$ as it mainly affects the respiratory and cardiovascular systems (Henning, 2023), and this inconsistency may also be reflected in self-perceived health outcomes. Apart from their size, UFPs are more toxic than larger PMs as they have a larger relative surface area and are highly reactive, meaning that they can absorb more hazardous metals and toxic organic compounds (Kwon et al., 2020). In summary, our mixed results for PM suggest that large-scale scientific studies are needed to determine the effects of $PM_{2.5}$ on self-perceived health status in more detail.

Within our study, 'one-item' measures (EQ-VAS and SRH) were more affected by air pollution than multi-dimensional measures (EQ-5D index value). In the EQ-VAS and SRH, respondents' perceptions of health on the day of the survey are presented straightforwardly, whereas the EQ-5D rates specific dimensions based on a certain weight (coefficient). In general, the EQ-VAS provides more granular information but is less focused on impairments in specific dimensions of health than the EQ-5D (EuroQol-Office, 2023). As a result, the EQ-VAS may be more sensitive when used in a general population sample than the EQ-5D. In addition, our less pronounced results for poor CSRH as compared to our results for poor SRH may be explained by a lack of clarity as to which people the participants were comparing themselves with, and detecting air pollution effects would be challenging if participants compared themselves to people in the same residential area since they would be exposed to air pollution at the same levels. As a result, worse CSRH might be underestimated. There were wider intervals of worse CSRH for $PM_{2.5abs}$ than for other air pollutants, likely due to the relatively narrow range of annual $PM_{2.5abs}$ levels and the gap in sample sizes across the three categories of CSRH.

We detected significant modification effects for the association between air pollution and EQ-VAS, with the effect modification being most apparent for BMI, with the detrimental impacts of ambient air pollution being stronger among those with a lower BMI. A similar higher susceptibility to air pollution among those with lower BMI was also found for cardiovascular and cerebrovascular diseases (Zhang et al., 2011). In contrast to our results, a previous study measured HRQoL using the EQ-5D-3L index value and revealed a stronger adverse health effect of air pollution in those with higher BMI (Tan et al., 2023). A higher susceptibility to air pollution among study participants with other diseases (type 2 diabetes, high blood pressure, and brain tumours) was also found among those with higher BMI (Jørgensen et al., 2016; Li et al., 2021; Liu et al., 2016). Exposed to short-term PM, overweight or obese people release a smaller amount of extracellular vesicles (particles released by cells in response to stimuli) which is associated with a lower risk of narrowing of the coronary arteries (Rota et al., 2020). A potential explanation for the attenuated effect of BMI is the obesity paradox, which suggests that obese people of advanced age have a better prognosis for chronic diseases due to their persistent low-grade inflammation, which is less likely to lead to chronic illnesses (Blum et al., 2011; Rota et al., 2020). Validating this finding will require further research.

Previous research has also found that people with a higher stress level appeared to be more vulnerable to air pollution (Schwartz et al., 2011). We also found that the perceived stress modified the association between air pollutants and EQ-VAS, with stronger adverse effects on EQ-VAS being found in the higher perceived stress group. Psychosocial stress increases vulnerability to the health effects of environmental hazards (Mehta et al., 2015). A higher self-perceived stress level might damage general feelings of optimism or promote pessimism about the future, worsening dynamic feelings of health (Smith et al., 2004). However, a cross-sectional study in the Arab-American community found no evidence of effect modification of perceived stress (Suleiman et al., 2021). As there is limited conclusive evidence accounting for comorbidity or stress-related vulnerability, more in-depth studies are required regarding their modification effects.

There are several strengths in the present study. First, this study was conducted based on the KORA-Fit cohort, a well-characterized study

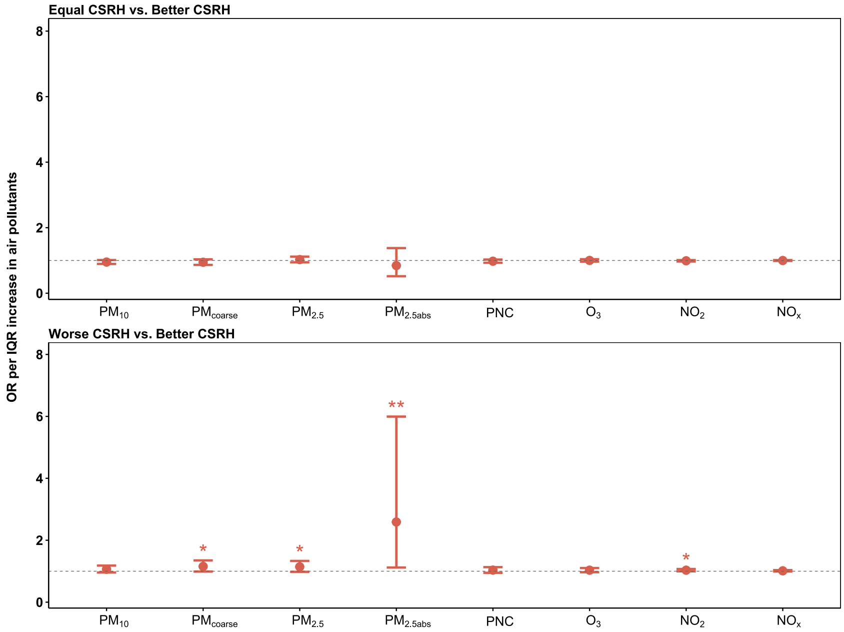

Fig. 3. Results of the main model of multinominal regression for the association of air pollution with the odds of reporting equal CSRH or worse CSRH. **Abbreviations**: CSRH, comparative self-rated health; OR, odds ratio; 95% CI, 95% confidence interval; IQR, interquartile range; PM_{10}, particulate matter (PM) with an aerodynamic diameter <10 μm (μg/m^3); PM_{coarse}, coarse particulate matter; $PM_{2.5}$, PM < 2.5 μm (μg/m^3); $PM_{2.5abs}$, the absorbance of $PM_{2.5}$; PNC, particle number concentration; O_3, Ozone (μg/m^3); NO_2, Nitrogen dioxide (μg/m^3); NO_X, Nitrogen oxide (μg/m^3). **Note:** With those reported "better CSRH" as reference group, estimates represented as ORs (with 95% CIs) of equal CSRH or worse CSRH for IQR increase in annual exposures to air pollutants (1.95 μg/m^2 for PM_{10}, 1.40 μg/m^2 for PM_{coarse}, 1.39 μg/m^2 for $PM_{2.5}$, 0.28 [10^{-5}/m] for $PM_{2.5abs}$, 1.92 [10^3/cm^3] for PNC, 3.54 μg/m^2 for O_3, 6.20 μg/m^2 for NO_2 and 8.41 μg/m^2 for NO_X). The plots were developed based on the main model, which was adjusted for age at the survey, sex, socioeconomic status (SES), living with a partner, physical activity, and smoking status.

with standardized and comprehensive information regarding subject characteristics and outcomes, which enhanced the reliability of our results. Second, our study examined the potential effect of eight commonly measured air pollutants, after checking for potential multicollinearity. This enables us to conclude consistent patterns across various air pollutants and to explore potential differences in sources and aerosol properties.

Our study also has some limitations. First, using spatial models, we estimated the annual average concentrations of air pollutants for 2014/2015, while outcome data were collected in 2018/2019. Yet, we believe these exposure estimates are valid since previous studies have shown that spatial variation in exposure over time is stable for historical spatial contrasts (de Hoogh et al., 2018; Wang et al., 2013). Second, we focused only on self-perceived 'physical' health states by asking the participants two SRH-related questions, rather than assessing 'general' health status. In part, this could be compensated by using the EQ-5D-5L instrument, which measures the self-perceived health from both physical and mental health (anxiety/depression) perspectives. Our use of EQ-VAS also helps to determine general health (EuroQol-Office, 2023). Third, our data may not be generalizable to other populations since KORA-Fit participants were mainly of European descent. Finally, the cross-sectional design prevented us from assessing the causality between self-perceived health status and air pollution.

5. Conclusions

Worse HRQoL (assessed with the EQ-5D index value and EQ-VAS), poor SRH, and worse CSRH were associated with increasing exposure to air pollution. These associations were modified by BMI and perceived stress level. In studies of the effects of air pollution, a single-item SRH indicator may be more suitable for assessing self-perceived health status among older people than multidimensional indicators.

CRediT authorship contribution statement

Minqi Liao: Writing – original draft, Visualization, Formal analysis. **Siqi Zhang:** Visualization, Software, Formal analysis. **Kathrin Wolf:** Writing – review & editing. **Gabriele Bolte:** Writing – review & editing. **Michael Laxy:** Writing – review & editing. **Lars Schwettmann:** Writing – review & editing. **Annette Peters:** Supervision. **Alexandra Schneider:** Supervision, Methodology, Conceptualization. **Ute Kraus:** Writing – review & editing, Methodology, Conceptualization.

Ethics statement

The use of data for this project was approved by the ethics board of the Bavarian Chamber of Physicians (KORA-Fit EC No.17040) in adherence to the declaration of Helsinki. All study participants gave written informed consent.

Data availability

Data will be made available on request.

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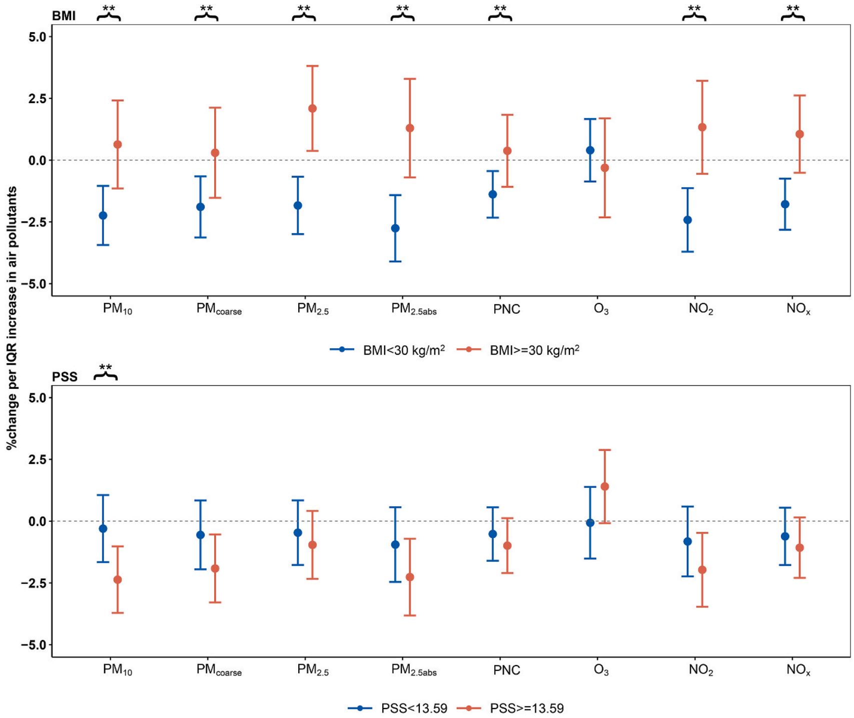

Fig. 4. Multiple linear regression results for the associations between annual air pollutant exposures and EQ-VAS modified by BMI and perceived stress.
Abbreviations: EQ-VAS, EuroQol group's visual analog scale; OR, odds ratio; 95% CI, 95% confidence interval; IQR, Interquartile range; PM_{10}, particulate matter (PM) with an aerodynamic diameter <10 μm (μg/m^3); PM_{coarse}, coarse particulate matter; $PM_{2.5}$, PM < 2.5 μm (μg/m^3); $PM_{2.5abs}$, the absorbance of $PM_{2.5}$; PNC, particle number concentration; O_3, Ozone (μg/m^3); NO_2, Nitrogen dioxide (μg/m^3); NO_X, Nitrogen oxide (μg/m^3); BMI, body mass index. **Note:** Estimates expressed as the percentage change in EQ-VAS mean for IQR increase in annual exposures to air pollutants (1.95 μg/m^2 for PM_{10}, 1.40 μg/m^2 for PM_{coarse}, 1.39 μg/m^2 for $PM_{2.5}$, 0.28 (10^{-5}/m) for $PM_{2.5abs}$, 1.92 (10^3/cm^3) for PNC, 3.54 μg/m^2 for O_3, 6.20 μg/m^2 for NO_2 and 8.41 μg/m^2 for NO_X).
The plots were developed based on the main model, which was adjusted for age at the survey, sex, socioeconomic status (SES), living with a partner, physical activity, and smoking status.

Declaration of competing interest

Authors declare that they have no financial or personal relationships that may have inappropriately influenced them in writing this article.

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Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.ijheh.2024.114513.

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Long-term associations between ambient air pollution and self-perceived health status: results from the population-based KORA-Fit study

(Appendix A.Supplementary data)

Table Legend

Table S1. Original and re-coding of outcome variables.

Table S2. Results from single-pollutant multiple regression models showing the association between annual air pollutant exposure and percentage changes in EQ-5D index value/ EQ-VAS.

Table S3. Results from single-pollutant multiple regression models show the association between annual air pollutant exposure and the absolute changes in EQ-VAS.

Table S4. Results of single-pollutant models showing the associations between annual air pollutant exposures and individual dichotomized EQ-5D-5L.

Table S5. Results from single-pollutant logistic regression models showing the association between annual air pollutant exposure and poor SRH.

Table S6. Results from multiple logistic regression showing the associations between annual air pollutant exposures and equal or worse CSRH, relative to reporting better CSRH.

Table S7. Results of two-pollutant multiple logistic regression or multiple regression models showing the associations between annual levels of air pollution exposures and the EQ-5D index value, EQ-VAS, poor SRH, equal or worse CSRH.

Table S8. Results of sensitivity analysis showing the associations between annual levels of air pollution exposures and the percentage changes in EQ-5D index value and EQ-VAS, and the odds of reporting poor SRH, equal or worse CSRH, in two main models.

Table S9. Results of sensitivity analysis showing the associations between annual levels of air pollution exposures and the percentage changes in EQ-5D index value and EQ-VAS, and the odds of reporting poor SRH, equal or worse CSRH, after further adjustment for residential duration of the current addresses.

Table S10. Results of interaction analysis for the association between annual levels of air pollutant exposures and percentage changes in EQ-VAS.

Figure Legend

Fig S1. Flowchart of study population selection.

Fig S2. Results of multiple linear regression models for the associations between air pollutants and EQ-5D index value and EQ-VAS.
Abbreviations: EQ-5D index value, the index of European Quality of Life 5-dimensional questionnaire; EQ-VAS, EQ visual analogue scale; IQR, interquartile range; PM_{10}, particulate matter (PM) with an aerodynamic diameter < 10µm (µg/m^3); PM_{coarse}, coarse particulate matter; $PM_{2.5}$, PM < 2.5µm (µg/m^3); $PM_{2.5abs}$, the absorbance of $PM_{2.5}$; PNC, particle number concentration; O_3, Ozone (µg/m^3); NO_2, Nitrogen dioxide (µg/m^3); NO_X, Nitrogen oxide (µg/m^3).

Note: Estimates represent percentage changes in EQ-5D index value/EQ-VAS mean for IQR increase in annual exposures to air pollutants (1.95 μg/m^2 for PM_{10}, 1.40 μg/m^2 for PM_{coarse}, 1.39 μg/m^2 for $PM_{2.5}$, 0.28 (10^{-5}/m) for $PM_{2.5abs}$, 1.92 (10^3/cm^3) for PNC, 3.54 μg/m^2 for O_3, 6.20 μg/m^2 for NO_2 and 8.41 μg/m^2 for NO_X).
The minimum model was adjusted for age at survey and sex.
The main model was further adjusted for socioeconomic status (SES), living with a partner, body mass index (BMI), physical activity, and smoking status.
The extended model 1 was further adjusted for variables in the main model plus the percentage of households with low income and degree of urbanization.
The extended model 2 was further adjusted for variables in the main model plus the General Self-Efficacy (ASKU) and Perceived Stress (PSS).

Fig S3. Results of multiple logistic regression model for dichotomized EQ-5D-5L dimensions.
Abbreviations: EQ-5D-5L, European Quality of Life 5 Dimension 5 Level questionnaire; OR, odds ratio; 95% CI, 95% confidence interval; IQR, Interquartile range; PM_{10}, particulate matter (PM) with an aerodynamic diameter < 10μm (μg/m^3); PM_{coarse}, coarse particulate matter; $PM_{2.5}$, PM < 2.5μm (μg/m^3); $PM_{2.5abs}$, the absorbance of $PM_{2.5}$; PNC, particle number concentration; O_3, Ozone (μg/m^3); NO_2, Nitrogen dioxide (μg/m^3); NO_X, Nitrogen oxide (μg/m^3).
Note: With those reported “had no problems” as the reference group, estimates represented as ORs (with 95%CIs) of “any problems” for IQR increase in annual exposures to air pollutants (1.95 μg/m^2 for PM_{10}, 1.40 μg/m^2 for PM_{coarse}, 1.39 μg/m^2 for $PM_{2.5}$, 0.28 (10^{-5}/m) for $PM_{2.5abs}$, 1.92 (10^3/cm^3) for PNC, 3.54 μg/m^2 for O_3, 6.20 μg/m^2 for NO_2 and 8.41 μg/m^2 for NO_X).
The minimum model was adjusted for age at the survey and sex.
The main model was further adjusted for (SES), living with a partner, body mass index (BMI), physical activity, and smoking status.
The extended model 1 was further adjusted for variables in the main model plus the percentage of households with low income and degree of urbanization.
The extended model 2 was further adjusted for variables in the main model plus the General Self-Efficacy (ASKU) and Perceived Stress (PSS).

Fig S4. Results of multiple logistic regression models for the associations between air pollutants and the odds of reporting poor SRH.
Abbreviations: SRH, self-rated health; IQR, interquartile range; PM_{10}, particulate matter (PM) with an aerodynamic diameter < 10μm (μg/m^3); PM_{coarse}, coarse particulate matter; $PM_{2.5}$, PM < 2.5μm (μg/m^3); $PM_{2.5abs}$, the absorbance of $PM_{2.5}$; PNC, particle number concentration; O_3, Ozone (μg/m^3); NO_2, Nitrogen dioxide (μg/m^3); NO_X, Nitrogen oxide (μg/m^3).
Note: With those reported “good SRH” as reference group, estimates represented as ORs (with 95%CIs) of poor SRH for IQR increase in annual exposures to air pollutants (1.95 μg/m^2 for PM_{10}, 1.40 μg/m^2 for PM_{coarse}, 1.39 μg/m^2 for $PM_{2.5}$, 0.28 (10^{-5}/m) for $PM_{2.5abs}$, 1.92 (10^3/cm^3) for PNC, 3.54 μg/m^2 for O_3, 6.20 μg/m^2 for NO_2 and 8.41 μg/m^2 for NO_X).
The minimum model was adjusted for age at survey and sex.
The main model was further adjusted for socioeconomic status (SES), living with a partner, body mass index (BMI), physical activity, and smoking status.
The extended model 1 was further adjusted for variables in the main model plus the percentage of households with low income and degree of urbanization.
The extended model 2 was further adjusted for variables in the main model plus the General Self-Efficacy (ASKU) and Perceived Stress (PSS).

Fig S5. Results of the main model of multinominal logistic regression for the association between air pollution and the odds of reporting: A) equal CSRH vs. better CSRH; B) worse CSRH vs. better CSRH, with the estimate for $PM_{2.5abs}$ being excluded due to the large confidence interval.
Abbreviations: CSRH, comparative self-rated health; OR, odds ratio; 95% CI, 95% confidence interval; IQR, interquartile range; PM_{10}, particulate matter (PM) with an aerodynamic diameter < 10μm (μg/m^3); PM_{coarse}, coarse particulate matter; $PM_{2.5}$, PM < 2.5μm (μg/m^3); $PM_{2.5abs}$, the

absorbance of $PM_{2.5}$; PNC, particle number concentration; O_3, Ozone ($\mu g/m^3$); NO_2, Nitrogen dioxide ($\mu g/m^3$); NO_X, Nitrogen oxide ($\mu g/m^3$).
Note: With those reported "better CSRH" as reference group, estimates represented as ORs (with 95% CIs) of equal CSRH or worse CSRH for IQR increase in annual exposures to air pollutants (1.95 $\mu g/m^2$ for PM_{10}, 1.40 $\mu g/m^2$ for PM_{coarse}, 1.39 $\mu g/m^2$ for $PM_{2.5}$, 0.28 [10^{-5}/m] for $PM_{2.5abs}$, 1.92 [$10^3/cm^3$] for PNC, 3.54 $\mu g/m^2$ for O_3, 6.20 $\mu g/m^2$ for NO_2 and 8.41 $\mu g/m^2$ for NO_X).
The plots were developed based on the main model, which was adjusted for age at the survey, sex, socioeconomic status (SES), living with a partner, physical activity, and smoking status.

Fig S6. Results of the multiple multinominal logistic regression models for the association between air pollution and the odds of reporting: A) equal CSRH vs. better CSRH; B) worse CSRH vs. better CSRH.
Abbreviations: CSRH, comparative self-rated health; OR, odds ratio; 95% CI, 95% confidence interval; IQR, interquartile range; PM_{10}, particulate matter (PM) with an aerodynamic diameter < 10µm ($\mu g/m^3$); PM_{coarse}, coarse particulate matter; $PM_{2.5}$, PM < 2.5µm ($\mu g/m^3$); $PM_{2.5abs}$, the absorbance of $PM_{2.5}$; PNC, particle number concentration; O_3, Ozone ($\mu g/m^3$); NO_2, Nitrogen dioxide ($\mu g/m^3$); NO_X, Nitrogen oxide ($\mu g/m^3$).
Note: With those reported "better CSRH" as reference group, estimates represented as ORs (with 95% CIs) of equal CSRH or worse CSRH for IQR increase in annual exposures to air pollutants (1.95 $\mu g/m^2$ for PM_{10}, 1.40 $\mu g/m^2$ for PM_{coarse}, 1.39 $\mu g/m^2$ for $PM_{2.5}$, 0.28 [10^{-5}/m] for $PM_{2.5abs}$, 1.92 [$10^3/cm^3$] for PNC, 3.54 $\mu g/m^2$ for O_3, 6.20 $\mu g/m^2$ for NO_2 and 8.41 $\mu g/m^2$ for NO_X).
The minimum model was adjusted for age at survey and sex.
The main model was further adjusted for socioeconomic status (SES), living with a partner, body mass index (BMI), physical activity, and smoking status.
The extended model 1 was further adjusted for variables in the main model plus percentage of households with low income and degree of urbanization.
The extended model 2 was further adjusted for variables in the main model plus the General Self-Efficacy (ASKU) and Perceived Stress (PSS).

Fig S7. Results of the multiple multinominal logistic regression models for the association between air pollution and the odds of reporting: A) equal CSRH vs. better CSRH; B) worse CSRH vs. better CSRH, with the estimate for $PM_{2.5abs}$ being excluded due to the large confidence interval.
Abbreviations: CSRH, comparative self-rated health; OR, odds ratio; 95% CI, 95% confidence interval; IQR, interquartile range; PM_{10}, particulate matter (PM) with an aerodynamic diameter < 10µm ($\mu g/m^3$); PM_{coarse}, coarse particulate matter; $PM_{2.5}$, PM < 2.5µm ($\mu g/m^3$); $PM_{2.5abs}$, the absorbance of $PM_{2.5}$; PNC, particle number concentration; O_3, Ozone ($\mu g/m^3$); NO_2, Nitrogen dioxide ($\mu g/m^3$); NO_X, Nitrogen oxide ($\mu g/m^3$).
Note: With those reported "better CSRH" as reference group, estimates represented as ORs (with 95% CIs) of equal CSRH or worse CSRH for IQR increase in annual exposures to air pollutants (1.95 $\mu g/m^2$ for PM_{10}, 1.40 $\mu g/m^2$ for PM_{coarse}, 1.39 $\mu g/m^2$ for $PM_{2.5}$, 0.28 [10^{-5}/m] for $PM_{2.5abs}$, 1.92 [$10^3/cm^3$] for PNC, 3.54 $\mu g/m^2$ for O_3, 6.20 $\mu g/m^2$ for NO_2 and 8.41 $\mu g/m^2$ for NO_X).
The minimum model was adjusted for age at survey and sex.
The main model was further adjusted for socioeconomic status (SES), living with a partner, body mass index (BMI), physical activity, and smoking status.
The extended model 1 was further adjusted for variables in the main model plus percentage of households with low income and degree of urbanization.
The extended model 2 was further adjusted for variables in the main model plus the General Self-Efficacy (ASKU) and Perceived Stress (PSS).

Fig S8. DAG plot for potential causal pathway

Fig S9. Sensitivity analysis for multiple linear regression models for the associations between air pollutants and EQ-5D index value and EQ-VAS in two main models.

Abbreviations: EQ-5D index value, the index of European Quality of Life 5-dimensional questionnaire; EQ-VAS, EQ visual analogue scale; IQR, interquartile range; PM_{10}, particulate matter (PM) with an aerodynamic diameter < 10μm (μg/m^3); PM_{coarse}, coarse particulate matter; $PM_{2.5}$, PM < 2.5μm (μg/m^3); $PM_{2.5abs}$, the absorbance of $PM_{2.5}$; PNC, particle number concentration; O_3, Ozone (μg/m^3); NO_2, Nitrogen dioxide (μg/m^3); NO_X, Nitrogen oxide (μg/m^3).
Note: Estimates represent percentage changes in EQ-5D index value/EQ-VAS mean for IQR increase in annual exposures to air pollutants (1.95 μg/m^2 for PM_{10}, 1.40 μg/m^2 for PM_{coarse}, 1.39 μg/m^2 for $PM_{2.5}$, 0.28 (10^{-5}/m) for $PM_{2.5abs}$, 1.92 (10^3/cm^3) for PNC, 3.54 μg/m^2 for O_3, 6.20 μg/m^2 for NO_2 and 8.41 μg/m^2 for NO_X).
The present main model was adjusted for age at survey, sex, socioeconomic status (SES), living with a partner, body mass index (BMI), physical activity, and smoking status.
The updated main model was adjusted for age at survey, sex, SES, living with a partner, and smoking status.

Fig S10. Sensitivity analysis for multiple logistic regression models for the associations between air pollutants and the odds of reporting poor SRH in two main models.
Abbreviations: SRH, self-rated health; IQR, interquartile range; PM_{10}, particulate matter (PM) with an aerodynamic diameter < 10μm (μg/m^3); PM_{coarse}, coarse particulate matter; $PM_{2.5}$, PM < 2.5μm (μg/m^3); $PM_{2.5abs}$, the absorbance of $PM_{2.5}$; PNC, particle number concentration; O_3, Ozone (μg/m^3); NO_2, Nitrogen dioxide (μg/m^3); NO_X, Nitrogen oxide (μg/m^3).
Note: With those reported “good SRH” as reference group, estimates represented as ORs (with 95%CIs) of poor SRH for IQR increase in annual exposures to air pollutants (1.95 μg/m^2 for PM_{10}, 1.40 μg/m^2 for PM_{coarse}, 1.39 μg/m^2 for $PM_{2.5}$, 0.28 (10^{-5}/m) for $PM_{2.5abs}$, 1.92 (10^3/cm^3) for PNC, 3.54 μg/m^2 for O_3, 6.20 μg/m^2 for NO_2 and 8.41 μg/m^2 for NO_X).
The present main model was adjusted for age at survey, sex, socioeconomic status (SES), living with a partner, body mass index (BMI), physical activity, and smoking status.
The updated main model was adjusted for age at survey, sex, SES, living with a partner, and smoking status.

Fig S11. Sensitivity analysis for the multiple multinominal logistic regression models for the association between air pollution and the odds of reporting: A) equal CSRH vs. better CSRH; B) worse CSRH vs. better CSRH in two main models.
Abbreviations: CSRH, comparative self-rated health; OR, odds ratio; 95% CI, 95% confidence interval; IQR, interquartile range; PM_{10}, particulate matter (PM) with an aerodynamic diameter < 10μm (μg/m^3); PM_{coarse}, coarse particulate matter; $PM_{2.5}$, PM < 2.5μm (μg/m^3); $PM_{2.5abs}$, the absorbance of $PM_{2.5}$; PNC, particle number concentration; O_3, Ozone (μg/m^3); NO_2, Nitrogen dioxide (μg/m^3); NO_X, Nitrogen oxide (μg/m^3).
Note: With those reported “better CSRH” as reference group, estimates represented as ORs (with 95% CIs) of equal CSRH or worse CSRH for IQR increase in annual exposures to air pollutants (1.95 μg/m^2 for PM_{10}, 1.40 μg/m^2 for PM_{coarse}, 1.39 μg/m^2 for $PM_{2.5}$, 0.28 (10^{-5}/m) for $PM_{2.5abs}$, 1.92 (10^3/cm^3) for PNC, 3.54 μg/m^2 for O_3, 6.20 μg/m^2 for NO_2 and 8.41 μg/m^2 for NO_X).
The present main model was adjusted for age at survey, sex, socioeconomic status (SES), living with a partner, body mass index (BMI), physical activity, and smoking status.
The updated main model was adjusted for age at survey, sex, SES, living with a partner, and smoking status.

Fig S12. Sensitivity analysis for the multiple multinominal logistic regression models for the association between air pollution and the odds of reporting: A) equal CSRH vs. better CSRH; B) worse CSRH vs. better CSRH, with the estimate for PM2.5abs being excluded due to the large confidence interval in two main models.

Abbreviations: CSRH, comparative self-rated health; OR, odds ratio; 95% CI, 95% confidence interval; IQR, interquartile range; PM_{10}, particulate matter (PM) with an aerodynamic diameter < 10µm (µg/m^3); PM_{coarse}, coarse particulate matter; $PM_{2.5}$, PM < 2.5µm (µg/m^3); $PM_{2.5abs}$, the absorbance of $PM_{2.5}$; PNC, particle number concentration; O_3, Ozone (µg/m^3); NO_2, Nitrogen dioxide (µg/m^3); NO_X, Nitrogen oxide (µg/m^3).
Note: With those reported "better CSRH" as reference group, estimates represented as ORs (with 95% CIs) of equal CSRH or worse CSRH for IQR increase in annual exposures to air pollutants (1.95 µg/m^2 for PM_{10}, 1.40 µg/m^2 for PM_{coarse}, 1.39 µg/m^2 for $PM_{2.5}$, 0.28 (10^{-5}/m) for $PM_{2.5abs}$, 1.92 (10^3/cm^3) for PNC, 3.54 µg/m^2 for O_3, 6.20 µg/m^2 for NO_2 and 8.41 µg/m^2 for NO_X).
The present main model was adjusted for age at survey, sex, socioeconomic status (SES), living with a partner, body mass index (BMI), physical activity, and smoking status.
The updated main model was adjusted for age at survey, sex, SES, living with a partner, and smoking status.

Fig S13. Exposure-response relationships for percentage change in EQ-5D index value with different air pollutants.
Abbreviations: EQ-5D index value, index of European Quality of Life 5 Dimension 5 Level questionnaire; PM_{10}, particulate matter (PM) with an aerodynamic diameter < 10µm (µg/m^3); PM_{coarse}, coarse particulate matter; $PM_{2.5}$, PM < 2.5µm (µg/m^3); $PM_{2.5abs}$, the absorbance of $PM_{2.5}$; PNC, particle number concentration; O_3, Ozone (µg/m^3); NO_2, Nitrogen dioxide (µg/m^3); NO_X, Nitrogen oxide (µg/m^3).
Note: These linearity plots were developed based on the main model, which was adjusted for the age at the survey, sex, socioeconomic status (SES), living with a partner, body mass index (BMI), physical activity, and smoking status.

Fig S14. Exposure-response relationships for percentage change in EQ-VAS with different air pollutants.
Abbreviations: EQ-VAS, EuroQol group's visual analog scale; PM_{10}, particulate matter (PM) with an aerodynamic diameter < 10µm (µg/m^3); PM_{coarse}, coarse particulate matter; $PM_{2.5}$, PM < 2.5µm (µg/m^3); $PM_{2.5abs}$, the absorbance of $PM_{2.5}$; PNC, particle number concentration; O_3, Ozone (µg/m^3); NO_2, Nitrogen dioxide (µg/m^3); NO_X, Nitrogen oxide (µg/m^3).
Note: These linearity plots were developed based on the main model, which was adjusted for age at the survey, sex, socioeconomic status (SES), living with a partner, body mass index (BMI), physical activity, and smoking status.

Table S1. Original and re-coding of outcome variables.

Variables	Original coding	Re-coding
EQ-5D-5L (mobility)	5-point scale: 1=I have no problems walking around; 2=I have slight problems walking around; 3=I have moderate problems walking around; 4=I have great problems walking around; 5=I am not able to walk around.	Binary variable: 0= have no problems (original answer 1); 1= any problems (original answers 2-5).
EQ-5D-5L (self-care)	5-point scale: 1=I have no problems washing or dressing myself; 2=I have slight problems washing or dressing myself; 3=I have moderate problems washing or dressing myself; 4=I have great problems washing or dressing myself; 5=I am unable to wash or dress myself.	Binary variable: 0= have no problems (original answer 1); 1= any problems (original answers 2-5).
EQ-5D-5L (usual activities)	5-piont scale: 1=I have no problems going about my daily activities; 2=I have slight problems in carrying out my daily activities; 3=I have moderate problems in carrying out my daily activities; 4=I have great problems in carrying out my daily activities; 5=I am not able to carry out my daily activities.	Binary variable: 0= have no problems (original answer 1); 1= any problems (original answers 2-5).
EQ-5D-5L (pain/discomfort)	5-point scale: 1=I have no pain or discomfort; 2=I have mild pain or discomfort; 3=I have moderate pain or discomfort; 4=I have severe pain or discomfort; 5=I have extreme pain or discomfort.	Binary variable: 0= have no problems (original answer 1); 1= any problems (original answers 2-5).
EQ-5D-5L (anxiety/depression)	5-point scale: 1=I am not anxious or depressed; 2=I am a little anxious or depressed; 3=I am moderately anxious or depressed; 4=I am very anxious or depressed; 5=I am extremely anxious or depressed.	Binary variable: 0= have no problems (original answer 1); 1= any problems (original answers 2-5).
EQ-5D-5L index	Continuous (-0.13 to 1)	Continuous (-0.13 to1)
EQ-VAS	Continuous (0 to 100)	Continuous (0 to 100)
SRH from KORA-Fit cohort [a]	1 = very good; 2 = good; 3 = less good; 4 = poor	1= good (original answers 1-2); 2= poor (original answers 3-4);
CSRH	1 = better; 2 = worse; 3 = equal; 4 = don´t know	0 = better; 1 = equal; 2 = worse; NA = don’t know

Abbreviations: EQ-5D-5L, European Quality of Life 5-dimensional questionnaire; EQ-VAS, EuroQol group's visual analog scale; SRH, self-rated health; CSRH, comparative self-rated health. [a] An SRH from the INGER study was not recorded.

Table S2. Results from single-pollutant multiple regression models showing the association between annual air pollutant exposure and percentage changes in EQ-5D index value/ EQ-VAS.

Air pollutants	Percentage changes (95% CIs)			
	Minimum model	Main model	Extended model 1	Extended model 2
EQ-5D index value				
PM_{10}	-0.85 (-1.65; -0.05)**	-0.74 (-1.53; 0.05)*	-0.55 (-1.49; 0.39)	-0.51 (-1.26; 0.24)
PM_{coarse}	-0.57 (-1.40; 0.25)	-0.57 (-1.39; 0.25)	-0.19 (-1.34; 0.96)	-0.48 (-1.25; 0.29)
$PM_{2.5}$	0.04 (-0.75; 0.83)	0.16 (-0.61; 0.93)	0.57 (-0.30; 1.44)	0.12 (-0.62; 0.85)
$PM_{2.5abs}$	-0.92 (-1.82; -0.01)**	-0.82 (-1.71; 0.08)*	-0.60 (-1.95; 0.76)	-0.87 (-1.72; -0.02)**
PNC	-0.46 (-1.11; 0.18)	-0.33 (-0.97; 0.30)	-0.09 (-0.83; 0.65)	-0.21 (-0.82; 0.39)
O_3	-0.65 (-1.52; 0.22)	-0.91 (-1.76; -0.06)**	-0.99 (-1.87; -0.10)**	-0.62 (-1.42; 0.19)
NO_2	-0.29 (-1.14; 0.57)	-0.16 (-1.01; 0.69)	1.09 (-0.33; 2.51)	-0.23 (-1.04; 0.57)
NO_X	-0.40 (-1.10; 0.30)	-0.27 (-0.96; 0.42)	0.03 (-0.78; 0.84)	-0.16 (-0.82; 0.49)
EQ-VAS				
PM_{10}	-1.47 (-2.47; -0.47)**	-1.38 (-2.37; -0.38)**	-1.04 (-2.22; 0.14)*	-1.24 (-2.17; -0.30)**
PM_{coarse}	-1.24 (-2.27; -0.20)**	-1.25 (-2.28; -0.23)**	-0.76 (-2.20; 0.68)	-1.08 (-2.04; -0.12)**
$PM_{2.5}$	-0.78 (-1.77; 0.21)	-0.64 (-1.60; 0.32)	-0.15 (-1.24; 0.94)	-0.58 (-1.50; 0.34)
$PM_{2.5abs}$	-1.64 (-2.77; -0.51)**	-1.57 (-2.69; -0.45)**	-1.28 (-2.98; 0.42)	-1.49 (-2.55; -0.43)**
PNC	-1.03 (-1.83; -0.22)**	-0.89 (-1.68; -0.10)**	-0.54 (-1.47; 0.38)	-0.73 (-1.49; 0.02)*
O_3	0.40 (-0.70; 1.49)	0.18 (-0.89; 1.25)	0.16 (-0.95; 1.27)	0.71 (-0.29; 1.72)
NO_2	-1.40 (-2.47; -0.32)**	-1.30 (-2.36; -0.23)**	-0.79 (-2.57; 0.99)	-1.25 (-2.25; -0.25)**
NO_X	-1.10 (-1.98; -0.22)**	-0.96 (-1.83; -0.10)**	-0.59 (-1.60; 0.42)	-0.81 (-1.63; 0.01)*

Abbreviations: EQ-5D index value, index of European Quality of Life 5 Dimension 5 Level questionnaire; EQ-VAS, EuroQol group's visual analog scale; IQR, Inter-quartile range; 95% CI, 95% confidence interval; PM_{10}, particulate matter (PM) with an aerodynamic diameter < 10µm (µg/m^3); PM_{coarse}, coarse particulate matter; $PM_{2.5}$, PM < 2.5µm (µg/m^3); $PM_{2.5abs}$, the absorbance of $PM_{2.5}$; PNC, particle number concentration; O_3, Ozone (µg/m^3); NO_2, Nitrogen dioxide (µg/m^3); NO_X, Nitrogen oxide (µg/m^3).
Note: Estimates represent the percentage changes in EQ-5D index value /EQ-VAS for IQR increase in annual exposures to air pollutants (1.95 µg/m^2 for PM_{10}, 1.40 µg/m^2 for PM_{coarse}, 1.39 µg/m^2 for $PM_{2.5}$, 0.28 (10^{-5}/m) for $PM_{2.5abs}$, 1.92 (10^3/cm^3) for PNC, 3.54 µg/m^2 for O_3, 6.20 µg/m^2 for NO_2 and 8.41 µg/m^2 for NO_X).
The minimum model was adjusted for age at the survey and sex.
The main model was further adjusted for socioeconomic status (SES), living with a partner, body mass index (BMI), physical activity, and smoking status.
The extended model 1 was further adjusted for variables in the main model plus the percentage of households with low income and degree of urbanization.
The extended model 2 was further adjusted for variables in the main model plus the General Self-Efficacy (ASKU) and Perceived Stress (PSS).
$^*P < 0.10$; $^{**}P < 0.05$.

Table S3. Results from single-pollutant multiple regression models show the association between annual air pollutant exposure and the absolute changes in EQ-VAS.

Air pollutants	Absolute changes (95% CIs)			
	Minimum model	Main model	Extended model 1	Extended model 2
PM_{10}	-1.17 (-1.96; -0.37)**	-1.09 (-1.88; -0.30)**	-0.82 (-1.76; 0.11)*	-0.98 (-1.73; -0.24)**
PM_{coarse}	-0.98 (-1.80; -0.16)**	-0.99 (-1.81; -0.18)**	-0.60 (-1.75; 0.54)	-0.86 (-1.62; -0.10)**
$PM_{2.5}$	-0.62 (-1.40; 0.17)	-0.51 (-1.27; 0.26)	-0.12 (-0.98; 0.74)	-0.46 (-1.19; 0.27)
$PM_{2.5abs}$	-1.30 (-2.20; -0.40)**	-1.25 (-2.13; -0.36)**	-1.02 (-2.36; 0.33)	-1.18 (-2.02; -0.34)**
PNC	-0.81 (-1.45; -0.17)**	-0.70 (-1.33; -0.08)**	-0.43 (-1.16; 0.30)	-0.58 (-1.18; 0.02)*
O_3	0.31 (-0.55; 1.18)	0.14 (-0.70; 0.99)	0.13 (-0.75; 1.00)	0.57 (-0.23; 1.37)
NO_2	-1.11 (-1.96; -0.26)**	-1.03 (-1.87; -0.18)**	-0.63 (-2.04; 0.79)	-0.99 (-1.79; -0.20)**
NO_X	-0.87 (-1.56; -0.17)**	-0.76 (-1.45; -0.08)**	-0.47 (-1.27; 0.34)	-0.65 (-1.30; 0.01)*

Abbreviations: EQ-VAS, EuroQol group's visual analog scale; IQR, Inter-quartile range; 95% CI, 95% confidence interval; PM_{10}, particulate matter (PM) with an aerodynamic diameter < 10µm (µg/m^3); PM_{coarse}, coarse particulate matter; $PM_{2.5}$, PM < 2.5µm (µg/m^3); $PM_{2.5abs}$, the absorbance of $PM_{2.5}$; PNC, particle number concentration; O_3, Ozone (µg/m^3); NO_2, Nitrogen dioxide (µg/m^3); NO_X, Nitrogen oxide (µg/m^3).

Note: Estimates represent the absolute changes in EQ-VAS for IQR increase in annual exposures to air pollutants (1.95 µg/m^2 for PM_{10}, 1.40 µg/m^2 for PM_{coarse}, 1.39 µg/m^2 for $PM_{2.5}$, 0.28 (10^{-5}/m) for $PM_{2.5abs}$, 1.92 (10^3/cm^3) for PNC, 3.54 µg/m^2 for O_3, 6.20 µg/m^2 for NO_2 and 8.41 µg/m^2 for NO_X).

The minimum model was adjusted for age at the survey and sex.

The main model was further adjusted for socioeconomic status (SES), living with a partner, body mass index (BMI), physical activity, and smoking status.

The extended model 1 was further adjusted for variables in the main model plus the percentage of households with low income and degree of urbanization.

The extended model 2 was further adjusted for variables in the main model plus the General Self-Efficacy (ASKU) and Perceived Stress (PSS).

* $P < 0.10$; ** $P < 0.05$.

Table S4. Results of single-pollutant models showing the associations between annual air pollutant exposures and the odds of having problems in individual dichotomized EQ-5D-5L.

Air pollutants	OR (95%CI)				
	Mobility	Self-care	Usual activities	Pain/discomfort	Anxiety/depression
PM_{10}	1.44 (0.65; 3.19)	1.00 (0.14; 6.96)	3.46 (1.32; 9.10)**	1.64 (0.79; 3.39)	1.24 (0.56; 2.72)
PM_{coarse}	1.28 (0.90; 1.80)	0.84 (0.37; 1.93)	1.36 (0.89; 2.08)	1.14 (0.83; 1.56)	1.06 (0.75; 1.49)
$PM_{2.5}$	0.58 (0.26; 1.33)	0.19 (0.03; 1.38)*	0.82 (0.29; 2.30)	1.05 (0.50; 2.20)	1.28 (0.57; 2.92)
$PM_{2.5abs}$	1.08 (0.70; 1.68)	0.96 (0.33; 2.80)	1.65 (0.96; 2.84)*	1.42 (0.95; 2.12)*	1.06 (0.69; 1.64)
PNC	1.07 (0.80; 1.43)	0.97 (0.47; 2.00)	1.53 (1.07; 2.19)**	1.20 (0.92; 1.57)	1.16 (0.87; 1.55)
O_3	1.43 (0.45; 4.60)	3.37 (0.17; 65.23)	1.51 (0.35; 6.50)	1.27 (0.45; 3.61)	1.19 (0.38; 3.73)
NO_2	1.00 (0.81; 1.23)	0.79 (0.47; 1.33)	1.16 (0.90; 1.50)	1.10 (0.91; 1.33)	1.07 (0.87; 1.31)
NO_X	1.05 (0.83; 1.32)	0.91 (0.51; 1.60)	1.31 (0.98; 1.75)*	1.14 (0.93; 1.41)	1.13 (0.90; 1.42)

Abbreviations: OR, odds ratio; 95% CI, 95% confidence interval; EQ-5D-5L, European Quality of Life 5 Dimension 5 Level questionnaire; IQR, Interquartile range; PM_{10}, particulate matter (PM) with an aerodynamic diameter < 10μm (μg/m^3); PM_{coarse}, coarse particulate matter; $PM_{2.5}$, PM < 2.5μm (μg/m^3); $PM_{2.5abs}$, the absorbance of $PM_{2.5}$; PNC, particle number concentration; O_3, Ozone (μg/m^3); NO_2, Nitrogen dioxide (μg/m^3); NO_X, Nitrogen oxide (μg/m^3).

Note: With those reported "had no problems" as the reference group, estimates represented as ORs (with 95%CIs) of "any problems" for IQR increase in annual exposures to air pollutants (1.95 μg/m^2 for PM_{10}, 1.40 μg/m^2 for PM_{coarse}, 1.39 μg/m^2 for $PM_{2.5}$, 0.28 (10^{-5}/m) for $PM_{2.5abs}$, 1.92 (10^3/cm^3) for PNC, 3.54 μg/m^2 for O_3, 6.20 μg/m^2 for NO_2 and 8.41 μg/m^2 for NO_X).

Analysis was conducted in the main model, which was adjusted for age, sex, socioeconomic status (SES), living with a partner, body mass index (BMI), physical activity, and smoking status.

* $P < 0.10$; ** $P < 0.05$.

Table S5. Results from single-pollutant logistic regression models showing the association between annual air pollutant exposure and the odds of reporting poor SRH.

Air pollutants	OR (95% CI)			
	Minimum model	Main model	Extended model 1	Extended model 2
PM_{10}	2.94 (1.23; 7.03)**	2.67 (1.07; 6.67)**	2.22 (0.74; 6.62)	2.50 (0.92; 6.78)*
PM_{coarse}	1.70 (1.16; 2.51)**	1.70 (1.14; 2.54)**	1.80 (1.02; 3.19)**	1.64 (1.06; 2.53)**
$PM_{2.5}$	2.07 (0.80; 5.34)	1.87 (0.70; 5.01)	1.32 (0.43; 4.05)	1.88 (0.65; 5.39)
$PM_{2.5abs}$	1.73 (1.06; 2.82)**	1.60 (0.96; 2.67)*	1.43 (0.64; 3.16)	1.55 (0.89; 2.70)
PNC	1.49 (1.08; 2.06)**	1.42 (1.01; 1.99)**	1.32 (0.89; 1.96)	1.37 (0.94; 1.99)*
O_3	2.09 (0.55; 7.88)	3.22 (0.81; 12.85)*	4.59 (1.09; 19.42)**	2.16 (0.47; 9.81)
NO_2	1.29 (1.02; 1.62)**	1.24 (0.98; 1.58)*	1.15 (0.76; 1.74)	1.22 (0.94; 1.59)
NO_X	1.41 (1.08; 1.83)**	1.36 (1.04; 1.79)**	1.29 (0.94; 1.78)	1.30 (0.97; 1.75)*

Abbreviations: SRH, self-rated health; OR, odds ratio; 95% CI, 95% confidence interval; PM_{10}, particulate matter (PM) with an aerodynamic diameter < 10µm (µg/m³); PM_{coarse}, coarse particulate matter; $PM_{2.5}$, PM < 2.5µm (µg/m³); $PM_{2.5abs}$, the absorbance of $PM_{2.5}$; PNC, particle number concentration; O_3, Ozone (µg/m³); NO_2, Nitrogen dioxide (µg/m³); NO_X, Nitrogen oxide (µg/m³).
Note: With those reported "good SRH" as the reference group, estimates represented as ORs (with 95% CIs) of poor SRH for IQR increase in annual exposures to air pollutants (1.95 µg/m² for PM_{10}, 1.40 µg/m² for PM_{coarse}, 1.39 µg/m² for $PM_{2.5}$, 0.28 (10^{-5}/m) for $PM_{2.5abs}$, 1.92 (10^3/cm³) for PNC, 3.54 µg/m² for O_3, 6.20 µg/m² for NO_2 and 8.41 µg/m² for NO_X).
The minimum model was adjusted for age at the survey and sex.
The main model was further adjusted for socioeconomic status (SES), living with a partner, body mass index (BMI), physical activity, and smoking status.
The extended model 1 was further adjusted for variables in the main model plus the percentage of households with low income and degree of urbanization.
The extended model 2 was further adjusted for variables in the main model plus the General Self-Efficacy (ASKU) and Perceived Stress (PSS).
$^{*}P < 0.10$; $^{**}P < 0.05$.

Table S6. Results from multiple logistic regression showing the associations between annual air pollutant exposures and the odds of reporting equal or worse CSRH, in relative to reporting better CSRH.

Air pollutants	OR (95%CI)							
	Minimum model		Main model		Extended model 1		Extended model 2	
	Equal	Worse	Equal	Worse	Equal	Worse	Equal	Worse
PM_{10}	0.93 (0.88; 0.99)**	1.07 (0.97; 1.18)	0.95 (0.89; 1.01)	1.06 (0.96; 1.18)	0.96 (0.89; 1.03)	1.00 (0.88; 1.13)	0.95 (0.89;1.01)*	1.06 (0.95;1.18)
PM_{coarse}	0.90 (0.83; 0.99)**	1.14 (0.98; 1.32)*	0.95 (0.86; 1.03)	1.15 (0.99; 1.35)*	0.96 (0.85; 1.09)	1.06 (0.85; 1.32)	0.94 (0.85;1.03)	1.14 (0.97;1.34)
$PM_{2.5}$	1.00 (0.92; 1.09)	1.14 (0.98; 1.32)*	1.03 (0.94; 1.12)	1.14 (0.98; 1.33)*	1.06 (0.96; 1.17)	1.07 (0.90; 1.27)	1.02 (0.93;1.11)	1.15 (0.98;1.35)*
$PM_{2.5abs}$	0.68 (0.42; 1.08)*	2.53 (1.13; 5.67)**	0.85 (0.52; 1.38)	2.59 (1.12; 5.99)**	1.09 (0.52; 2.29)	1.89 (0.51; 7.04)	0.89 (0.53;1.48)	2.39 (0.99;5.76)*
PNC	0.96 (0.92; 1.01)	1.04 (0.96; 1.13)	0.98 (0.93; 1.03)	1.04 (0.95; 1.13)	0.99 (0.93; 1.05)	0.98 (0.88; 1.09)	0.98 (0.93;1.03)	1.03 (0.93;1.13)
O_3	1.00 (0.96; 1.03)	1.02 (0.96; 1.09)	1.00 (0.97; 1.04)	1.03 (0.97; 1.10)	1.00 (0.97; 1.04)	1.05 (0.98; 1.12)	0.99 (0.95;1.03)	1.03 (0.96;1.10)
NO_2	0.98 (0.96; 1.00)*	1.03 (1.00; 1.07)*	0.99 (0.97; 1.01)	1.03 (1.00; 1.07)*	1.00 (0.96; 1.03)	1.00 (0.94; 1.07)	0.99 (0.97;1.01)	1.03 (0.99;1.07)
NO_X	0.99 (0.98; 1.01)	1.01 (0.99; 1.04)	1.00 (0.99; 1.01)	1.01 (0.99; 1.04)	1.00 (0.99; 1.02)	1.00 (0.97; 1.03)	1.00 (0.99;1.01)	1.01 (0.99;1.03)

Abbreviations: OR, odds ratio; 95% CI, 95% confidence interval; PM_{10}, particulate matter (PM) with an aerodynamic diameter < 10µm (µg/m^3); PM_{coarse}, coarse particulate matter; $PM_{2.5}$, PM < 2.5µm (µg/m^3); $PM_{2.5abs}$, the absorbance of $PM_{2.5}$; PNC, particle number concentration; O_3, Ozone (µg/m^3); NO_2, Nitrogen dioxide (µg/m^3); NO_X, Nitrogen oxide (µg/m^3).
Note: With "better CSRH" as the reference, estimates represented as ORs (with 95% CIs) of equal/worse CSRH for IQR increase in annual exposures to air pollutants (1.95 µg/m^2 for PM_{10}, 1.40 µg/m^2 for PM_{coarse}, 1.39 µg/m^2 for $PM_{2.5}$, 0.28 (10^{-5}/m) for $PM_{2.5abs}$, 1.92 (10^3/cm^3) for PNC, 3.54 µg/m^2 for O_3, 6.20 µg/m^2 for NO_2 and 8.41 µg/m^2 for NO_X).
The minimum model was adjusted for age at the survey and sex.
The main model was further adjusted for socioeconomic status (SES), living with a partner, body mass index (BMI), physical activity, and smoking status.
The extended model 1 was further adjusted for variables in the main model plus the percentage of households with low income and degree of urbanization.
The extended model 2 was further adjusted for variables in the main model plus the General Self-Efficacy (ASKU) and Perceived Stress (PSS).
$^{*}P < 0.10$; $^{**}P < 0.05$.

Table S7. Results of sensitivity analysis showing the associations between annual levels of air pollution exposures and the percentage changes in EQ-5D index value and EQ-VAS, and the odds of reporting poor SRH, equal or worse CSRH, in two main adjustment models.

Air pollutants	Parameters				
	EQ-5D index value Percentage changes (95% CIs)	EQ-VAS Percentage changes (95% CIs)	Poor SRH OR (95% CI) [a]	Equal CSRH OR (95% CI) [a]	Worse CSRH OR (95% CI) [a]
PM_{10}					
Present main model[b]	**-0.74 (-1.53; 0.05)***	**-1.38 (-2.37; -0.38)****	**2.67 (1.07; 6.67)****	**0.95 (0.89; 1.01)**	**1.06 (0.96; 1.18)**
Updated main model[c]	-0.73 (-1.54; 0.08)*	-1.37 (-2.39; -0.36)**	2.52 (1.03; 6.20)**	0.95 (0.89; 1.01)*	1.06 (0.96; 1.18)
PM_{coarse}					
Present main model[b]	**-0.57 (-1.39; 0.25)**	**-1.25 (-2.28; -0.23)****	**1.70 (1.14; 2.54)****	**0.95 (0.86; 1.03)**	**1.15 (0.99; 1.35)***
Updated main model[c]	-0.45 (-1.29; 0.38)	-1.12 (-2.16; -0.07)**	1.58 (1.06; 2.35)**	0.93 (0.85; 1.02)	1.13 (0.96; 1.31)
$PM_{2.5}$					
Present main model[b]	**0.16 (-0.61; 0.93)**	**-0.64 (-1.60; 0.32)**	**1.87 (0.70; 5.01)**	**1.03 (0.94; 1.12)**	**1.14 (0.98; 1.33)***
Updated main model[c]	0.22 (-0.57; 1.00)	-0.58 (-1.56; 0.41)	1.66 (0.63; 4.38)	1.02 (0.94; 1.10)	1.12 (0.96; 1.31)
$PM_{2.5abs}$					
Present main model[b]	**-0.82 (-1.71; 0.08)***	**-1.57 (-2.69; -0.45)****	**1.60 (0.96; 2.67)***	**0.85 (0.52; 1.38)**	**2.59 (1.12; 5.99)****
Updated main model[c]	-0.73 (-1.64; 0.18)	-1.48 (-2.62; -0.34)**	1.52 (0.92; 2.51)	0.77 (0.48; 1.24)	2.32 (1.01; 5.33)**
PNC					
Present main model[b]	**-0.33 (-0.97; 0.30)**	**-0.89 (-1.68; -0.10)****	**1.42 (1.01; 1.99)****	**0.98 (0.93; 1.03)**	**1.04 (0.95; 1.13)**
Updated main model[c]	-0.28 (-0.93; 0.37)	-0.83 (-1.64; -0.02)**	1.36 (0.97; 1.89)*	0.97 (0.92; 1.02)	1.02 (0.94; 1.12)
O_3					
Present main model[b]	**-0.91 (-1.76; -0.06)****	**0.18 (-0.89; 1.25)**	**3.22 (0.81; 12.85)***	**1.00 (0.97; 1.04)**	**1.03 (0.97; 1.10)**
Updated main model[c]	-0.84 (-1.71; 0.02)*	0.27 (-0.82; 1.35)	2.76 (0.71; 10.67)	1.00 (0.96; 1.04)	1.03 (0.96; 1.10)
NO_2					
Present main model[b]	**-0.16 (-1.01; 0.69)**	**-1.30 (-2.36; -0.23)****	**1.24 (0.98; 1.58)***	**0.99 (0.97; 1.01)**	**1.03 (1.00; 1.07)***
Updated main model[c]	-0.07 (-0.94; 0.80)	-1.2 (-2.29; -0.12)**	1.20 (0.95; 1.53)	0.99 (0.97; 1.01)	1.03 (0.99; 1.06)
NO_X					
Present main model[b]	**-0.27 (-0.96; 0.42)**	**-0.96 (-1.83; -0.10)****	**1.36 (1.04; 1.79)****	**1.00 (0.99; 1.01)**	**1.01 (0.99; 1.04)**
Updated main model[c]	-0.19 (-0.90; 0.51)	-0.88 (-1.76; 0.00)*	1.30 (1.00; 1.70)*	1.00 (0.98; 1.01)	1.01 (0.99; 1.03)

Abbreviations: EQ-5D index value, index of European Quality of Life 5 Dimension 5 Level questionnaire; EQ-VAS, EuroQol group's visual analog scale; SRH, self-rated health; CSRH, comparative self-rated health; OR, odds ratio; 95% CI, 95% confidence interval; PM_{10}, particulate matter (PM) with an aerodynamic diameter < 10µm (µg/m^3); PM_{coarse}, coarse particulate matter; $PM_{2.5}$, PM < 2.5µm (µg/m^3); $PM_{2.5abs}$, the absorbance of $PM_{2.5}$; PNC, particle number concentration; O_3, Ozone (µg/m^3); NO_2, Nitrogen dioxide (µg/m^3); NO_X, Nitrogen oxide (µg/m^3).
Note: Estimates represented as the percentage changes (with 95% CIs) in EQ-5D index value/EQ-VAS or ORs (with 95%CIs) of poor SRH/equal CSRH/worse CSHR for IQR increase in annual exposures to air pollutants (1.95 µg/m^2 for PM_{10}, 1.40 µg/m^2 for PM_{coarse}, 1.39 µg/m^2 for $PM_{2.5}$, 0.28 [10^{-5}/m] for $PM_{2.5abs}$, 1.92 [10^3/cm^3] for PNC, 3.54 µg/m^2 for O_3, 6.20 µg/m^2 for NO_2 and 8.41 µg/m^2 for NO_X).
[a] The ORs (95%CIs) were calculated with the category “good SRH” as the reference for “poor SRH”; “better CSRH” as the reference for “equal CSRH” or “worse CSRH”.
[b] The present main model was adjusted for age at survey, sex, socioeconomic status (SES), living with a partner, body mass index (BMI), physical activity, and smoking status.

[c] The updated main model was adjusted for age at survey, sex, socioeconomic status (SES), living with a partner, and smoking status.
[*] $P < 0.10$; [**] $P < 0.05$.

Table S8. Results of two-pollutant multiple logistic regression or multiple regression models showing the associations between annual levels of air pollution exposures and the percentage changes in EQ-5D index value and EQ-VAS, and the odds of reporting poor SRH, equal or worse CSRH.

Air pollutants	Parameters				
	EQ-5D index value Percentage changes (95% CIs)	EQ-VAS Percentage changes (95% CIs)	Poor SRH OR (95% CI) [a]	Equal CSRH OR (95% CI) [a]	Worse CSRH OR (95% CI) [a]
PM_{10} [b]	**-0.74 (-1.53; 0.05)***	**-1.38 (-2.37; -0.38)****	**2.67 (1.07; 6.67)****	**0.95 (0.89; 1.01)**	**1.06 (0.96; 1.18)**
+ $PM_{2.5}$	-1.08 (-1.99; -0.17)**	-1.41 (-2.56; -0.27)**	1.08 (0.99; 1.18)*	0.93 (0.86; 0.99)**	1.02 (0.90; 1.15)
+ O_3	-0.72 (-1.51; 0.07)*	-1.40 (-2.40; -0.41)**	1.08 (1.00; 1.17)**	0.95 (0.89; 1.01)*	1.06 (0.96; 1.18)
PM_{coarse} [b]	**-0.57 (-1.39; 0.25)**	**-1.25 (-2.28; -0.23)****	**1.70 (1.14; 2.54)****	**0.95 (0.86; 1.03)**	**1.15 (0.99; 1.35)***
+ $PM_{2.5}$	-0.57 (-1.39; 0.25)	-1.24 (-1.20; -0.06)**	1.16 (1.02; 1.32)**	0.91 (0.82; 1.01)*	1.11 (0.92; 1.33)
+ O_3	-0.39 (-1.23; 0.45)	-1.38 (-2.43; -0.33)**	1.14 (1.02; 1.28)**	0.94 (0.86; 1.03)	1.14 (0.98; 1.34)*
+ NO_X	-0.64 (-1.73; 0.45)	-0.92 (-2.28; 0.45)	1.12 (0.96; 1.30)	0.92 (0.82; 1.03)	1.18 (0.95; 1.46)
$PM_{2.5}$ [b]	**0.16 (-0.61; 0.93)**	**-0.64 (-1.60; 0.32)**	**1.87 (0.70; 5.01)**	**1.03 (0.94; 1.12)**	**1.14 (0.98; 1.33)***
+ $PM_{2.5abs}$	0.80 (-0.12; 1.73)*	0.17 (-1.00; 1.33)	1.02 (0.89; 1.16)	1.06 (0.96; 1.18)	1.05 (0.87; 1.27)
+ PNC	0.66 (-0.32; 1.63)	0.03 (-1.19; 1.26)	1.00 (0.88; 1.15)	1.08 (0.97; 1.21)	1.17 (0.96; 1.41)
+ O_3	0.00 (-0.79; 0.79)	0.01 (-1.63; 0.34)	1.09 (0.98; 1.22)	1.03 (0.94; 1.12)	1.16 (1.00; 1.36)*
+ NO_2	0.47 (-0.57; 1.51)	0.40 (-0.89; 1.70)	1.01 (0.87; 1.16)	1.10 (0.98; 1.24)*	1.07 (0.87; 1.32)
+ NDVI	0.61(-0.39; 1.61)	-0.35 (-1.61; 0.92)	1.03 (0.89; 1.18)	1.09 (0.98; 1.22)	1.10 (0.90; 1.36)
$PM_{2.5abs}$ [b]	**-0.82 (-1.71; 0.08)***	**-1.57 (-2.69; -0.45)****	**1.60 (0.96; 2.67)***	**0.85 (0.52; 1.38)**	**2.59 (1.12; 5.99)****
+ O_3	-0.92 (-1.83; -0.01)**	-1.61 (-2.76; -0.47)**	1.84 (1.00; 3.38)**	0.85 (0.52; 1.38)	2.74 (1.17; 6.40)**
+ NO_X	-1.07 (-2.29; 0.15)*	-1.38 (-2.92; 0.15)*	1.19 (0.53; 2.69)	0.79 (0.41; 1.53)	3.24 (1.03; 10.21)**
PNC [b]	**-0.33 (-0.97; 0.30)**	**-0.89 (-1.68; -0.10)****	**1.42 (1.01; 1.99)****	**0.98 (0.93; 1.03)**	**1.04 (0.95; 1.13)**
+ O_3	-0.38 (-0.98; 0.25)	-0.90 (-1.69; -0.10)**	1.07 (1.00; 1.14)**	0.98 (0.93; 1.03)	1.04 (0.95; 1.13)
O_3 [b]	**-0.91 (-1.76; -0.06)****	**0.18 (-0.89; 1.25)**	**3.22 (0.81; 12.85)***	**1.00 (0.97; 1.04)**	**1.03 (0.97; 1.10)**
+ NO_2	-0.97 (-1.84; -0.11)**	-0.07 (-1.16; 1.01)	1.05 (1.00; 1.10)**	1.00 (0.96; 1.03)	1.03 (0.96; 1.11)
+ NO_X	-0.97 (-1.83; -0.12)**	0.00 (-1.08; 1.08)	1.05 (1.00; 1.10)*	1.00 (0.96; 1.03)	1.03 (0.96; 1.10)
+ NDVI	-0.76 (-1.60; 0.08)*	0.33 (-0.73; 1.39)	1.03 (0.98; 1.08)	1.00 (0.96; 1.04)	1.02 (0.96; 1.09)

Abbreviations: EQ-5D index value, index of European Quality of Life 5 Dimension 5 Level questionnaire; EQ-VAS, EuroQol group's visual analog scale; SRH, self-rated health; CSRH, comparative self-rated health; OR, odds ratio; 95% CI, 95% confidence interval; PM_{10}, particulate matter (PM) with an aerodynamic diameter < 10μm (μg/m^3); PM_{coarse}, coarse particulate matter; $PM_{2.5}$, PM < 2.5μm (μg/m^3); $PM_{2.5abs}$, the absorbance of $PM_{2.5}$; PNC, particle number concentration; O_3, Ozone (μg/m^3); NO_2, Nitrogen dioxide (μg/m^3); NO_X, Nitrogen oxide (μg/m^3); NDVI; normalized difference vegetation index.

Note: Estimates represented as the percentage changes (with 95% CIs) in EQ-5D index value/EQ-VAS or ORs (with 95%CIs) of poor SRH/equal CSRH/worse CSHR for IQR increase in annual exposures to air pollutants (1.95 μg/m^2 for PM_{10}, 1.40 μg/m^2 for PM_{coarse}, 1.39 μg/m^2 for $PM_{2.5}$, 0.28 [10^{-5}/m] for $PM_{2.5abs}$, 1.92 [10^3/cm^3] for PNC, 3.54 μg/m^2 for O_3, 6.20 μg/m^2 for NO_2 and 8.41 μg/m^2 for NO_X).

Only air pollutants showing a Spearman correlation coefficient < 0.7 would be selected into the models.

Analysis was conducted in the main model, which was adjusted for age at survey, sex, socioeconomic status (SES), living with a partner, body mass index (BMI), physical activity and smoking status.

[a] The ORs (95%CIs) were calculated with the category “good SRH” as the reference for “poor SRH”; “better CSRH” as the reference for “equal CSRH” or “worse CSRH”.
[b] The results from the single-pollutant model.
* $P < 0.10$; ** $P < 0.05$.

Table S9. Results of sensitivity analysis showing the associations between annual levels of air pollution exposures and the percentage changes in EQ-5D index value and EQ-VAS, and the odds of reporting poor SRH, equal or worse CSRH, after further adjustment for residential duration of the current addresses.

Air pollutants	Parameters				
	EQ-5D index value Percentage changes (95% CIs)	EQ-VAS Percentage changes (95% CIs)	Poor SRH OR (95% CI) [a]	Equal CSRH OR (95% CI) [a]	Worse CSRH OR (95% CI) [a]
PM_{10} [b]	**-0.74 (-1.53; 0.05)***	**-1.38 (-2.37; -0.38)****	**2.67 (1.07; 6.67)****	**0.95 (0.89; 1.01)**	**1.06 (0.96; 1.18)**
+ residential duration[c]	-0.72 (-1.52; 0.07)*	-1.33 (-2.32; -0.33)**	2.66 (1.06; 6.66)**	0.96 (0.90; 1.02)	1.06 (0.95; 1.18)
PM_{coarse} [b]	**-0.57 (-1.39; 0.25)**	**-1.25 (-2.28; -0.23)****	**1.70 (1.14; 2.54)****	**0.95 (0.86; 1.03)**	**1.15 (0.99; 1.35)***
+ residential duration[c]	-0.55 (-1.37; 0.27)	-1.18 (-2.21; -0.15)**	1.70 (1.13; 2.54)**	0.96 (0.87; 1.04)	1.15 (0.98; 1.34)*
$PM_{2.5}$ [b]	**0.16 (-0.61; 0.93)**	**-0.64 (-1.60; 0.32)**	**1.87 (0.70; 5.01)**	**1.03 (0.94; 1.12)**	**1.14 (0.98; 1.33)***
+ residential duration[c]	0.17 (-0.60; 0.94)	-0.63 (-1.59; 0.34)	1.87 (0.70; 5.00)*	1.03 (0.94; 1.12)	1.14 (0.98; 1.33)*
$PM_{2.5abs}$ [b]	**-0.82 (-1.71; 0.08)***	**-1.57 (-2.69; -0.45)****	**1.60 (0.96; 2.67)***	**0.85 (0.52; 1.38)**	**2.59 (1.12; 5.99)****
+ residential duration[c]	-0.80 (-1.69; 0.10)*	-1.51 (-2.64; -0.39)**	1.60 (0.96; 2.67)	0.88 (0.54; 1.43)	2.51 (1.08; 5.83)**
PNC [b]	**-0.33 (-0.97; 0.30)**	**-0.89 (-1.68; -0.10)****	**1.42 (1.01; 1.99)****	**0.98 (0.93; 1.03)**	**1.04 (0.95; 1.13)**
+ residential duration[c]	-0.33 (-0.96; 0.30)	-0.88 (-1.67; -0.09)**	1.42 (1.01; 1.99)**	0.98 (0.93; 1.03)	1.03 (0.95; 1.13)
O_3 [b]	**-0.91 (-1.76; -0.06)****	**0.18 (-0.89; 1.25)**	**3.22 (0.81; 12.85)***	**1.00 (0.97; 1.04)**	**1.03 (0.97; 1.10)**
+ residential duration[c]	-0.89 (-1.75; -0.04)**	0.26 (-0.81; 1.33)	3.19 (0.80; 12.80)	1.01 (0.97; 1.04)	1.03 (0.96; 1.10)
NO_2[b]	**-0.16 (-1.01; 0.69)**	**-1.30 (-2.36; -0.23)****	**1.24 (0.98; 1.58)***	**0.99 (0.97; 1.01)**	**1.03 (1.00; 1.07)***
+ residential duration[c]	-0.14 (-1.00; 0.71)	-1.25 (-2.32; -0.19)**	1.24 (0.98; 1.58)*	0.99 (0.97; 1.01)	1.03 (1.00; 1.07)*
NO_X[b]	**-0.27 (-0.96; 0.42)**	**-0.96 (-1.83; -0.10)****	**1.36 (1.04; 1.79)****	**1.00 (0.99; 1.01)**	**1.01 (0.99; 1.04)**
+ residential duration[c]	-0.27 (-0.96; 0.42)	-0.96 (-1.82; -0.09)**	1.36 (1.04; 1.78)**	1.00 (0.99; 1.01)	1.01 (0.99; 1.03)

Abbreviations: EQ-5D index value, index of European Quality of Life 5 Dimension 5 Level questionnaire; EQ-VAS, EuroQol group's visual analog scale; SRH, self-rated health; CSRH, comparative self-rated health; OR, odds ratio; 95% CI, 95% confidence interval; PM_{10}, particulate matter (PM) with an aerodynamic diameter < 10μm (μg/m^3); PM_{coarse}, coarse particulate matter; $PM_{2.5}$, PM < 2.5μm (μg/m^3); $PM_{2.5abs}$, the absorbance of $PM_{2.5}$; PNC, particle number concentration; O_3, Ozone (μg/m^3); NO_2, Nitrogen dioxide (μg/m^3); NO_X, Nitrogen oxide (μg/m^3).
Note: Estimates represented as the percentage changes (with 95% CIs) in EQ-5D index value/EQ-VAS or ORs (with 95%CIs) of poor SRH/equal CSRH/worse CSHR for IQR increase in annual exposures to air pollutants (1.95 μg/m^2 for PM_{10}, 1.40 μg/m^2 for PM_{coarse}, 1.39 μg/m^2 for $PM_{2.5}$, 0.28 [10^{-5}/m] for $PM_{2.5abs}$, 1.92 [10^3/cm^3] for PNC, 3.54 μg/m^2 for O_3, 6.20 μg/m^2 for NO_2 and 8.41 μg/m^2 for NO_X).

[a] The ORs (95%CIs) were calculated with the category "good SRH" as the reference for "poor SRH"; "better CSRH" as the reference for "equal CSRH" or "worse CSRH".

[b] The results from the present main model.

[c] Analysis was conducted in the extended model 3, which was adjusted for covariates in the main model (age at survey, sex, socioeconomic status (SES), living with a partner, body mass index [BMI], physical activity and smoking status) plus residential duration (years).

* $P < 0.10$; ** $P < 0.05$.

Table S10. Results of interaction analysis for the association between annual levels of air pollutant exposures and percentage changes in EQ-VAS.

Pollutants	Groups	n (%)	EQ-VAS: Percentage changes (95% CIs)	*P*-interaction [a]
PM_{10}				
Sex	Female	1428 (54.71)	-1.68 (-3.03; -0.34)	0.540
	Male	1182 (45.29)	-1.07 (-2.53; 0.38)	
Age, years [b]	<65.0	1373 (52.61)	-1.95 (-3.35; -0.56)	0.300
	≥65.0	1237 (47.39)	-0.92 (-2.31; 0.48)	
BMI, kg/m^2	<30.0	1854 (71.03)	-2.24 (-3.43; -1.04)	0.008
	≥30.0	756 (28.97)	0.64 (-1.15; 2.42)	
SES, points	1.0-12.0	664 (25.53)	-1.60 (-3.61; 0.40)	Ref
	≥12.0-16.5	1048 (40.29)	-1.13 (-2.66; 0.40)	0.710
	≥16.5	889 (34.18)	-1.48 (-3.16; 0.19)	0.928
Self-perception of residential greenness	Very green	2062 (79.49)	-1.10 (-2.33; 0.13)	0.904
	Hardly green	532 (20.51)	-0.96 (-2.93; 1.01)	
NDVI [c]	<0.43	1316 (50.42)	-1.73 (-3.16; -0.29)	0.996
	≥0.43	1294 (49.58)	-1.72 (-4.22; 0.78)	
ASKU [c]	<4.02	1821 (71.83)	-1.30 (-2.45; -0.15)	0.751
	≥4.02	714 (28.17)	-1.65 (-3.51; 0.20)	
PSS [c]	<13.59	1331 (53.54)	-0.30 (-1.66; 1.06)	0.033
	≥13.59	1155 (46.46)	-2.37 (-3.71; -1.02)	
PM_{coarse}				
Sex	Female	1428 (54.71)	-1.53 (-2.90; -0.15)	0.596
	Male	1182 (45.29)	-0.98 (-2.49; 0.53)	
Age, years [b]	<65.0	1373 (52.61)	-1.97 (-3.39; -0.56)	0.182
	≥65.0	1237 (47.39)	-0.61 (-2.07; 0.85)	
BMI, kg/m^2	<30.0	1854 (71.03)	-1.89 (-3.13; -0.65)	0.050
	≥30.0	756 (28.97)	0.30 (-1.52; 2.12)	
SES	1.0-12.0 points	664 (25.53)	-1.94 (-3.84; -0.05)	Ref
	≥12.0-16.5 points	1048 (40.29)	-0.67 (-2.28; 0.94)	0.311
	≥16.5 points	889 (34.18)	-1.32 (-3.13; 0.48)	0.639
Self-perception of residential greenness	Very green	2062 (79.49)	-0.77 (-1.99; 0.45)	0.651
	Hardly green	532 (20.51)	-1.36 (-3.60; 0.89)	
NDVI [c]	<0.43	1316 (50.42)	-1.52 (-3.35; 0.30)	0.806

	≥0.43	1294 (49.58)	-1.87 (-3.94; 0.20)	
ASKU [c]	<4.02	1821 (71.83)	-1.21 (-2.39; -0.03)	0.896
	≥4.02	714 (28.17)	-1.36 (-3.24; 0.53)	
PSS [c]	<13.59	1331 (53.54)	-0.56 (-1.95; 0.84)	0.170
	≥13.59	1155 (46.46)	-1.91 (-3.29; -0.54)	
$PM_{2.5}$				
Sex	Female	1428 (54.71)	-0.05 (-1.37; 1.27)	0.193
	Male	1182 (45.29)	-1.32 (-2.72; 0.08)	
Age, years [b]	<65.0	1373 (52.61)	-0.73 (-2.07; 0.60)	0.894
	≥65.0	1237 (47.39)	-0.60 (-1.99; 0.78)	
BMI, kg/m²	<30.0	1854 (71.03)	-1.83 (-2.99; -0.67)	<0.001
	≥30.0	756 (28.97)	2.09 (0.38; 3.81)	
SES	1.0-12.0 points	664 (25.53)	0.26 (-1.66; 2.18)	Ref
	≥12.0-16.5 points	1048 (40.29)	-0.47 (-1.96; 1.03)	0.557
	≥16.5 points	889 (34.18)	-1.51 (-3.16; 0.14)	0.171
Self-perception of residential greenness	Very green	2062 (79.49)	-0.16 (-1.26; 0.94)	0.534
	Hardly green	532 (20.51)	-1.01 (-3.46; 1.43)	
NDVI [c]	<0.43	1316 (50.42)	-1.83 (-3.64; -0.03)	0.076
	≥0.43	1294 (49.58)	0.26 (-1.18; 1.71)	
ASKU [c]	<4.02	1821 (71.83)	-0.58 (-1.71; 0.55)	0.644
	≥4.02	714 (28.17)	-1.09 (-2.91; 0.73)	
PSS [c]	<13.59	1331 (53.54)	-0.47 (-1.77; 0.84)	0.608
	≥13.59	1155 (46.46)	-0.96 (-2.33; 0.41)	
$PM_{2.5abs}$				
Sex	Female	1428 (54.71)	-1.86 (-3.38; -0.34)	0.607
	Male	1182 (45.29)	-1.28 (-2.91; 0.35)	
Age, years [b]	<65.0	1373 (52.61)	-1.54 (-3.08; -0.01)	0.858
	≥65.0	1237 (47.39)	-1.74 (-3.35; -0.14)	
BMI, kg/m²	<30.0	1854 (71.03)	-2.75 (-4.10; -1.41)	<0.001
	≥30.0	756 (28.97)	1.30 (-0.70; 3.29)	
SES	1.0-12.0 points	664 (25.53)	-1.56 (-3.69; 0.57)	Ref
	≥12.0-16.5 points	1048 (40.29)	-1.14 (-2.89; 0.61)	0.763
	≥16.5 points	889 (34.18)	-2.11 (-4.04; -0.18)	0.705
Self-perception of residential greenness	Very green	2062 (79.49)	-1.37 (-2.73; -0.02)	0.549
	Hardly green	532 (20.51)	-0.53 (-2.95; 1.88)	

NDVI [c]	<0.43	1316 (50.42)	-2.14 (-4.02; -0.26)	1.000
	≥0.43	1294 (49.58)	-2.14 (-4.51; 0.23)	
ASKU [c]	<4.02	1821 (71.83)	-1.55 (-2.84; -0.26)	0.828
	≥4.02	714 (28.17)	-1.83 (-3.98; 0.32)	
PSS [c]	<13.59	1331 (53.54)	-0.95 (-2.46; 0.57)	0.230
	≥13.59	1155 (46.46)	-2.26 (-3.82; -0.71)	
PNC				
Sex	Female	1428 (54.71)	-1.20 (-2.26; -0.13)	0.409
	Male	1182 (45.29)	-0.53 (-1.71; 0.64)	
Age, years [b]	<65.0	1373 (52.61)	-1.01 (-2.10; 0.08)	0.846
	≥65.0	1237 (47.39)	-0.86 (-2.00; 0.28)	
BMI, kg/m^2	<30.0	1854 (71.03)	-1.38 (-2.32; -0.44)	0.046
	≥30.0	756 (28.97)	0.38 (-1.08; 1.84)	
SES	1.0-12.0 points	664 (25.53)	-1.65 (-3.23; -0.07)	Ref
	≥12.0-16.5 points	1048 (40.29)	-0.93 (-2.17; 0.30)	0.480
	≥16.5 points	889 (34.18)	-0.29 (-1.62; 1.04)	0.194
Self-perception of residential greenness	Very green	2062 (79.49)	-0.50 (-1.44; 0.43)	0.622
	Hardly green	532 (20.51)	-0.99 (-2.72; 0.74)	
NDVI [c]	<0.43	1316 (50.42)	-0.89 (-2.21; 0.43)	0.649
	≥0.43	1294 (49.58)	-1.37 (-2.97; 0.23)	
ASKU [c]	<4.02	1821 (71.83)	-0.98 (-1.90; -0.06)	0.812
	≥4.02	714 (28.17)	-0.77 (-2.25; 0.71)	
PSS [c]	<13.59	1331 (53.54)	-0.52 (-1.60; 0.56)	0.548
	≥13.59	1155 (46.46)	-0.99 (-2.10; 0.12)	
O_3				
Sex	Female	1428 (54.71)	-0.27 (-1.70; 1.17)	0.392
	Male	1182 (45.29)	0.67 (-0.91; 2.25)	
Age, years [b]	<65.0	1373 (52.61)	0.32 (-1.14; 1.78)	0.762
	≥65.0	1237 (47.39)	-0.01 (-1.57; 1.55)	
BMI, kg/m^2	<30.0	1854 (71.03)	0.40 (-0.86; 1.66)	0.556
	≥30.0	756 (28.97)	-0.31 (-2.31; 1.70)	
SES	1.0-12.0 points	664 (25.53)	-1.26 (-3.30; 0.77)	Ref
	≥12.0-16.5 points	1048 (40.29)	0.43 (-1.25; 2.11)	0.208
	≥16.5 points	889 (34.18)	1.16 (-0.72; 3.04)	0.086
	Very green	2062 (79.49)	0.10 (-1.09; 1.29)	0.943

Self-perception of residential greenness	Hardly green	532 (20.51)	-0.00 (-2.46; 2.46)	
NDVI [c]	<0.43	1316 (50.42)	0.13 (-1.42; 1.69)	0.876
	≥0.43	1294 (49.58)	0.30 (-1.17; 1.78)	
ASKU [c]	<4.02	1821 (71.83)	0.78 (-0.46; 2.03)	0.255
	≥4.02	714 (28.17)	-0.60 (-2.62; 1.43)	
PSS [c]	<13.59	1331 (53.54)	-0.07 (-1.52; 1.38)	0.165
	≥13.59	1155 (46.46)	1.40 (-0.08; 2.88)	
NO_2				
Sex	Female	1428 (54.71)	-1.05 (-2.48; 0.39)	0.594
	Male	1182 (45.29)	-1.62 (-3.18; -0.06)	
Age, years [b]	<65.0	1373 (52.61)	-1.58 (-3.04; -0.12)	0.657
	≥65.0	1237 (47.39)	-1.11 (-2.64; 0.43)	
BMI, kg/m^2	<30.0	1854 (71.03)	-2.42 (-3.70; -1.13)	0.001
	≥30.0	756 (28.97)	1.33 (-0.55; 3.22)	
SES	1.0-12.0 points	664 (25.53)	-1.65 (-3.72; 0.42)	Ref
	≥12.0-16.5 points	1048 (40.29)	-0.86 (-2.53; 0.81)	0.558
	≥16.5 points	889 (34.18)	-1.55 (-3.35; 0.25)	0.942
Self-perception of residential greenness	Very green	2062 (79.49)	-0.87 (-2.15; 0.41)	0.942
	Hardly green	532 (20.51)	-0.97 (-3.24; 1.30)	
NDVI [c]	<0.43	1316 (50.42)	-1.96 (-3.76; -0.15)	0.690
	≥0.43	1294 (49.58)	-1.36 (-3.67; 0.95)	
ASKU [c]	<4.02	1821 (71.83)	-1.33 (-2.56; -0.11)	0.953
	≥4.02	714 (28.17)	-1.40 (-3.39; 0.58)	
PSS [c]	<13.59	1331 (53.54)	-0.82 (-2.24; 0.59)	0.269
	≥13.59	1155 (46.46)	-1.97 (-3.46; -0.47)	
NO_X				
Sex	Female	1428 (54.71)	-1.14 (-2.32; 0.03)	0.664
	Male	1182 (45.29)	-0.76 (-2.02; 0.49)	
Age, years [b]	<65.0	1373 (52.61)	-1.12 (-2.29; 0.05)	0.774
	≥65.0	1237 (47.39)	-0.87 (-2.13; 0.39)	
BMI, kg/m^2	<30.0	1854 (71.03)	-1.78 (-2.81; -0.75)	0.003
	≥30.0	756 (28.97)	1.05 (-0.51; 2.62)	
SES	1.0-12.0 points	664 (25.53)	-1.94 (-3.70; -0.18)	Ref
	≥12.0-16.5 points	1048 (40.29)	-0.85 (-2.18; 0.48)	0.330

	≥16.5 points	889 (34.18)	-0.43 (-1.87; 1.02)	0.191
Self-perception of residential greenness	Very green	2062 (79.49)	-0.52 (-1.51; 0.47)	0.484
	Hardly green	532 (20.51)	-1.34 (-3.41; 0.74)	
NDVI [c]	<0.43	1316 (50.42)	-1.68 (-3.38; 0.02)	0.433
	≥0.43	1294 (49.58)	-0.79 (-2.24; 0.66)	
ASKU [c]	<4.02	1821 (71.83)	-1.01 (-2.02; -0.00)	0.958
	≥4.02	714 (28.17)	-0.96 (-2.57; 0.65)	
PSS [c]	<13.59	1331 (53.54)	-0.61 (-1.78; 0.55)	0.591
	≥13.59	1155 (46.46)	-1.07 (-2.29; 0.15)	

Abbreviations: EQ-VAS, EuroQol group's visual analog scale; 95% CI, 95% confidence interval; IQR, Interquartile range; BMI, body mass index; SES, Socioeconomic status; NDVI, normalized difference vegetation index; ASKU, General Self-Efficacy Short Scale; PSS, Perceived stress scale; PM_{10}, particulate matter (PM) with an aerodynamic diameter < 10μm (μg/m^3); PM_{coarse}, coarse particulate matter; $PM_{2.5}$, PM < 2.5μm (μg/m^3); $PM_{2.5abs}$, the absorbance of $PM_{2.5}$; PNC, particle number concentration; O_3, Ozone (μg/m^3); NO_2, Nitrogen dioxide (μg/m^3); NO_X, Nitrogen oxide (μg/m^3).
Note: Estimates represent the percentage and absolute changes (with 95% CIs) in the EQ-VAS for IQR increase in annual exposures to air pollutants (1.95 μg/m^2 for PM_{10}, 1.40 μg/m^2 for PM_{coarse}, 1.39 μg/m^2 for $PM_{2.5}$, 0.28 [10^{-5}/m] for $PM_{2.5abs}$, 1.92 [10^3/cm^3] for PNC, 3.54 μg/m^2 for O_3, 6.20 μg/m^2 for NO_2 and 8.41 μg/m^2 for NO_X). Analysis was conducted in the main model, which was adjusted for age at the survey, sex, socioeconomic status (SES), living with a partner, body mass index (BMI), physical activity, and smoking status.
[a] *p*-interaction was calculated by using multiple generalized additive models.
[b] The age was divided by the tertiles.
[c] The NDVI, ASKU and PSS were divided by their mean values.

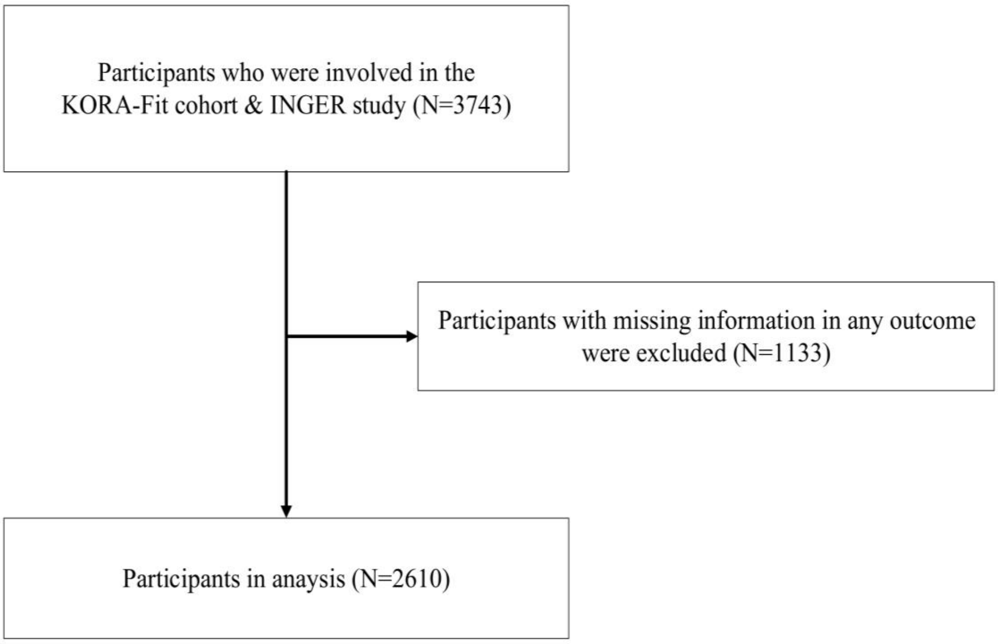

Fig S1. Flowchart of study population selection.

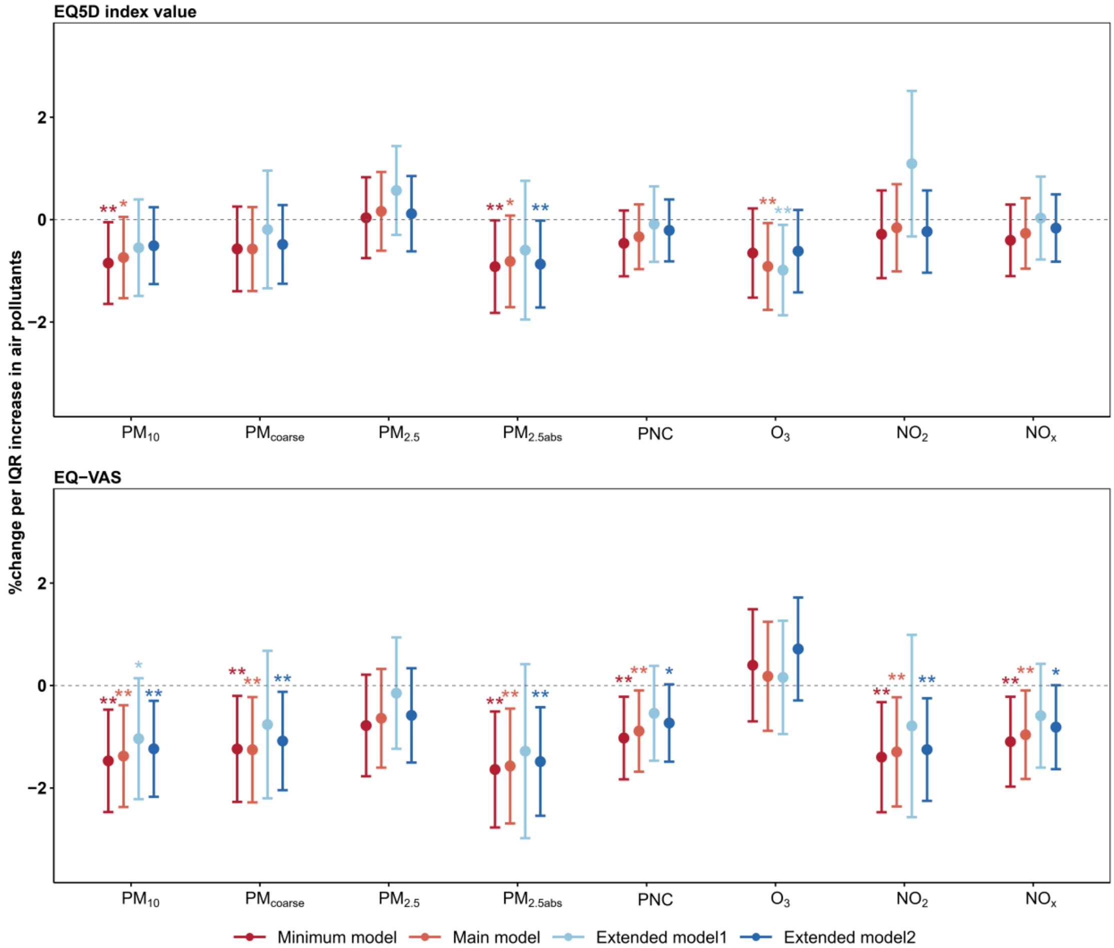

Fig S2. Results of multiple linear regression models for the associations between air pollutants and EQ-5D index value and EQ-VAS.

Abbreviations: EQ-5D index value, the index of European Quality of Life 5-dimensional questionnaire; EQ-VAS, EQ visual analogue scale; IQR, interquartile range; PM_{10}, particulate matter (PM) with an aerodynamic diameter < 10µm (µg/m^3); PM_{coarse}, coarse particulate matter; $PM_{2.5}$, PM < 2.5µm (µg/m^3); $PM_{2.5abs}$, the absorbance of $PM_{2.5}$; PNC, particle number concentration; O_3, Ozone (µg/m^3); NO_2, Nitrogen dioxide (µg/m^3); NO_X, Nitrogen oxide (µg/m^3).

Note: Estimates represent percentage changes in EQ-5D index value/EQ-VAS mean for IQR increase in annual exposures to air pollutants (1.95 µg/m^2 for PM_{10}, 1.40 µg/m^2 for PM_{coarse}, 1.39 µg/m^2 for $PM_{2.5}$, 0.28 (10^{-5}/m) for $PM_{2.5abs}$, 1.92 (10^3/cm^3) for PNC, 3.54 µg/m^2 for O_3, 6.20 µg/m^2 for NO_2 and 8.41 µg/m^2 for NO_X).

The minimum model was adjusted for age at survey and sex.

The main model was further adjusted for socioeconomic status (SES), living with a partner, body mass index (BMI), physical activity, and smoking status.

The extended model 1 was further adjusted for variables in the main model plus the percentage of households with low income and degree of urbanization.

The extended model 2 was further adjusted for variables in the main model plus the General Self-Efficacy (ASKU) and Perceived Stress (PSS).

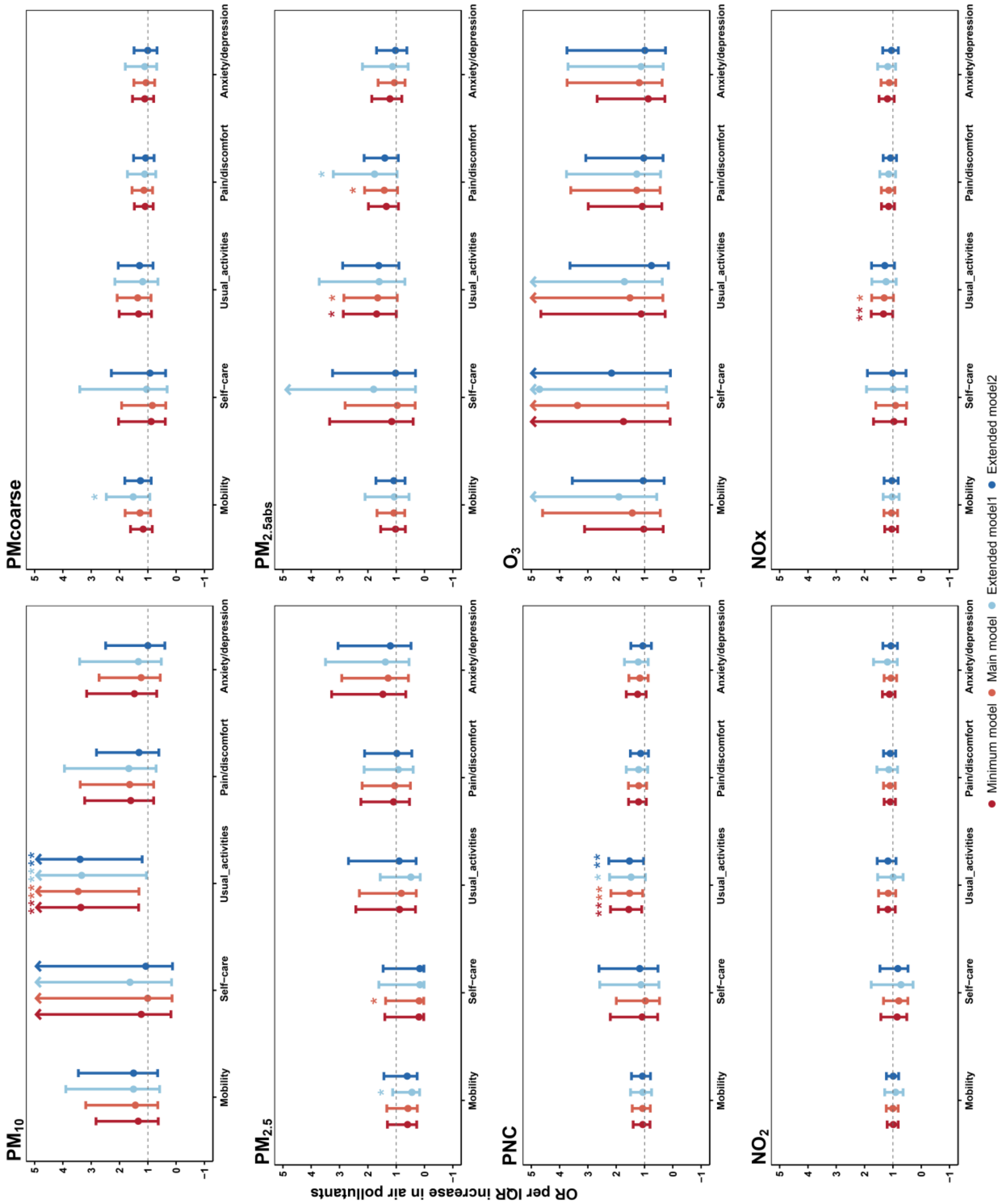
PM10
PMcoarse
PM2.5
PM2.5abs
PNC
O3
NO2
NOx
Mobility
Self-care
Usual_activities
Pain/discomfort
Anxiety/depression
OR per IQR increase in air pollutants
Minimum model
Main model
Extended model1
Extended model2

Fig S3. Results of multiple logistic regression model for dichotomized EQ-5D-5L dimensions.
Abbreviations: EQ-5D-5L, European Quality of Life 5 Dimension 5 Level questionnaire; OR, odds ratio; 95% CI, 95% confidence interval; IQR, Interquartile range; PM_{10}, particulate matter (PM) with an aerodynamic diameter < 10μm (μg/m^3); PM_{coarse}, coarse particulate matter; $PM_{2.5}$, PM < 2.5μm (μg/m^3); $PM_{2.5abs}$, the absorbance of $PM_{2.5}$; PNC, particle number concentration; O_3, Ozone (μg/m^3); NO_2, Nitrogen dioxide (μg/m^3); NO_X, Nitrogen oxide (μg/m^3).
Note: With those reported "had no problems" as the reference group, estimates represented as ORs (with 95%CIs) of "any problems" for IQR increase in annual exposures to air pollutants (1.95 μg/m^2 for PM_{10}, 1.40 μg/m^2 for PM_{coarse}, 1.39 μg/m^2 for $PM_{2.5}$, 0.28 (10^{-5}/m) for $PM_{2.5abs}$, 1.92 (10^3/cm^3) for PNC, 3.54 μg/m^2 for O_3, 6.20 μg/m^2 for NO_2 and 8.41 μg/m^2 for NO_X).
The minimum model was adjusted for age at the survey and sex.
The main model was further adjusted for (SES), living with a partner, body mass index (BMI), physical activity, and smoking status.
The extended model 1 was further adjusted for variables in the main model plus the percentage of households with low income and degree of urbanization.
The extended model 2 was further adjusted for variables in the main model plus the General Self-Efficacy (ASKU) and Perceived Stress (PSS).

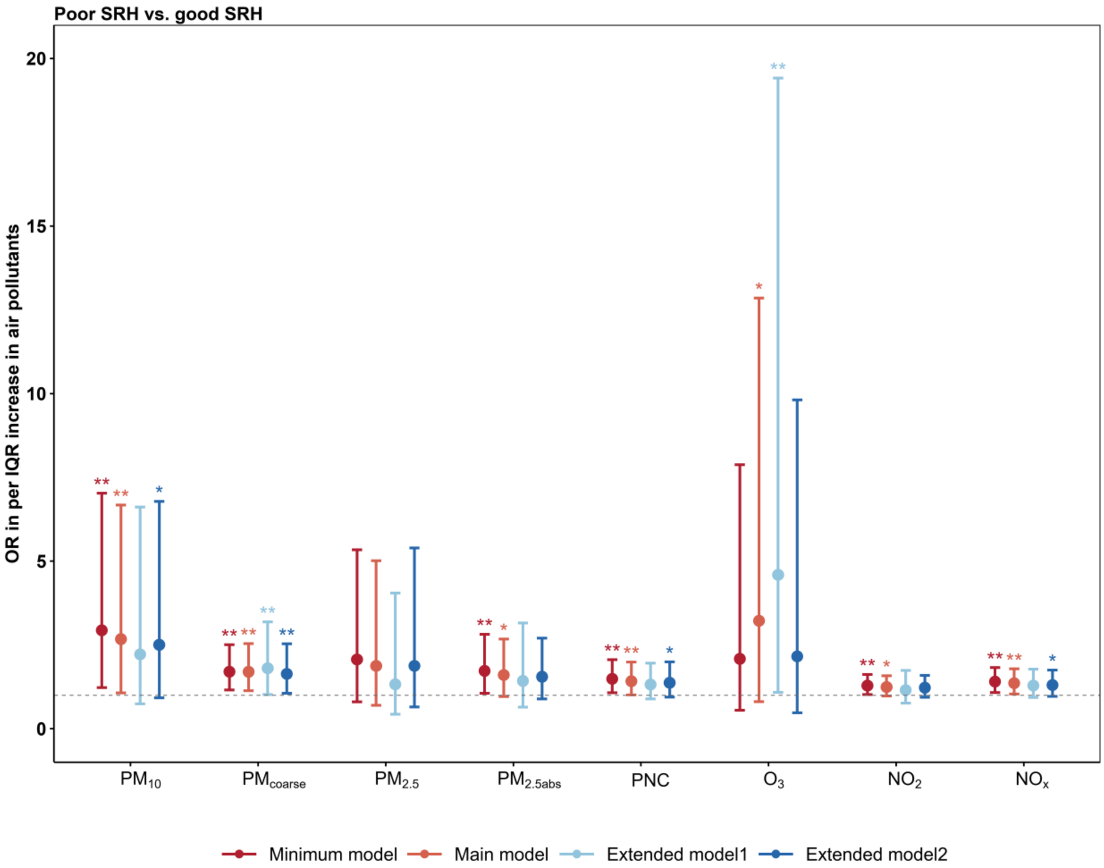

Fig S4. Results of multiple logistic regression models for the associations between air pollutants and the odds of reporting poor SRH.
Abbreviations: SRH, self-rated health; IQR, interquartile range; PM_{10}, particulate matter (PM) with an aerodynamic diameter < 10μm (μg/m^3); PM_{coarse}, coarse particulate matter; $PM_{2.5}$, PM < 2.5μm (μg/m^3); $PM_{2.5abs}$, the absorbance of $PM_{2.5}$; PNC, particle number concentration; O_3, Ozone (μg/m^3); NO_2, Nitrogen dioxide (μg/m^3); NO_X, Nitrogen oxide (μg/m^3).
Note: With those reported "good SRH" as reference group, estimates represented as ORs (with 95%CIs) of poor SRH for IQR increase in annual exposures to air pollutants (1.95 μg/m^2 for PM_{10}, 1.40 μg/m^2 for PM_{coarse}, 1.39 μg/m^2 for $PM_{2.5}$, 0.28 (10^{-5}/m) for $PM_{2.5abs}$, 1.92 (10^3/cm^3) for PNC, 3.54 μg/m^2 for O_3, 6.20 μg/m^2 for NO_2 and 8.41 μg/m^2 for NO_X).
The minimum model was adjusted for age at survey and sex.
The main model was further adjusted for socioeconomic status (SES), living with a partner, body mass index (BMI), physical activity, and smoking status.
The extended model 1 was further adjusted for variables in the main model plus the percentage of households with low income and degree of urbanization.
The extended model 2 was further adjusted for variables in the main model plus the General Self-Efficacy (ASKU) and Perceived Stress (PSS).

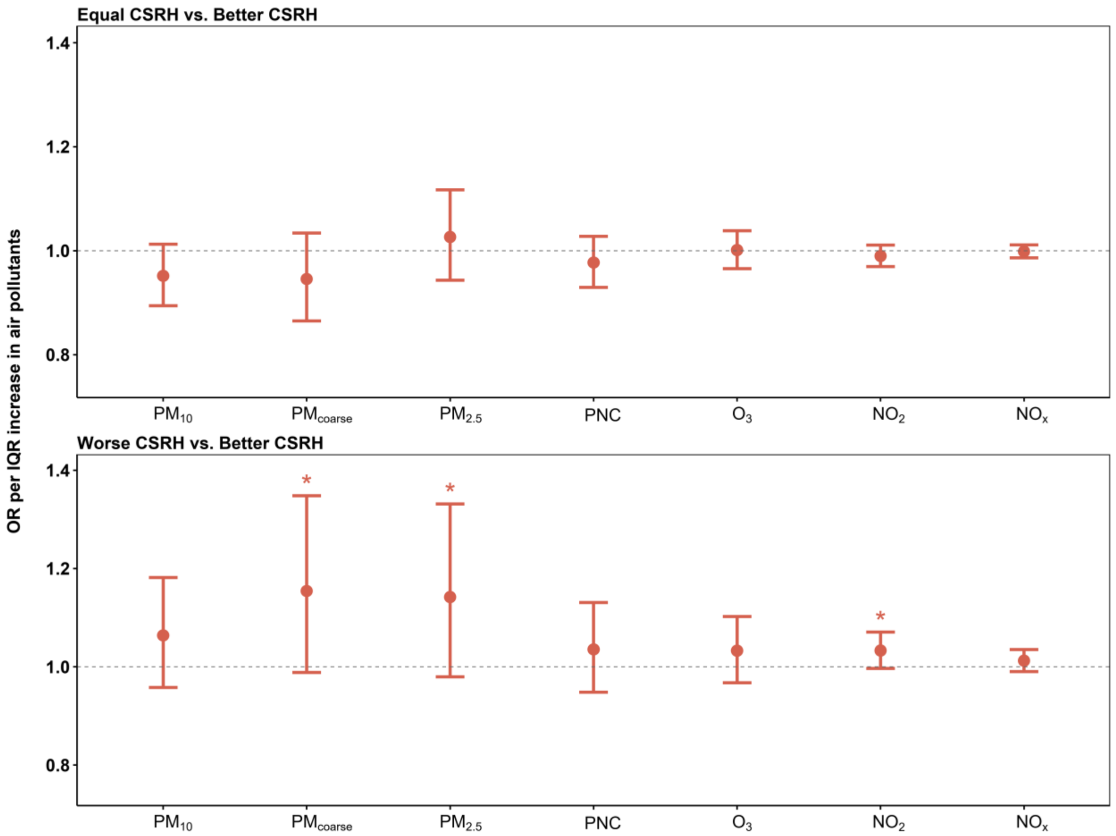

Fig S5. Results of the main model of multinominal logistic regression for the association between air pollution and the odds of reporting: A) equal CSRH vs. better CSRH; B) worse CSRH vs. better CSRH, with the estimate for $PM_{2.5abs}$ being excluded due to the large confidence interval.
Abbreviations: CSRH, comparative self-rated health; OR, odds ratio; 95% CI, 95% confidence interval; IQR, interquartile range; PM_{10}, particulate matter (PM) with an aerodynamic diameter < 10µm (µg/m^3); PM_{coarse}, coarse particulate matter; $PM_{2.5}$, PM < 2.5µm (µg/m^3); $PM_{2.5abs}$, the absorbance of $PM_{2.5}$; PNC, particle number concentration; O_3, Ozone (µg/m^3); NO_2, Nitrogen dioxide (µg/m^3); NO_X, Nitrogen oxide (µg/m^3).
Note: With those reported “better CSRH” as reference group, estimates represented as ORs (with 95% CIs) of equal CSRH or worse CSRH for IQR increase in annual exposures to air pollutants (1.95 µg/m^2 for PM_{10}, 1.40 µg/m^2 for PM_{coarse}, 1.39 µg/m^2 for $PM_{2.5}$, 0.28 [10^{-5}/m] for $PM_{2.5abs}$, 1.92 [10^3/cm^3] for PNC, 3.54 µg/m^2 for O_3, 6.20 µg/m^2 for NO_2 and 8.41 µg/m^2 for NO_X).
The plots were developed based on the main model, which was adjusted for age at the survey, sex, socioeconomic status (SES), living with a partner, physical activity, and smoking status.

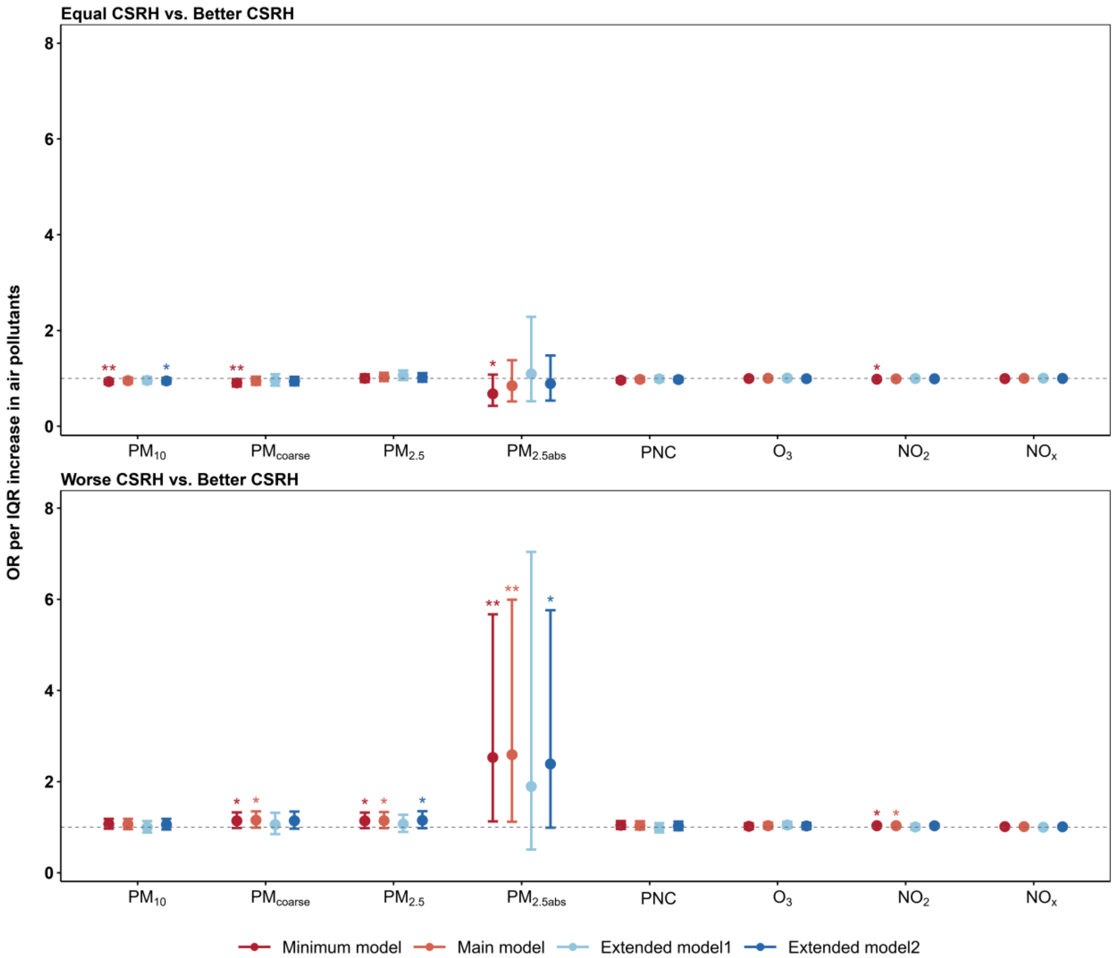

Fig S6. Results of the multiple multinominal logistic regression models for the association between air pollution and the odds of reporting: A) equal CSRH vs. better CSRH; B) worse CSRH vs. better CSRH.
Abbreviations: CSRH, comparative self-rated health; OR, odds ratio; 95% CI, 95% confidence interval; IQR, interquartile range; PM_{10}, particulate matter (PM) with an aerodynamic diameter < 10µm (µg/m^3); PM_{coarse}, coarse particulate matter; $PM_{2.5}$, PM < 2.5µm (µg/m^3); $PM_{2.5abs}$, the absorbance of $PM_{2.5}$; PNC, particle number concentration; O_3, Ozone (µg/m^3); NO_2, Nitrogen dioxide (µg/m^3); NO_X, Nitrogen oxide (µg/m^3).
Note: With those reported "better CSRH" as reference group, estimates represented as ORs (with 95% CIs) of equal CSRH or worse CSRH for IQR increase in annual exposures to air pollutants (1.95 µg/m^2 for PM_{10}, 1.40 µg/m^2 for PM_{coarse}, 1.39 µg/m^2 for $PM_{2.5}$, 0.28 [10^{-5}/m] for $PM_{2.5abs}$, 1.92 [10^3/cm^3] for PNC, 3.54 µg/m^2 for O_3, 6.20 µg/m^2 for NO_2 and 8.41 µg/m^2 for NO_X).
The minimum model was adjusted for age at survey and sex.
The main model was further adjusted for socioeconomic status (SES), living with a partner, body mass index (BMI), physical activity, and smoking status.
The extended model 1 was further adjusted for variables in the main model plus percentage of households with low income and degree of urbanization.
The extended model 2 was further adjusted for variables in the main model plus the General Self-Efficacy (ASKU) and Perceived Stress (PSS).

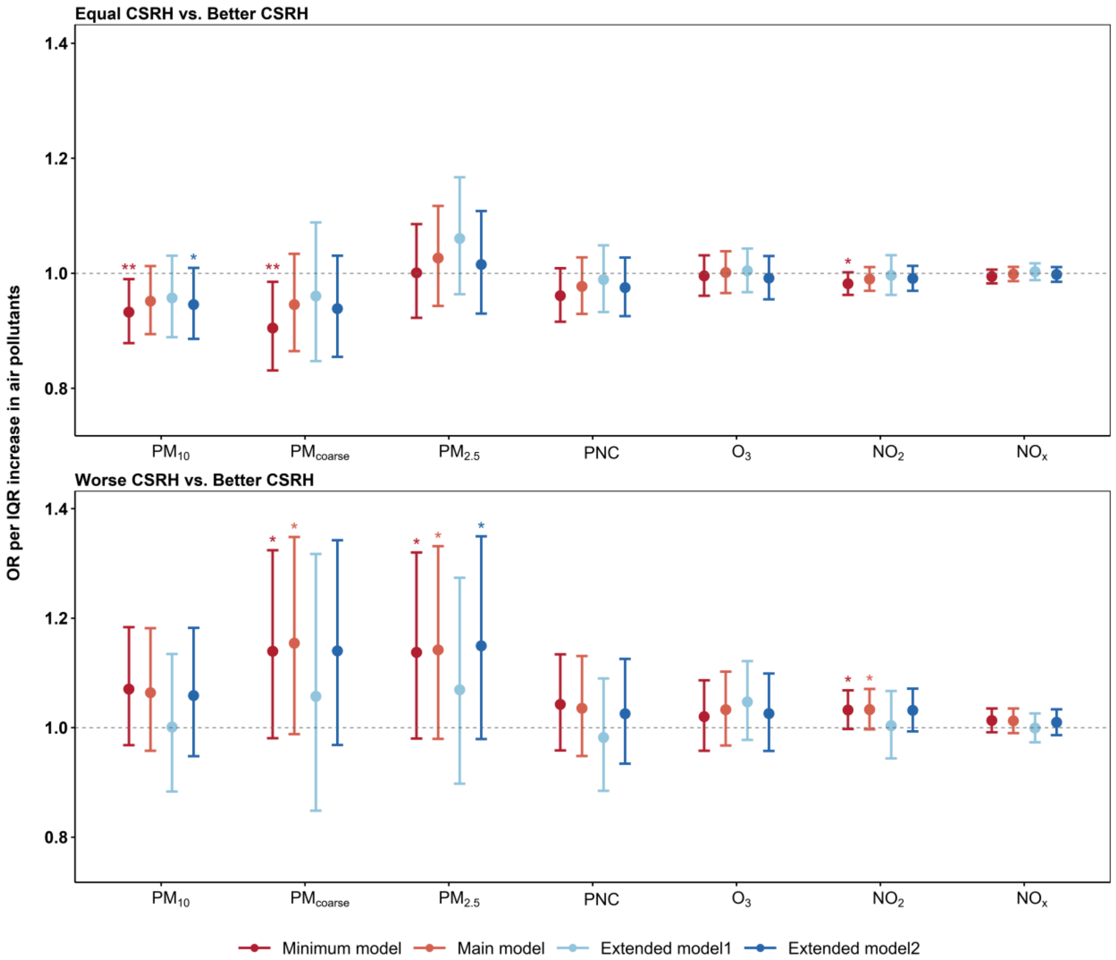

Fig S7. Results of the multiple multinominal logistic regression models for the association between air pollution and the odds of reporting: A) equal CSRH vs. better CSRH; B) worse CSRH vs. better CSRH, with the estimate for $PM_{2.5abs}$ being excluded due to the large confidence interval.

Abbreviations: CSRH, comparative self-rated health; OR, odds ratio; 95% CI, 95% confidence interval; IQR, interquartile range; PM_{10}, particulate matter (PM) with an aerodynamic diameter < 10μm (μg/m^3); PM_{coarse}, coarse particulate matter; $PM_{2.5}$, PM < 2.5μm (μg/m^3); $PM_{2.5abs}$, the absorbance of $PM_{2.5}$; PNC, particle number concentration; O_3, Ozone (μg/m^3); NO_2, Nitrogen dioxide (μg/m^3); NO_X, Nitrogen oxide (μg/m^3).

Note: With those reported “better CSRH” as reference group, estimates represented as ORs (with 95% CIs) of equal CSRH or worse CSRH for IQR increase in annual exposures to air pollutants (1.95 μg/m^2 for PM_{10}, 1.40 μg/m^2 for PM_{coarse}, 1.39 μg/m^2 for $PM_{2.5}$, 0.28 [10^{-5}/m] for $PM_{2.5abs}$, 1.92 [10^3/cm^3] for PNC, 3.54 μg/m^2 for O_3, 6.20 μg/m^2 for NO_2 and 8.41 μg/m^2 for NO_X).

The minimum model was adjusted for age at survey and sex.

The main model was further adjusted for socioeconomic status (SES), living with a partner, body mass index (BMI), physical activity, and smoking status.

The extended model 1 was further adjusted for variables in the main model plus percentage of households with low income and degree of urbanization.

The extended model 2 was further adjusted for variables in the main model plus the General Self-Efficacy (ASKU) and Perceived Stress (PSS).

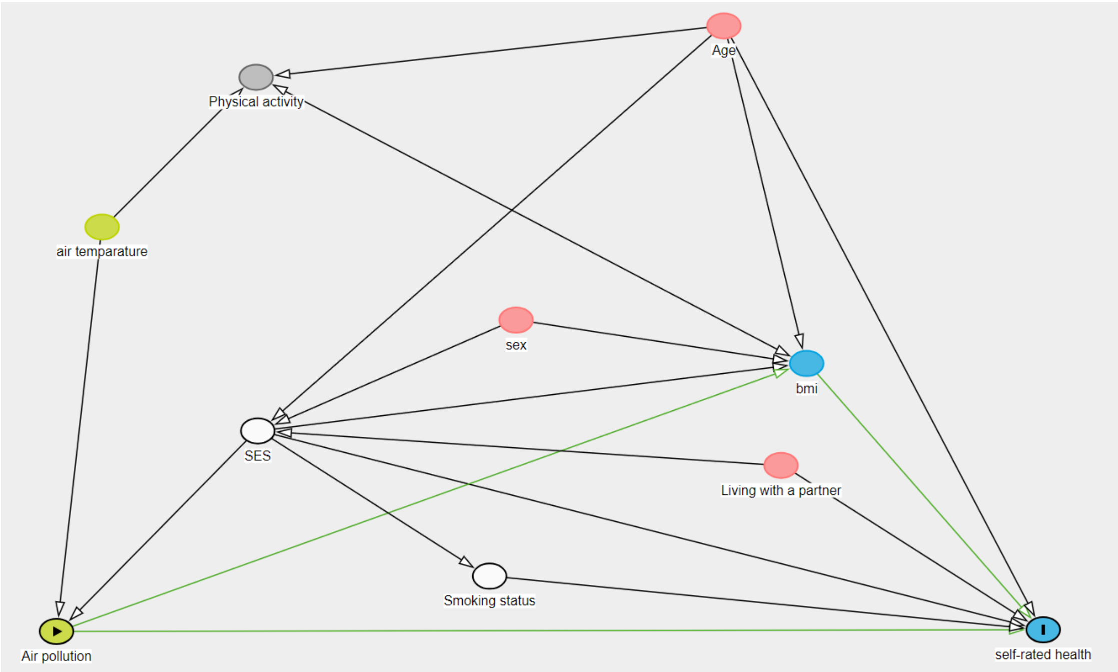

Fig S8. DAG plot for potential causal pathway

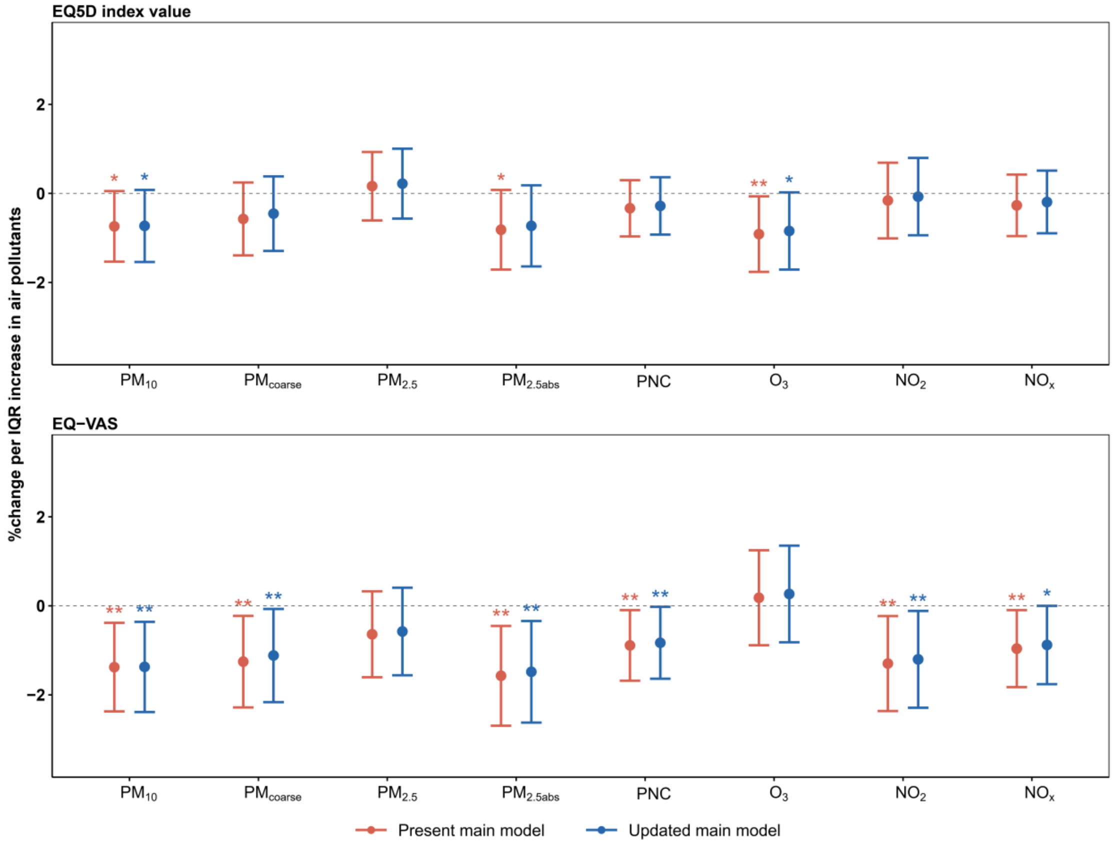

Fig S9. Sensitivity analysis for multiple linear regression models for the associations between air pollutants and EQ-5D index value and EQ-VAS in two main models.
Abbreviations: EQ-5D index value, the index of European Quality of Life 5-dimensional questionnaire; EQ-VAS, EQ visual analogue scale; IQR, interquartile range; PM_{10}, particulate matter (PM) with an aerodynamic diameter < 10µm (µg/m^3); PM_{coarse}, coarse particulate matter; $PM_{2.5}$, PM < 2.5µm (µg/m^3); $PM_{2.5abs}$, the absorbance of $PM_{2.5}$; PNC, particle number concentration; O_3, Ozone (µg/m^3); NO_2, Nitrogen dioxide (µg/m^3); NO_X, Nitrogen oxide (µg/m^3).
Note: Estimates represent percentage changes in EQ-5D index value/EQ-VAS mean for IQR increase in annual exposures to air pollutants (1.95 µg/m^2 for PM_{10}, 1.40 µg/m^2 for PM_{coarse}, 1.39 µg/m^2 for $PM_{2.5}$, 0.28 (10^{-5}/m) for $PM_{2.5abs}$, 1.92 (10^3/cm^3) for PNC, 3.54 µg/m^2 for O_3, 6.20 µg/m^2 for NO_2 and 8.41 µg/m^2 for NO_X).
The present main model was adjusted for age at survey, sex, socioeconomic status (SES), living with a partner, body mass index (BMI), physical activity, and smoking status.
The updated main model was adjusted for age at survey, sex, SES, living with a partner, and smoking status.

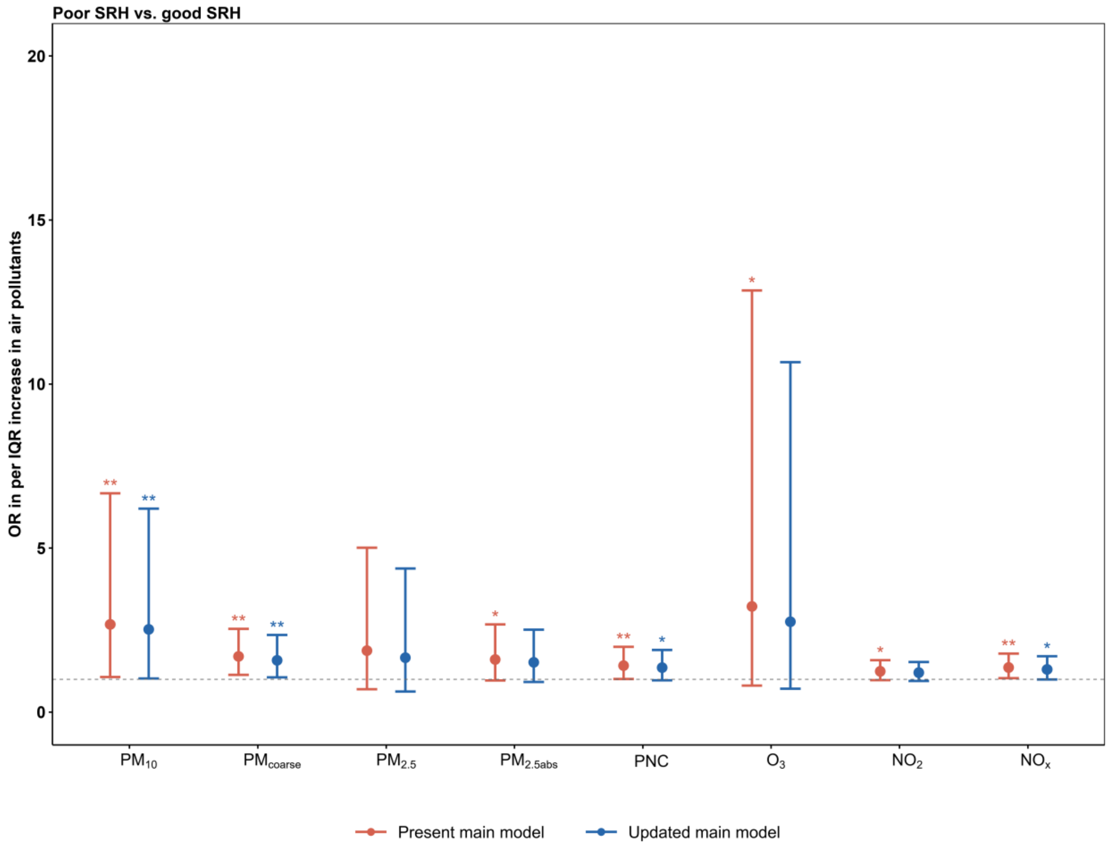

Fig S10. Sensitivity analysis for multiple logistic regression models for the associations between air pollutants and the odds of reporting poor SRH in two main models.

Abbreviations: SRH, self-rated health; IQR, interquartile range; PM_{10}, particulate matter (PM) with an aerodynamic diameter < 10μm (μg/m^3); PM_{coarse}, coarse particulate matter; $PM_{2.5}$, PM < 2.5μm (μg/m^3); $PM_{2.5abs}$, the absorbance of $PM_{2.5}$; PNC, particle number concentration; O_3, Ozone (μg/m^3); NO_2, Nitrogen dioxide (μg/m^3); NO_X, Nitrogen oxide (μg/m^3).

Note: With those reported "good SRH" as reference group, estimates represented as ORs (with 95%CIs) of poor SRH for IQR increase in annual exposures to air pollutants (1.95 μg/m^2 for PM_{10}, 1.40 μg/m^2 for PM_{coarse}, 1.39 μg/m^2 for $PM_{2.5}$, 0.28 (10^{-5}/m) for $PM_{2.5abs}$, 1.92 (10^3/cm^3) for PNC, 3.54 μg/m^2 for O_3, 6.20 μg/m^2 for NO_2 and 8.41 μg/m^2 for NO_X).

The present main model was adjusted for age at survey, sex, socioeconomic status (SES), living with a partner, body mass index (BMI), physical activity, and smoking status.

The updated main model was adjusted for age at survey, sex, SES, living with a partner, and smoking status.

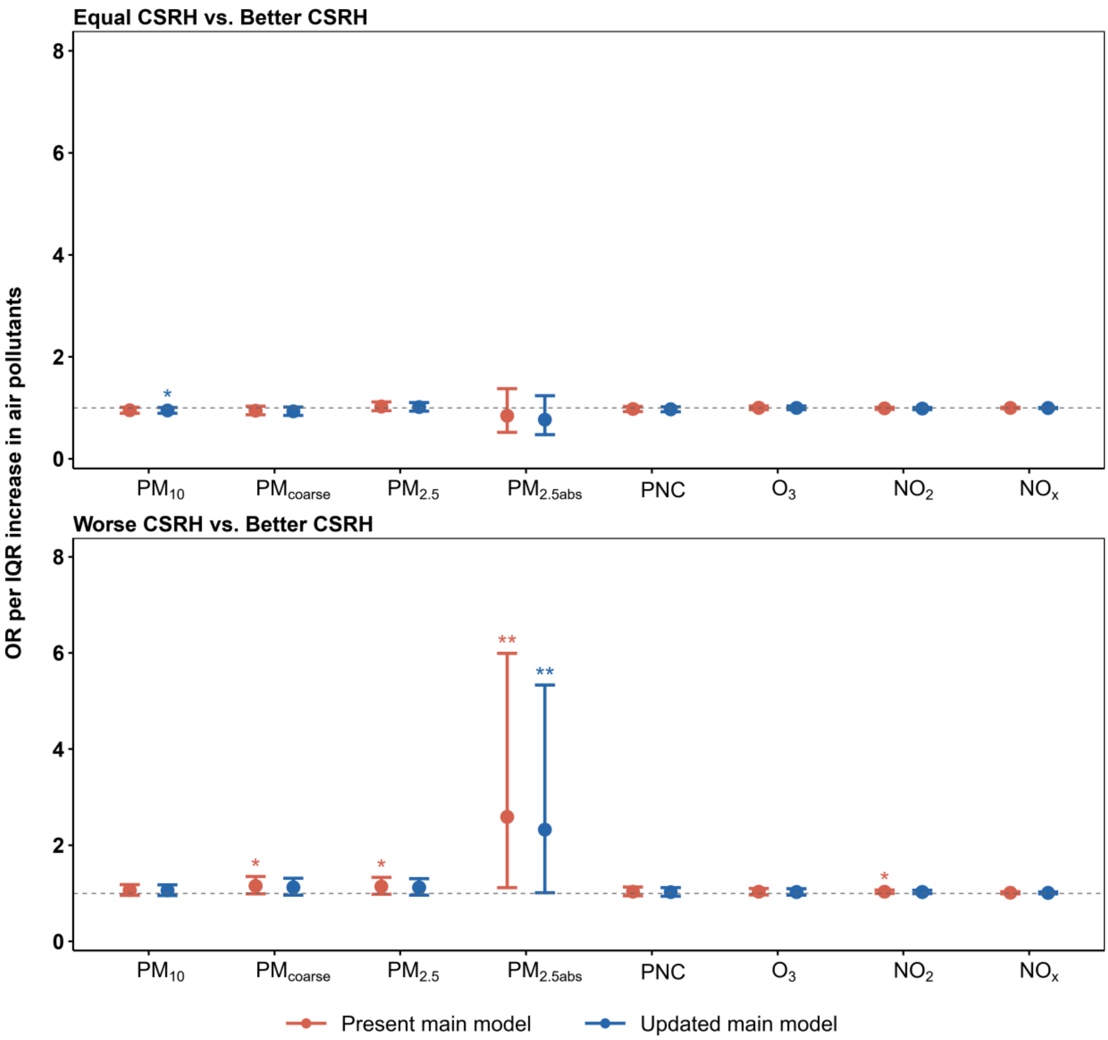

Fig S11. Sensitivity analysis for the multiple multinominal logistic regression models for the association between air pollution and the odds of reporting: A) equal CSRH vs. better CSRH; B) worse CSRH vs. better CSRH in two main models. Abbreviations: CSRH, comparative self-rated health; OR, odds ratio; 95% CI, 95% confidence interval; IQR, interquartile range; PM_{10}, particulate matter (PM) with an aerodynamic diameter < 10μm (μg/m^3); PM_{coarse}, coarse particulate matter; $PM_{2.5}$, PM < 2.5μm (μg/m^3); $PM_{2.5abs}$, the absorbance of $PM_{2.5}$; PNC, particle number concentration; O_3, Ozone (μg/m^3); NO_2, Nitrogen dioxide (μg/m^3); NO_X, Nitrogen oxide (μg/m^3).

Note: With those reported "better CSRH" as reference group, estimates represented as ORs (with 95% CIs) of equal CSRH or worse CSRH for IQR increase in annual exposures to air pollutants (1.95 μg/m^2 for PM_{10}, 1.40 μg/m^2 for PM_{coarse}, 1.39 μg/m^2 for $PM_{2.5}$, 0.28 [10^{-5}/m] for $PM_{2.5abs}$, 1.92 [10^3/cm^3] for PNC, 3.54 μg/m^2 for O_3, 6.20 μg/m^2 for NO_2 and 8.41 μg/m^2 for NO_X).

The present main model was adjusted for age at survey, sex, socioeconomic status (SES), living with a partner, body mass index (BMI), physical activity, and smoking status.

The updated main model was adjusted for age at survey, sex, SES, living with a partner, and smoking status.

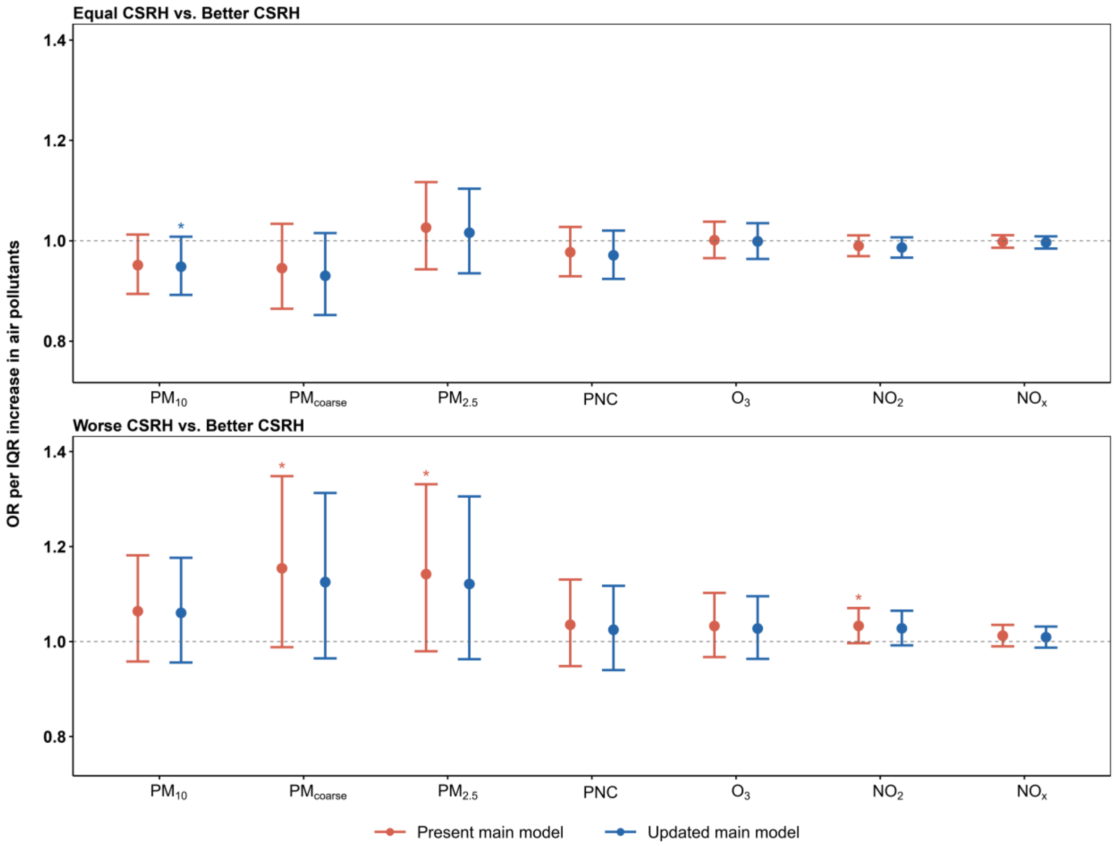

Fig S12. Sensitivity analysis for the multiple multinominal logistic regression models for the association between air pollution and the odds of reporting: A) equal CSRH vs. better CSRH; B) worse CSRH vs. better CSRH, with the estimate for $PM_{2.5abs}$ being excluded due to the large confidence interval in two main models.

Abbreviations: CSRH, comparative self-rated health; OR, odds ratio; 95% CI, 95% confidence interval; IQR, interquartile range; PM_{10}, particulate matter (PM) with an aerodynamic diameter < 10µm (µg/m^3); PM_{coarse}, coarse particulate matter; $PM_{2.5}$, PM < 2.5µm (µg/m^3); $PM_{2.5abs}$, the absorbance of $PM_{2.5}$; PNC, particle number concentration; O_3, Ozone (µg/m^3); NO_2, Nitrogen dioxide (µg/m^3); NO_X, Nitrogen oxide (µg/m^3).

Note: With those reported "better CSRH" as reference group, estimates represented as ORs (with 95% CIs) of equal CSRH or worse CSRH for IQR increase in annual exposures to air pollutants (1.95 µg/m^2 for PM_{10}, 1.40 µg/m^2 for PM_{coarse}, 1.39 µg/m^2 for $PM_{2.5}$, 0.28 [10^{-5}/m] for $PM_{2.5abs}$, 1.92 [10^3/cm^3] for PNC, 3.54 µg/m^2 for O_3, 6.20 µg/m^2 for NO_2 and 8.41 µg/m^2 for NO_X).

The present main model was adjusted for age at survey, sex, socioeconomic status (SES), living with a partner, body mass index (BMI), physical activity, and smoking status.

The updated main model was adjusted for age at survey, sex, SES, living with a partner, and smoking status.

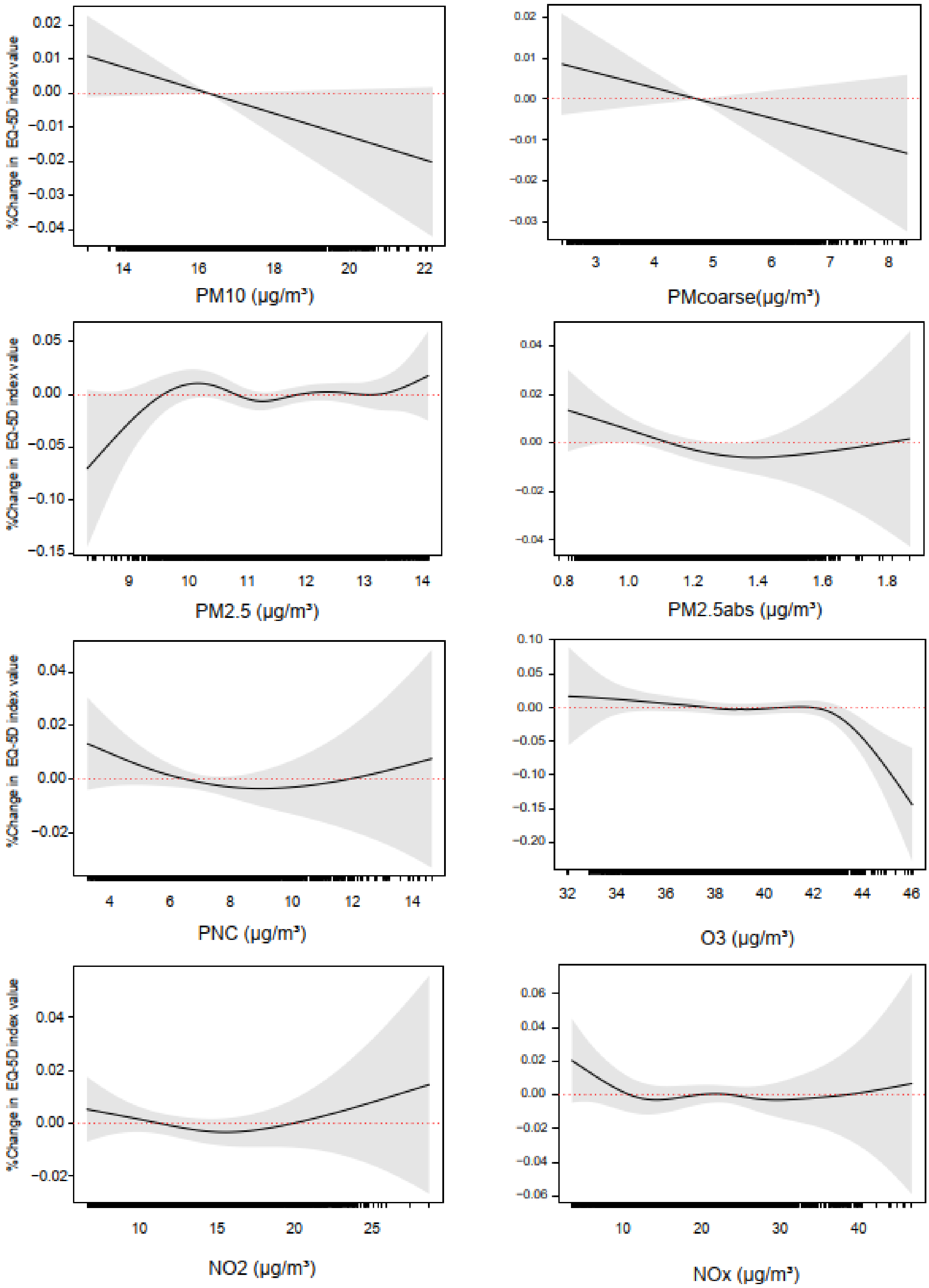

Fig S13. Exposure-response relationships for percentage change in EQ-5D index value with different air pollutants.
Abbreviations: EQ-5D index value, index of European Quality of Life 5 Dimension 5 Level questionnaire; PM_{10}, particulate matter (PM) with an aerodynamic diameter < 10µm (µg/m^3); PM_{coarse}, coarse particulate matter; $PM_{2.5}$, PM < 2.5µm (µg/m^3); $PM_{2.5abs}$, the absorbance of $PM_{2.5}$; PNC, particle number concentration; O_3, Ozone (µg/m^3); NO_2, Nitrogen dioxide (µg/m^3); NO_X, Nitrogen oxide (µg/m^3).
Note: These linearity plots were developed based on the main model, which was adjusted for the age at the survey, sex, socioeconomic status (SES), living with a partner, body mass index (BMI), physical activity, and smoking status.

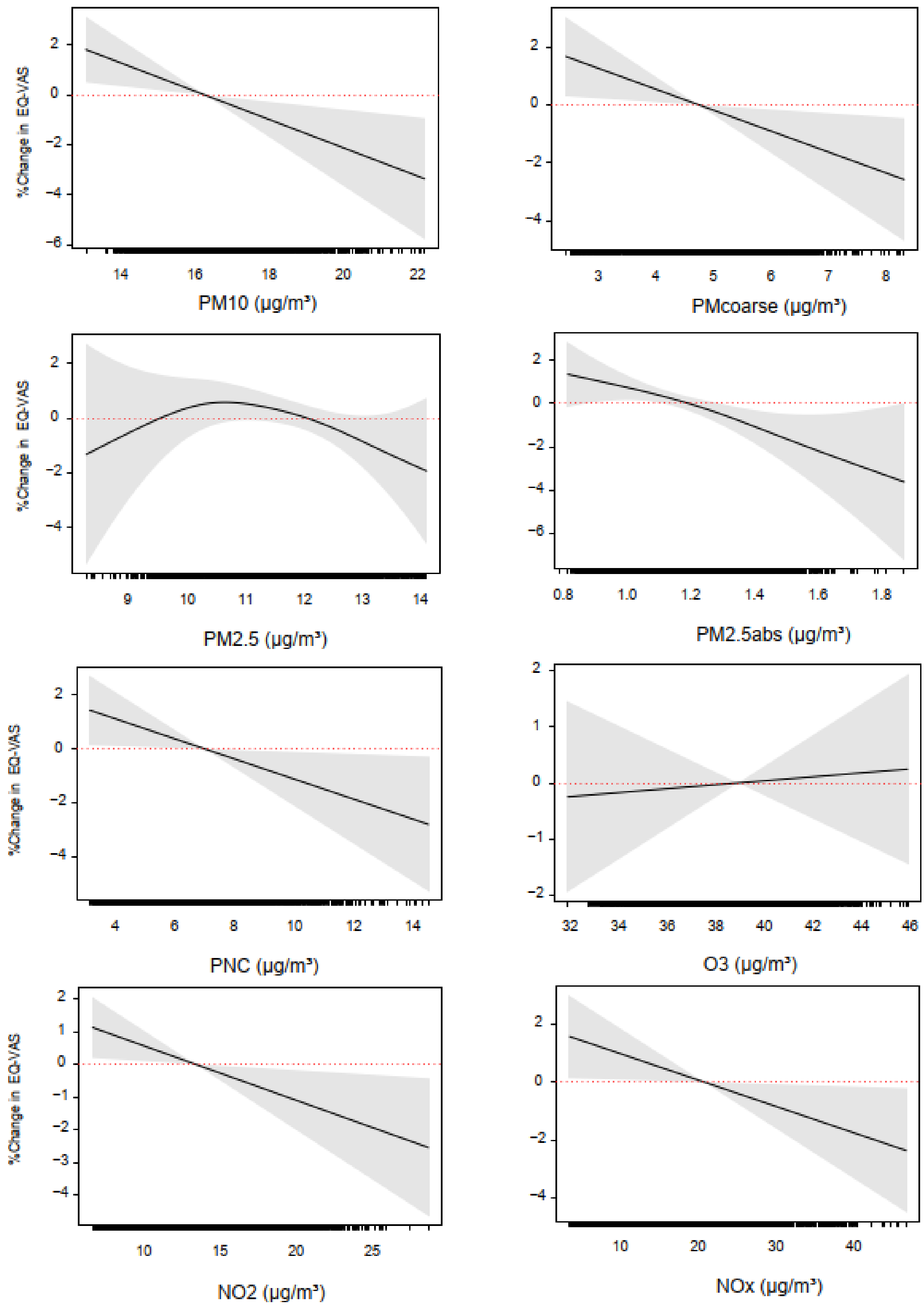

Fig S14. Exposure-response relationships for percentage change in EQ-VAS with different air pollutants.
Abbreviations: EQ-VAS, EuroQol group's visual analog scale; PM_{10}, particulate matter (PM) with an aerodynamic diameter < 10µm (µg/m^3); PM_{coarse}, coarse particulate matter; $PM_{2.5}$, PM < 2.5µm (µg/m^3); $PM_{2.5abs}$, the absorbance of $PM_{2.5}$; PNC, particle number concentration; O_3, Ozone (µg/m^3); NO_2, Nitrogen dioxide (µg/m^3); NO_X, Nitrogen oxide (µg/m^3).
Note: These linearity plots were developed based on the main model, which was adjusted for age at the survey, sex, socioeconomic status (SES), living with a partner, body mass index (BMI), physical activity, and smoking status.

Paper II

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

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A R T I C L E I N F O

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A B S T R A C T

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 < 10μm (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

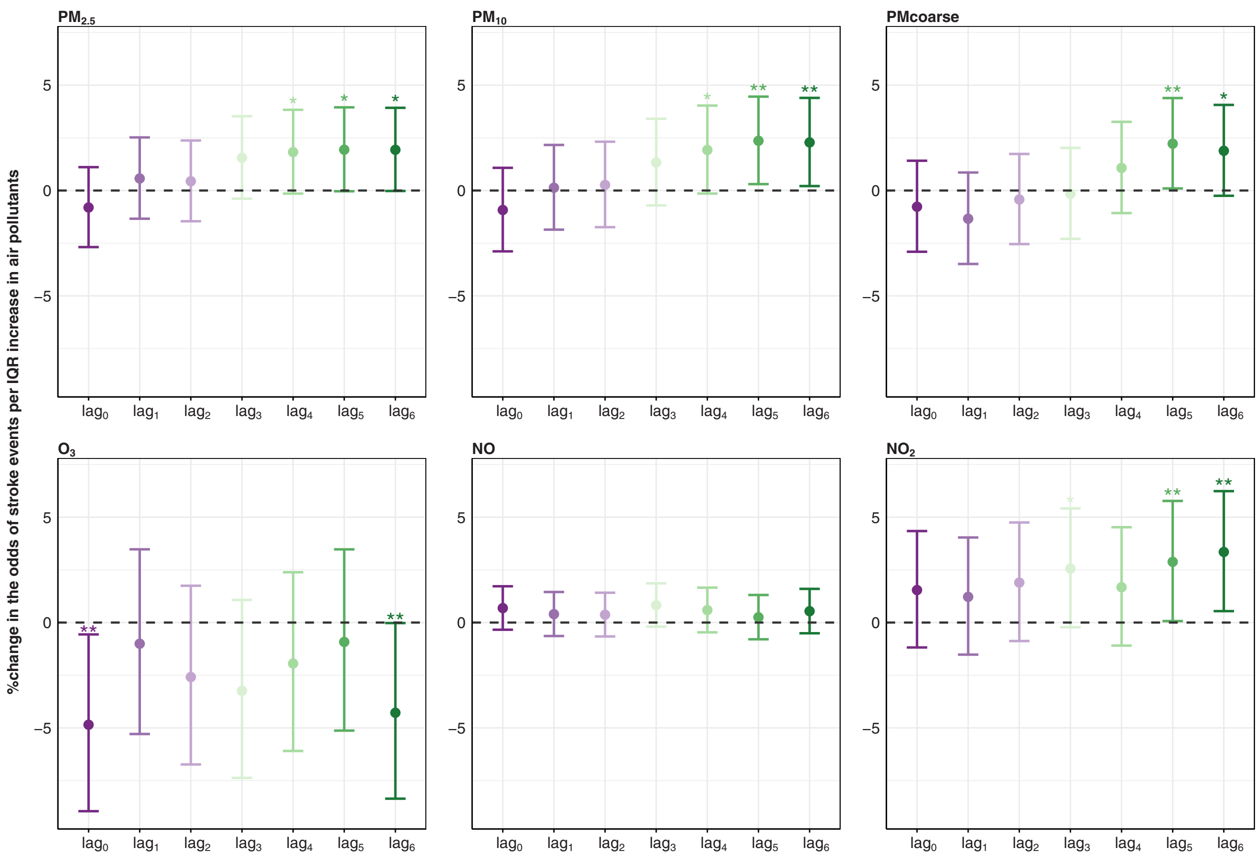

Fig. 1. Percent change (95 % CI) in the odds of overall stroke events in each interquartile range (IQR) increase in single-day lagged air pollutants. **Note:** * , $P < 0.10$; * *, $P < 0.05$.

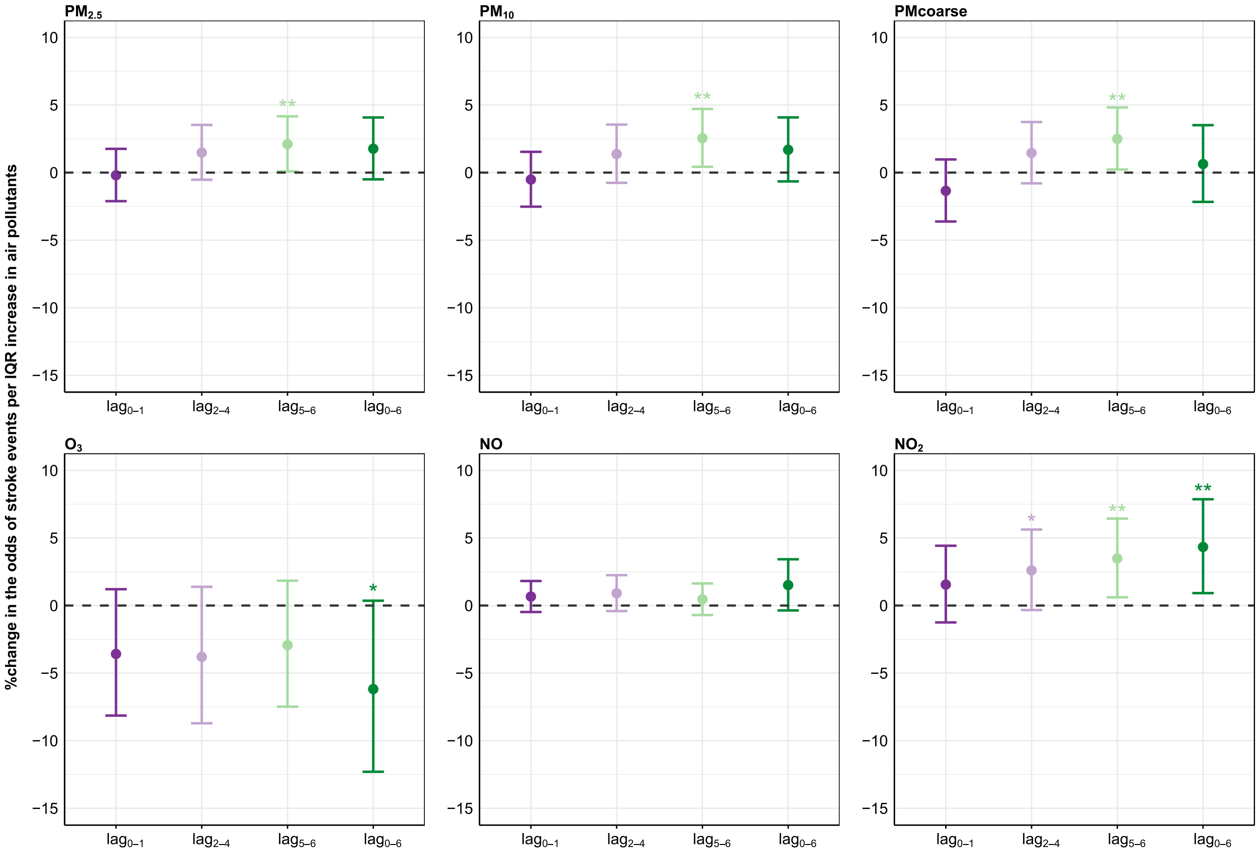

Fig. 2. Percent change (95 % CI) in the odds of overall stroke events in each interquartile range (IQR) increase in moving averaged air pollutants. **Note:** * , $P < 0.10$; * *, $P < 0.05$.

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.,

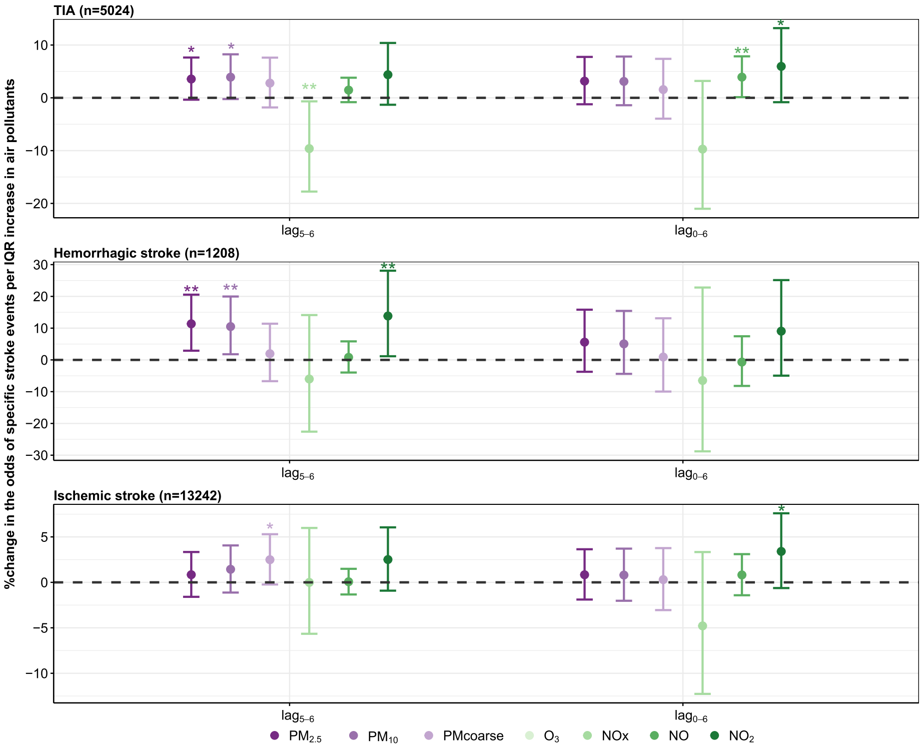

Fig. 3. Subgroup percent change (95 % CI) in the odds of stroke events in each interquartile range (IQR) increase in moving averaged air pollutants (over lag 5–6 and lag 0–6 days) by three subtypes. **Note**: Different scaling on the y-axis for better visibility. * , $P < 0.10$; * *, $P < 0.05$.

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

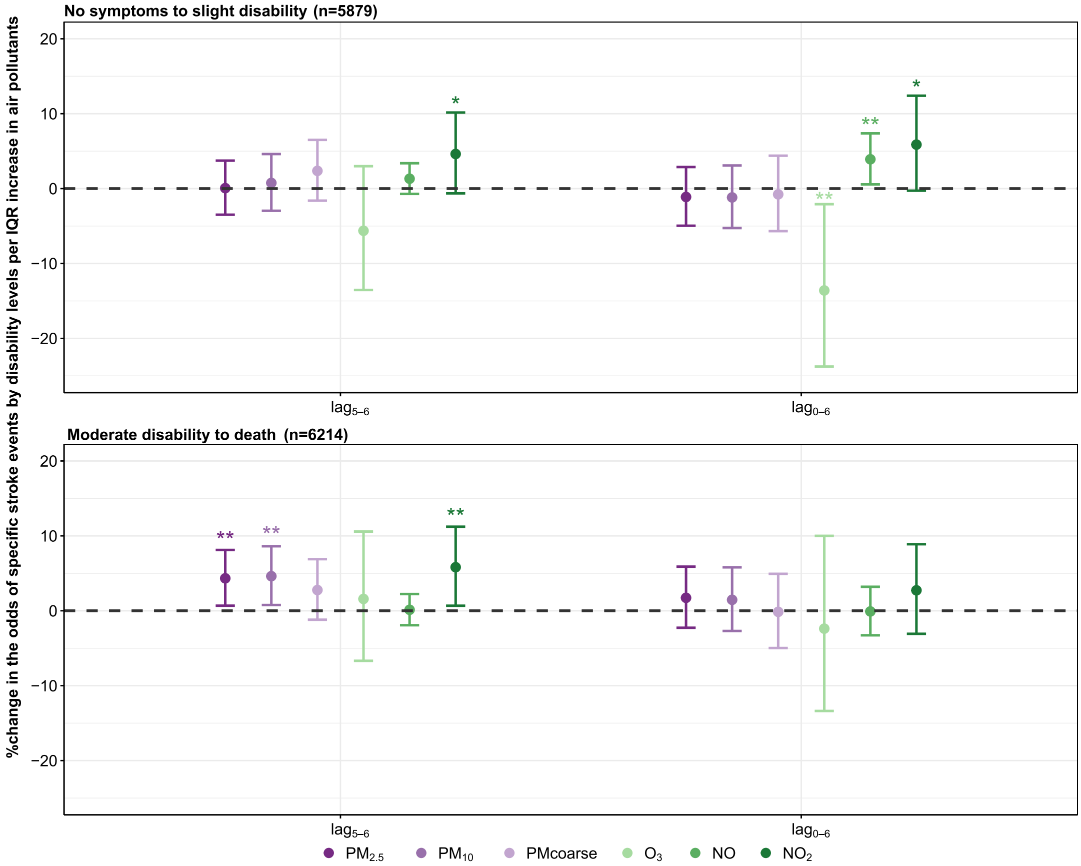

Fig. 4. Stratified percent change (95 % CI) in the odds of overall stroke events in each interquartile range (IQR) increase in moving averaged air pollutants (over lag 5–6 and lag 0–6 days) by disability levels. **Note**: * , $P < 0.10$; * *, $P < 0.05$.

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

(Supplementary materials)

Table Legends

sTable 1. Seasons-stratified summary of daily ambient air pollutants and meteorological parameters in Augsburg, Germany, from 2006 to 2020.

sTable 2. Spearman correlation coefficients between daily air pollutants and meteorological parameters in Augsburg, Germany, from 2006 to 2020.

sTable 3. Percent changes and 95% CIs in the odds of overall stroke events associated with each IQR increase in single-day lagged ambient air pollutant concentrations over lag 0 to lag 6 days.

sTable 4. Percent changes and 95% CIs in the odds of overall stroke events associated with each IQR increase in lagged moving average ambient air pollutant concentrations over lag 0 to lag 6 days.

sTable 5. Subgroup percent changes and 95% CIs in the odds of stroke events associated with each IQR increase in single-day lagged ambient air pollutant concentrations over lag 4 to lag 6 days by three subtypes.

sTable 6. Subgroup percent changes and 95% CIs in the odds of stroke events associated with each IQR increase in lagged moving average ambient air pollutant concentrations over lag 5 to lag 6 days by three subtypes.

sTable 7. Stratified percent changes and 95% CIs in the odds of overall stroke events associated with each IQR increase in single-day lagged ambient air pollutant concentrations over lag 4 to lag 6 days by disability due to strokes or stroke severity.

sTable 8. Stratified percent changes and 95% CIs in the odds of overall stroke events associated with each IQR increase in lagged moving average ambient air pollutant concentrations over lag 5 to lag 6 days by disability due to strokes or stroke severity.

sTable 9. The effect modification on the overall stroke events associated with each IQR increase in ambient air pollutant concentrations.

sTable 10. Percent changes and 95% CIs in the odds of overall stroke events associated with each IQR increase in single-day lagged ambient air pollutant concentrations (over lag 5 and lag 6 days) in the two-pollutant models.

sTable 11. Percent changes and 95% CIs in the odds of overall stroke events associated with each IQR increase in lagged moving average ambient air pollutant concentrations (over lag 5-6 and lag 0-6 days) in the two-pollutant models.

sTable 12. Summary of cited epidemiological evidence on the associations between air pollution and strokes.

Figure Legends

sFig 1. The time series of annual cases of overall stroke events from Augsburg, Germany, from 2006 to 2020. Note: The red dashed line represents the smooth curve of stroke cases across years.

sFig 2. The daily average concentrations of six air pollutants from Augsburg, Germany, from 2006 to 2020.

sFig 3. Subgroup percent changes (95% CIs) in the odds of stroke events in each interquartile range (IQR) increase in single-day lagged air pollutants by three subtypes. **Note**: *, $P<0.10$; **, $P<0.05$.

sFig 4. Stratified percent change (95% CI) in the overall stroke events in each interquartile range (IQR) increase in single-day lagged air pollutants by disability levels. **Note**: *, $P<0.10$; **, $P<0.05$.

sFig 5. Stratified percent change (95% CI) in the overall stroke events in each interquartile range (IQR) increase in single-day lagged air pollutants by severity levels. **Note**: *, *P*<0.10; **, *P*<0.05.

sFig 6. Stratified percent change (95% CI) in the overall stroke events in each interquartile range (IQR) increase in moving average air pollutants by severity levels. **Note**: *, *P*<0.10; **, *P*<0.05.

sFig 7. Percent changes (95% CIs) in the odds of overall stroke events in each interquartile range (IQR) increase in lag 5-6 and 0-6 days of air pollutants modified by sex. **Note**: *, *P*<0.10; **, *P*<0.05.

sFig 8. Percent changes (95% CIs) in the odds of daily overall stroke events in each interquartile range (IQR) increase in lag 5-6 and 0-6 days of air pollutants modified by seasons. **Note**: *, *P*<0.10; **, *P*<0.05.

sFig 9. Percent changes (95% CIs) in the odds of daily overall stroke events in each interquartile range (IQR) increase in lag 5-6 and 0-6 days of air pollutants modified by 5-year periods. **Note**: *, *P*<0.10; **, *P*<0.05.

sFig 10. The exposure-response analysis between seven air pollutants and the odds of overall stroke events at lag 5-6 days using the restricted cubic splines.

sTable 1. Seasons-stratified 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
Warm seasons [a]							
$PM_{2.5}$ (μg/m^3)	14.7±7.8	0.0	9.2	13.4	18.7	86.7	9.5
PM_{10} (μg/m^3)	10.1±5.8	0.0	6.0	9.1	12.7	48.3	6.7
PM_{coarse} (μg/m^3)	4.6±3.3	0.0	2.4	4.1	6.2	48.7	3.8
O_3 (μg/m^3)	54.2±21.6	2.2	39.2	56.5	68.9	127.8	29.7
NO (μg/m^3)	7.6±10.1	0.0	2.2	4.2	8.6	112.6	6.4
NO_2 (μg/m^3)	26.1±10.2	3.8	18.3	25.2	32.9	66.2	14.6
Air temperature (°C)	16.4±5.2	0.0	12.9	16.5	20.3	30.3	7.4
Relative humidity (%)	70.8±11.1	43.0	62.2	70.4	79.2	97.9	17.0
Cold seasons [b]							
$PM_{2.5}$ (μg/m^3)	19.9±15.0	0.0	9.4	16.6	26.1	138.7	16.7
PM_{10} (μg/m^3)	16.0±13.2	0.0	7.0	12.9	20.7	126.4	13.7
PM_{coarse} (μg/m^3)	3.9±4.1	0.0	1.2	2.8	5.2	50.6	4.0
O_3 (μg/m^3)	37.8±21.9	0.6	19.0	37.4	55.1	106.7	36.1
NO (μg/m^3)	16.3±23.7	0.0	3.0	8.3	19.4	238.8	16.4
NO_2 (μg/m^3)	32.2±14.5	3.6	22.1	30.5	40.9	113.3	18.8
Air temperature (°C)	4.3±5.4	-13.9	0.8	4.0	7.8	22.2	7.0
Relative humidity (%)	77.6±11.7	38.4	69.8	79.5	87.0	99.0	17.2

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 measured consecutively between 2006 and 2020. [a] Warm seasons: May to October; [b] Cold seasons: November to April.

sTable 2. Spearman correlation coefficients between daily air pollutants and meteorological parameters in Augsburg, Germany, from 2006 to 2020.

	$PM_{2.5}$	PM_{10}	PM_{coarse}	O_3	NO	NO_2	Air temperature	Relative humidity
$PM_{2.5}$ (µg/m^3)	1.00							
PM_{10} (µg/m^3)	0.95	1.00						
PM_{coarse} (µg/m^3)	0.34	0.59	1.00					
O_3 (µg/m^3)	-0.33	-0.25	0.09	1.00				
NO (µg/m^3)	0.57	0.55	0.25	-0.70	1.00			
NO_2 (µg/m^3)	0.65	0.67	0.38	-0.44	0.81	1.00		
Air temperature (°C)	-0.22	-0.09	0.36	0.59	-0.36	-0.22	1.00	
Relative humidity (%)	0.06	-0.07	-0.38	-0.64	0.27	0.06	-0.60	1.00

Abbreviations: $PM_{2.5}$, 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.

sTable 3. Percent changes and 95% CIs in the odds of overall stroke events associated with each IQR increase in single-day lagged ambient air pollutant concentrations over lag 0 to lag 6 days.

	Percent changes (95%CIs) in the odds of overall stroke events					
	$PM_{2.5}$	**PM_{10}**	**PM_{coarse}**	**O_3**	**NO**	**NO_2**
Lag0	-0.81 (-2.69; 1.11)	-0.93 (-2.89; 1.08)	-0.77 (-2.91; 1.41)	-4.85 (-8.95; -0.56)**	0.69 (-0.34; 1.72)	1.54 (-1.18; 4.34)
Lag1	0.57 (-1.34; 2.52)	0.13 (-1.86; 2.16)	-1.34 (-3.49; 0.86)	-1.00 (-5.29; 3.48)	0.40 (-0.64; 1.45)	1.22 (-1.52; 4.04)
Lag2	0.44 (-1.46; 2.37)	0.27 (-1.74; 2.32)	-0.43 (-2.54; 1.74)	-2.59 (-6.74; 1.75)	0.37 (-0.66; 1.42)	1.90 (-0.88; 4.75)
Lag3	1.55 (-0.39; 3.53)	1.33 (-0.71; 3.41)	-0.16 (-2.30; 2.02)	-3.24 (-7.37; 1.07)	0.83 (-0.20; 1.86)	2.56 (-0.22; 5.42)*
Lag4	1.82 (-0.15; 3.83)*	1.92 (-0.14; 4.03)*	1.07 (-1.07; 3.26)	-1.95 (-6.10; 2.39)	0.59 (-0.47; 1.66)	1.68 (-1.10; 4.52)
Lag5	1.94 (-0.04; 3.95)*	2.36 (0.30; 4.46)**	2.22 (0.10; 4.39)**	-0.92 (-5.13; 3.47)	0.25 (-0.79; 1.31)	2.88 (0.07; 5.77)**
Lag6	1.93 (-0.02; 3.92)*	2.28 (0.21; 4.40)**	1.88 (-0.25; 4.06)*	-4.28 (-8.36; -0.02)**	0.54 (-0.51; 1.60)	3.35 (0.54; 6.24)**

Abbreviations: CIs, confidence intervals; 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: *, *P*<0.10; **, *P*<0.05; Percent changes were estimated based on the odds ratios using conditional logistic regression; The model was adjusted for the corresponding lagged days of air temperature and relative humidity.

sTable 4. Percent changes and 95% CIs in the odds of overall stroke events associated with each IQR increase in moving average lagged ambient air pollutant concentrations over lag 0 to lag 6 days.

	Percent changes (95%CIs) in the odds of overall stroke events			
	Lag 0-1	**Lag 2-4**	**Lag 5-6**	**Lag 0-6**
$PM_{2.5}$	-0.20 (-2.11; 1.76)	1.48 (-0.53; 3.53)	2.11 (0.09; 4.17)**	1.77 (-0.50; 4.08)
PM_{10}	-0.51 (-2.52; 1.54)	1.37 (-0.76; 3.55)	2.55 (0.43; 4.71)**	1.69 (-0.65; 4.08)
PM_{coarse}	-1.35 (-3.62; 0.97)	1.45 (-0.79; 3.74)	2.50 (0.23; 4.82)**	0.63 (-2.17; 3.51)
O_3	-3.58 (-8.14; 1.21)	-3.80 (-8.71; 1.38)	-2.93 (-7.48; 1.84)	-6.19 (-12.30; 0.36)*
NO	0.66 (-0.48; 1.82)	0.91 (-0.41; 2.25)	0.46 (-0.70; 1.63)	1.51 (-0.36; 3.42)
NO_2	1.55 (-1.25; 4.42)	2.60 (-0.33; 5.62)*	3.48 (0.61; 6.44)**	4.33 (0.92; 7.87)**

Abbreviations: CIs, confidence intervals; 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: *, $P<0.10$; **, $P<0.05$; Percent changes were estimated based on the odds ratios using conditional logistic regression; The model was adjusted for the corresponding lagged days of air temperature and relative humidity.

sTable 5. Subgroup percent changes and 95% CIs in the odds of stroke events associated with each IQR increase in single-day lagged ambient air pollutant concentrations over lag 4 to lag 6 days by three subtypes.

	Percent changes (95%CIs) in the odds of specific stroke events		
	Lag 4	**Lag 5**	**Lag 6**
Transient ischemic attack			
$PM_{2.5}$	2.44 (-1.41; 6.44)	1.53 (-2.31; 5.52)	4.85 (1.00; 8.83)**
PM_{10}	2.50 (-1.53; 6.70)	1.69 (-2.29; 5.83)	5.27 (1.19; 9.51)**
PM_{coarse}	1.21 (-3.00; 5.60)	1.24 (-3.05; 5.71)	3.21 (-1.09; 7.69)
O_3	-1.43 (-9.52; 7.38)	-3.33 (-11.29; 5.34)	-12.49 (-19.73; -4.60)**
NO	0.28 (-1.81; 2.40)	0.52 (-1.55; 2.63)	1.79 (-0.25; 3.88)*
NO_2	-1.66 (-6.94; 3.93)	1.95 (-3.52; 7.73)	5.78 (0.25; 11.60)**
Hemorrhagic stroke			
$PM_{2.5}$	4.67 (-3.13; 13.10)	9.00 (0.89; 17.75)**	11.78 (3.36; 20.89)**
PM_{10}	3.95 (-4.12; 12.74)	7.77 (-0.59; 16.83)*	11.64 (2.73; 21.33)**
PM_{coarse}	-0.67 (-8.90; 8.29)	-0.14 (-7.91; 8.29)	3.63 (-4.95; 12.97)
O_3	-8.89 (-23.45; 8.44)	-7.18 (-22.50; 11.16)	-0.98 (-16.76; 17.79)
NO	2.20 (-1.80; 6.36)	-0.36 (-4.49; 3.96)	1.59 (-2.68; 6.03)
NO_2	13.19 (1.30; 26.47)**	13.06 (0.72; 26.92)**	10.68 (-1.09; 23.84)*
Ischemic stroke			
$PM_{2.5}$	1.43 (-0.95; 3.87)	1.52 (-0.86; 3.96)	0.06 (-2.28; 2.47)
PM_{10}	1.64 (-0.87; 4.21)	2.21 (-0.29; 4.77)*	0.43 (-2.05; 2.98)
PM_{coarse}	1.24 (-1.34; 3.89)	2.86 (0.30; 5.48)**	1.24 (-1.33; 3.86)
O_3	-1.53 (-6.55; 3.76)	0.55 (-4.59; 5.96)	-1.24 (-6.33; 4.12)
NO	0.58 (-0.71; 1.88)	0.21 (-1.05; 1.49)	-0.03 (-1.29; 1.25)
NO_2	2.10 (-1.25; 5.56)	2.59 (-0.77; 6.06)	1.90 (-1.47; 5.38)

Abbreviations: CIs, confidence intervals; $PM_{2.5}$, 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: *, $P<0.10$; **, $P<0.05$; Percent changes were estimated based on the odds ratios using conditional logistic regression; The model was adjusted for the corresponding lagged days of air temperature and relative humidity.

sTable 6. Subgroup percent changes and 95% CIs in the odds of stroke events associated with each IQR increase in moving average lagged ambient air pollutant concentrations over lag 5 to lag 6 days by three subtypes.

	Percent changes (95%CIs) in the odds of specific stroke events	
	Lag 5-6	**Lag 0-6**
Transient ischemic attack		
$PM_{2.5}$	3.56 (-0.36; 7.63)*	3.17 (-1.22; 7.75)
PM_{10}	3.92 (-0.24; 8.24)*	3.11 (-1.40; 7.82)
PM_{coarse}	2.79 (-1.82; 7.61)	1.56 (-3.95; 7.38)
O_3	-9.62 (-17.76; -0.67)**	-9.72 (-21.01; 3.20)
NO	1.47 (-0.82; 3.81)	3.92 (0.13; 7.86)**
NO_2	4.38 (-1.31; 10.39)	5.95 (-0.83; 13.20)*
Hemorrhagic stroke		
$PM_{2.5}$	11.37 (2.90; 20.54)**	5.59 (-3.74; 15.81)
PM_{10}	10.50 (1.79; 19.96)**	5.05 (-4.39; 15.43)
PM_{coarse}	1.95 (-6.69; 11.40)	0.91 (-9.97; 13.11)
O_3	-6.01 (-22.59; 14.12)	-6.49 (-28.78; 22.79)
NO	0.81 (-3.97; 5.84)	-0.68 (-8.19; 7.45)
NO_2	13.83 (1.16; 28.09)**	9.05 (-4.96; 25.12)
Ischemic stroke		
$PM_{2.5}$	0.84 (-1.59; 3.34)	0.84 (-1.89; 3.64)
PM_{10}	1.44 (-1.12; 4.06)	0.80 (-2.02; 3.71)
PM_{coarse}	2.49 (-0.23; 5.29)*	0.30 (-3.05; 3.77)
O_3	-0.01 (-5.66; 5.98)	-4.79 (-12.27; 3.33)
NO	0.07 (-1.33; 1.49)	0.82 (-1.42; 3.10)
NO_2	2.51 (-0.91; 6.05)	3.40 (-0.63; 7.60)*

Abbreviations: CIs, confidence intervals; $PM_{2.5}$, 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: *, P<0.10; **, P<0.05; Percent changes were estimated based on the odds ratios using conditional logistic regression; The model was adjusted for the corresponding lagged days of air temperature and relative humidity.

sTable 7. Stratified percent changes and 95% CIs in the odds of overall stroke events associated with each IQR increase in single-day lagged ambient air pollutant concentrations over lag 4 to lag 6 days by disability due to strokes or stroke severity.

	Stratified percent changes (95%CIs) in the odds of overall stroke events		
	Lag 4	**Lag 5**	**Lag 6**
Disability due to strokes			
No symptoms to slight disability [a]			
$PM_{2.5}$	-0.41 (-3.81; 3.12)	-0.94 (-4.36; 2.60)	1.20 (-2.32; 4.85)
PM_{10}	-0.23 (-3.87; 3.54)	-0.41 (-4.01; 3.33)	1.90 (-1.84; 5.77)
PM_{coarse}	0.40 (-3.33; 4.27)	1.24 (-2.45; 5.07)	2.55 (-1.20; 6.44)
O_3	-4.37 (-11.73; 3.60)	-3.29 (-10.71; 4.75)	-6.57 (-13.80; 1.27)*
NO	1.69 (-0.15; 3.56)*	1.19 (-0.66; 3.07)	1.06 (-0.77; 2.93)
NO_2	2.67 (-2.36; 7.97)	3.29 (-1.78; 8.62)	4.84 (-0.34; 10.30)*
Moderate disability to death [b]			
$PM_{2.5}$	2.31 (-1.11; 5.85)	4.91 (1.38; 8.56)**	2.74 (-0.74; 6.35)
PM_{10}	2.46 (-1.19; 6.23)	5.46 (1.73; 9.32)**	2.66 (-1.05; 6.50)
PM_{coarse}	1.35 (-2.43; 5.28)	3.74 (-0.03; 7.66)*	0.74 (-2.94; 4.56)
O_3	0.22 (-7.15; 8.16)	0.43 (-6.95; 8.40)	1.26 (-6.32; 9.46)
NO	0.17 (-1.71; 2.08)	-0.02 (-1.86; 1.86)	0.30 (-1.59; 2.23)
NO_2	1.94 (-2.93; 7.05)	5.93 (0.87; 11.25)**	4.37 (-0.66; 9.64)*
Stroke severity			
No to minor stroke [c]			
$PM_{2.5}$	1.76 (-1.20; 4.81)	1.45 (-1.52; 4.50)	1.44 (-1.55; 4.52)
PM_{10}	1.94 (-1.22; 5.20)	1.81 (-1.34; 5.07)	1.73 (-1.44; 5.00)
PM_{coarse}	1.21 (-2.01; 4.53)	1.67 (-1.51; 4.95)	1.44 (-1.78; 4.76)
O_3	-2.88 (-9.19; 3.86)	-4.35 (-10.54; 2.28)	-5.56 (-11.72; 1.04)*
NO	1.48 (-0.12; 3.10)*	0.90 (-0.67; 2.49)	0.16 (-1.41; 1.75)
NO_2	1.52 (-2.73; 5.95)	2.54 (-1.73; 6.99)	2.17 (-2.11; 6.64)
Moderate to severe stroke [d]			
$PM_{2.5}$	0.50 (-3.17; 4.31)	2.73 (-1.00; 6.60)	1.16 (-2.55; 5.01)
PM_{10}	0.45 (-3.45; 4.51)	3.38 (-0.54; 7.45)*	1.34 (-2.59; 5.42)
PM_{coarse}	0.02 (-4.03; 4.23)	3.25 (-0.77; 7.44)	0.98 (-2.94; 5.06)
O_3	0.51 (-7.33; 9.02)	4.12 (-4.16; 13.11)	3.68 (-4.62; 12.69)
NO	-0.01 (-2.04; 2.05)	0.02 (-1.99; 2.07)	0.98 (-1.07; 3.07)
NO_2	0.75 (-4.35; 6.12)	4.03 (-1.24; 9.57)	4.21 (-1.09; 9.80)

Abbreviations: CIs, confidence intervals; $PM_{2.5}$, 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: *, $P<0.10$; **, $P<0.05$; Percent changes were estimated based on the odds ratios using conditional logistic regression; The model was adjusted for the corresponding lagged days of air temperature and relative humidity. [a] the mRS score of 0-2 is “no symptoms to slight disability”; [b] mRS 3-6 is “moderate disability to death”. [c] NIHSS score of 0-3 is “no to minor stroke”; [d] NIHSS score of 4-42 is “moderate to severe stroke”.

sTable 8. Stratified percent changes and 95% CIs in the odds of overall stroke events associated with each IQR increase in moving average lagged ambient air pollutant concentrations over lag 5 to lag 6 days by disability due to strokes or stroke severity.

	Stratified percent changes (95%CIs) in the odds of overall stroke events	
	Lag 5-6	**Lag 0-6**
Disability due to strokes		
No symptoms to slight disability [a]		
$PM_{2.5}$	0.06 (-3.49; 3.73)	-1.12 (-4.96; 2.88)
PM_{10}	0.76 (-2.96; 4.61)	-1.18 (-5.27; 3.09)
PM_{coarse}	2.38 (-1.61; 6.50)	-0.77 (-5.68; 4.39)
O_3	-5.63 (-13.54; 2.99)	-13.60 (-23.76; -2.08)**
NO	1.32 (-0.71; 3.39)	3.91 (0.56; 7.37)**
NO_2	4.62 (-0.64; 10.16)*	5.87 (-0.28; 12.40)*
Moderate disability to death [b]		
$PM_{2.5}$	4.33 (0.68; 8.12)**	1.73 (-2.27; 5.89)
PM_{10}	4.62 (0.77; 8.62)**	1.46 (-2.70; 5.80)
PM_{coarse}	2.77 (-1.19; 6.89)	-0.14 (-4.97; 4.93)
O_3	1.58 (-6.68; 10.58)	-2.38 (-13.38; 10.00)
NO	0.13 (-1.93; 2.23)	-0.09 (-3.27; 3.20)
NO_2	5.82 (0.67; 11.22)**	2.73 (-3.08; 8.89)
Stroke severity		
No to minor stroke [c]		
$PM_{2.5}$	1.57 (-1.52; 4.75)	-0.45 (-3.77; 3.00)
PM_{10}	1.93 (-1.29; 5.25)	-0.12 (-3.64; 3.53)
PM_{coarse}	1.95 (-1.47; 5.49)	1.16 (-3.07; 5.57)
O_3	-5.86 (-12.55; 1.34)	-10.60 (-19.55; -0.66)**
NO	0.62 (-1.11; 2.38)	2.21 (-0.70; 5.21)
NO_2	2.68 (-1.71; 7.27)	3.44 (-1.64; 8.79)
Moderate to severe stroke [d]		
$PM_{2.5}$	2.15 (-1.65; 6.11)	0.54 (-3.71; 4.98)
PM_{10}	2.64 (-1.37; 6.81)	0.04 (-4.35; 4.64)
PM_{coarse}	2.61 (-1.61; 7.02)	-1.81 (-6.97; 3.63)
O_3	5.60 (-3.68; 15.78)	2.40 (-9.75; 16.17)
NO	0.57 (-1.69; 2.88)	0.71 (-2.67; 4.20)
NO_2	4.63 (-0.78; 10.33)*	2.08 (-4.03; 8.57)

Abbreviations: CIs, confidence intervals; $PM_{2.5}$, 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: *, *P*<0.10; **, *P*<0.05; Percent changes were estimated based on the odds ratios using conditional logistic regression; The model was adjusted for the corresponding lagged days of air temperature and relative humidity. [a] the mRS score of 0-2 is “no symptoms to slight disability”; [b] mRS 3-6 is “moderate disability to death”. [c] NIHSS score of 0-3 is “no to minor stroke”; [d] NIHSS score of 4-42 is “moderate to severe stroke”.

sTable 9. The effect modification on the overall stroke events associated with each IQR increase in ambient air pollutant concentrations.

	Single-day lagged model				Moving average lagged model			
	Lag 5		Lag 6		Lag 5-6		Lag 0-6	
	Estimates [a]	***P*** **[b]**	**Estimates [a]**	***P*** **[b]**	**Estimates [a]**	***P*** **[b]**	**Estimates [a]**	***P*** **[b]**
Sex								
$PM_{2.5}$								
Men	-0.10 (-3.24; 3.14)	1(Ref)	-0.20 (-3.30; 3.01)	1(Ref)	-0.21 (-3.38; 3.07)	1(Ref)	0.35 (-3.10; 3.91)	1(Ref)
Women	2.36 (-0.48; 5.29)	0.235	3.12 (0.28; 6.05)	0.107	2.97 (0.06; 5.96)	0.129	2.45 (-0.76; 5.77)	0.343
PM_{10}								
Men	-0.14 (-3.42; 3.25)	1(Ref)	0.17 (-3.12; 3.57)	1(Ref)	-0.01 (-3.35; 3.44)	1(Ref)	0.67 (-2.95; 4.43)	1(Ref)
Women	3.69 (0.71; 6.76)	0.078	3.88 (0.86; 6.99)	0.090	4.14 (1.08; 7.30)	0.060	2.90 (-0.44; 6.34)	0.343
PM_{coarse}								
Men	-0.19 (-3.68; 3.42)	1(Ref)	1.17 (-2.9; 4.74)	1(Ref)	0.66 (-3.00; 4.46)	1(Ref)	1.85 (-2.72; 6.63)	1(Ref)
Women	5.41 (2.32; 8.60)	**0.015**	3.74 (0.60; 6.98)	0.263	5.60 (2.29; 9.02)	**0.041**	3.26 (-0.74; 7.41)	0.629
O_3								
Men	0.96 (-6.03; 8.48)	1(Ref)	-4.16 (-10.82; 2.99)	1(Ref)	-1.67 (-9.09; 6.37)	1(Ref)	-8.33 (-17.56; 1.94)	1(Ref)
Women	-0.68 (-6.59; 5.62)	0.716	-5.50 (-11.15; 0.51)	0.755	-3.40 (-9.70; 3.34)	0.714	-4.51 (-12.98; 4.77)	0.523
NO								
Men	0.60 (-1.18; 2.42)	1(Ref)	1.27 (-0.48; 3.05)	1(Ref)	1.14 (-0.82; 3.14)	1(Ref)	4.40 (1.20; 7.71)	1(Ref)
Women	0.48 (-1.08; 2.07)	0.924	0.71 (-0.88; 2.31)	0.642	0.71 (-1.03; 2.48)	0.749	0.53 (-2.31; 3.44)	0.078
NO_2								
Men	0.76 (-3.89; 5.63)	1(Ref)	4.39 (-0.39; 9.40)	1(Ref)	2.89 (-1.91; 7.93)	1(Ref)	4.08 (-1.65; 10.13)	1(Ref)
Women	5.59 (1.40; 9.95)	0.129	4.62 (0.48; 8.94)	0.942	5.79 (1.54; 10.22)	0.372	5.41 (0.41; 10.67)	0.729
Age, years								
$PM_{2.5}$								
<67.0	3.80 (0.63; 7.08)	1(Ref)	3.97 (0.83; 7.21)	1(Ref)	4.22 (1.01; 7.52)	1(Ref)	1.45 (-1.99; 5.02)	1(Ref)
67.0-78.0	1.66 (-1.61; 5.03)	0.345	0.99 (-2.22; 4.31)	0.185	1.41 (-1.87; 4.81)	0.220	2.40 (-1.16; 6.10)	0.695
≥78.0	0.39 (-2.68; 3.55)	0.120	0.76 (-2.30; 3.92)	0.142	0.62 (-2.51; 3.86)	0.105	1.48 (-1.98; 5.05)	0.993
PM_{10}								
<67.0	3.72 (0.39; 7.16)	1(Ref)	4.21 (0.87; 7.67)	1(Ref)	4.33 (0.95; 7.83)	1(Ref)	1.06 (-2.55; 4.80)	1(Ref)
67.0-78.0	1.87 (-1.52; 5.38)	0.436	0.91 (-2.49; 4.43)	0.166	1.51 (-1.94; 5.08)	0.240	2.15 (-1.58; 6.01)	0.669
≥78.0	1.51 (-1.69; 4.80)	0.336	1.64 (-1.60; 4.98)	0.268	1.74 (-1.55; 5.13)	0.267	1.89 (-1.70; 5.61)	0.738
PM_{coarse}								
<67.0	1.20 (-2.27; 4.79)	1(Ref)	2.18 (-1.29; 5.77)	1(Ref)	2.06 (-1.60; 5.86)	1(Ref)	-1.09 (-5.48; 3.51)	1(Ref)
67.0-78.0	1.39 (-2.09; 4.99)	0.938	0.04 (-3.48; 3.70)	0.388	0.91 (-2.77; 4.73)	0.656	0.02 (-4.45; 4.71)	0.721
≥78.0	3.88 (0.55; 7.33)	0.265	3.17 (-0.16; 6.60)	0.683	4.25 (0.74; 7.89)	0.386	2.65 (-1.60; 7.09)	0.216
O_3								
<67.0	-3.91 (-10.40; 3.05)	1(Ref)	-6.80 (-13.13; -0.02)	1(Ref)	-6.23 (-13.13; 1.22)	1(Ref)	-7.49 (-16.55; 2.56)	1(Ref)
67.0-78.0	1.80 (-5.08; 9.18)	0.230	-2.32 (-8.96; 4.79)	0.331	-0.13 (-7.47; 7.79)	0.226	-5.83 (-15.07; 4.42)	0.795
≥78.0	-0.59 (-7.05; 6.31)	0.471	-3.73 (-9.97; 2.94)	0.490	-2.41 (-9.29; 5.00)	0.432	-5.30 (-14.29; 4.63)	0.728
NO								
<67.0	0.79 (-1.04; 2.64)	1(Ref)	1.14 (-0.66; 2.98)	1(Ref)	1.18 (-0.83; 3.23)	1(Ref)	1.29 (-1.95; 4.63)	1(Ref)
67.0-78.0	0.94 (-0.94; 2.86)	0.907	0.53 (-1.39; 2.49)	0.652	0.88 (-1.23; 3.04)	0.843	1.37 (-2.02; 4.88)	0.973
≥78.0	-0.79 (-2.50; 0.96)	0.221	0.01 (-1.69; 1.74)	0.375	-0.51 (-2.40; 1.41)	0.233	1.82 (-1.19; 4.92)	0.816
NO_2								
<67.0	4.49 (-0.29; 9.50)	1(Ref)	6.50 (1.68; 11.56)	1(Ref)	6.20 (1.30; 11.33)	1(Ref)	4.09 (-1.58; 10.07)	1(Ref)
67.0-78.0	3.07 (-1.69; 8.07)	0.682	2.87 (-1.85; 7.82)	0.294	3.30 (-1.52; 8.36)	0.410	3.63 (-2.08; 9.67)	0.912

≥78.0	1.27 (-3.16; 5.91)	0.334	0.96 (-3.45; 5.56)	0.096	1.21 (-3.28; 5.90)	0.141	5.19 (-0.29; 10.97)	0.785
Seasons [c]								
$PM_{2.5}$								
Warm seasons	8.55 (2.01; 15.51)	1(Ref)	3.53 (-2.75; 10.21)	1(Ref)	6.62 (-0.05; 13.74)	1(Ref)	1.37 (-5.56; 8.81)	1(Ref)
Cold seasons	2.48 (0.09; 4.93)	0.089	2.15 (-0.19; 4.53)	0.692	2.65 (0.21; 5.14)	0.280	2.79 (0.01; 5.65)	0.720
PM_{10}								
Warm seasons	8.43 (2.58; 14.60)	1(Ref)	4.68 (-1.07; 10.76)	1(Ref)	7.46 (1.36; 13.93)	1(Ref)	2.84 (-3.64; 9.76)	1(Ref)
Cold seasons	3.16 (0.58; 5.82)	0.109	2.41 (-0.16; 5.05)	0.489	3.20 (0.54; 5.92)	0.215	2.61 (-0.37; 5.68)	0.951
PM_{coarse}								
Warm seasons	4.60 (0.55; 8.80)	1(Ref)	3.59 (-0.39; 7.73)	1(Ref)	5.23 (0.82; 9.83)	1(Ref)	4.22 (-1.39; 10.14)	1(Ref)
Cold seasons	3.74 (0.66; 6.92)	0.744	1.65 (-1.49; 4.89)	0.458	3.40 (0.09; 6.82)	0.520	-0.03 (-4.22; 4.35)	0.242
O_3								
Warm seasons	-0.59 (-8.38; 7.85)	1(Ref)	-10.79 (-17.78; -3.20)	1(Ref)	-7.80 (-15.97; 1.16)	1(Ref)	-10.33 (-21.43; 2.34)	1(Ref)
Cold seasons	-1.95 (-7.55; 3.99)	0.786	-1.14 (-6.74; 4.80)	**0.041**	-1.45 (-7.54; 5.04)	0.237	-5.54 (-13.74; 3.45)	0.514
NO								
Warm seasons	2.55 (-2.86; 8.27)	1(Ref)	8.26 (2.59; 14.24)	1(Ref)	7.42 (0.98; 14.27)	1(Ref)	11.28 (0.43; 23.30)	1(Ref)
Cold seasons	0.13 (-0.97; 1.24)	0.397	0.29 (-0.81; 1.40)	**0.006**	0.24 (-0.97; 1.46)	**0.031**	1.30 (-0.65; 3.30)	0.078
NO_2								
Warm seasons	2.52 (-3.56; 8.98)	1(Ref)	12.27 (5.63; 19.32)	1(Ref)	9.12 (2.29; 16.39)	1(Ref)	5.78 (-1.90; 14.06)	1(Ref)
Cold seasons	3.04 (-0.66; 6.88)	0.889	2.09 (-1.54; 5.85)	**0.009**	2.84 (-0.85; 6.67)	0.117	5.00 (0.51; 9.69)	0.867
Air temperature [d]**, °C**								
$PM_{2.5}$								
T1	1.13 (-0.96; 3.26)	1(Ref)	1.56 (-0.50; 3.67)	1(Ref)	1.43 (-0.66; 3.56)	1(Ref)	0.72 (-1.45; 2.94)	1(Ref)
T2	1.23 (-2.47; 5.07)	0.961	-0.23 (-3.90; 3.58)	0.412	0.03 (-3.69; 3.89)	0.525	1.46 (-2.60; 5.68)	0.749
T3	2.94 (-3.16; 9.43)	0.590	3.78 (-2.34; 10.29)	0.510	4.80 (-1.58; 11.59)	0.333	2.62 (-4.02; 9.73)	0.600
PM_{10}								
T1	1.37 (-0.95; 3.75)	1(Ref)	1.83 (-0.50; 4.22)	1(Ref)	1.64 (-0.69; 4.03)	1(Ref)	0.48 (-1.90; 2.92)	1(Ref)
T2	1.71 (-1.86; 5.40)	0.879	0.17 (-3.43; 3.91)	0.454	0.77 (-2.84; 4.52)	0.694	1.29 (-2.63; 5.36)	0.726
T3	2.95 (-1.96; 8.11)	0.576	4.20 (-0.84; 9.50)	0.410	4.56 (-0.66; 10.06)	0.324	3.63 (-2.08; 9.67)	0.323
PM_{coarse}								
T1	1.78 (-1.74; 5.43)	1(Ref)	1.74 (-1.73; 5.33)	1(Ref)	1.67 (-1.97; 5.44)	1(Ref)	-1.93 (-5.87; 2.17)	1(Ref)
T2	1.98 (-1.24; 5.32)	0.934	0.87 (-2.40; 4.25)	0.720	1.98 (-1.36; 5.43)	0.900	0.36 (-3.57; 4.45)	0.399
T3	2.02 (-1.26; 5.41)	0.925	3.06 (-0.26; 6.50)	0.592	3.08 (-0.48; 6.78)	0.589	3.78 (-0.80; 8.57)	0.062
O_3								
T1	-0.82 (-6.29; 4.97)	1(Ref)	-2.66 (-8.01; 3.00)	1(Ref)	-1.48 (-7.33; 4.74)	1(Ref)	-5.46 (-12.90; 2.62)	1(Ref)
T2	-2.07 (-8.13; 4.38)	0.740	-6.54 (-12.37; -0.33)	0.289	-4.74 (-11.07; 2.05)	0.407	-3.90 (-11.91; 4.85)	0.735
T3	1.03 (-5.80; 8.36)	0.678	-0.08 (-6.82; 7.14)	0.555	-0.03 (-7.39; 7.92)	0.762	-3.77 (-12.95; 6.37)	0.775
NO								
T1	0.04 (-1.17; 1.28)	1(Ref)	0.42 (-0.79; 1.64)	1(Ref)	0.35 (-1.01; 1.72)	1(Ref)	1.32 (-0.83; 3.51)	1(Ref)
T2	0.89 (-1.03; 2.86)	0.458	0.51 (-1.47; 2.53)	0.938	0.43 (-1.68; 2.57)	0.952	0.94 (-2.29; 4.28)	0.844
T3	-2.25 (-7.97; 3.82)	0.459	1.48 (-4.36; 7.67)	0.734	1.17 (-5.62; 8.46)	0.821	10.19 (-1.59; 23.38)	0.152
NO_2								
T1	1.89 (-1.82; 5.74)	1(Ref)	1.66 (-2.00; 5.46)	1(Ref)	1.90 (-1.79; 5.74)	1(Ref)	3.18 (-1.09; 7.63)	1(Ref)
T2	4.96 (0.54; 9.58)	0.285	3.35 (-1.00; 7.88)	0.552	3.92 (-0.52; 8.55)	0.483	4.01 (-1.09; 9.37)	0.799
T3	-0.28 (-5.63; 5.39)	0.523	6.54 (0.81; 12.59)	0.163	4.72 (-1.05; 10.84)	0.424	5.57 (-1.20; 12.81)	0.561
5-year periods								
$PM_{2.5}$								
2006-2010	0.31 (-2.32; 3.01)	1(Ref)	-0.59 (-3.18; 2.07)	1(Ref)	-0.10 (-2.72; 2.58)	1(Ref)	0.48 (-2.34; 3.37)	1(Ref)

2011-2015	2.84 (-0.51; 6.30)	0.229	3.41 (0.11; 6.82)	0.053	3.51 (0.04; 7.10)	0.089	2.22 (-1.55; 6.14)	0.438
2016-2020	4.56 (0.55; 8.74)	0.076	6.07 (1.97; 10.34)	**0.006**	6.01 (1.81; 10.38)	**0.013**	5.09 (0.35; 10.05)	0.089
PM_{10}								
2006-2010	0.75 (-2.07; 3.65)	1(Ref)	-0.14 (-2.97; 2.77)	1(Ref)	0.37 (-2.46; 3.27)	1(Ref)	0.67 (-2.35; 3.79)	1(Ref)
2011-2015	2.83 (-0.70; 6.48)	0.353	3.69 (0.14; 7.36)	0.087	3.70 (0.00; 7.52)	0.146	1.90 (-2.08; 6.04)	0.612
2016-2020	4.84 (0.99; 8.84)	0.086	5.32 (1.36; 9.43)	**0.025**	5.70 (1.69; 9.87)	**0.029**	3.79 (-0.65; 8.43)	0.240
PM_{coarse}								
2006-2010	2.05 (-1.36; 5.57)	1(Ref)	1.95 (-1.47; 5.48)	1(Ref)	2.41 (-1.16; 6.11)	1(Ref)	1.87 (-2.48; 6.41)	1(Ref)
2011-2015	1.02 (-2.75; 4.94)	0.684	2.14 (-1.67; 6.11)	0.939	1.98 (-2.07; 6.19)	0.871	-0.36 (-5.17; 4.69)	0.482
2016-2020	3.14 (-0.05; 6.42)	0.643	1.66 (-1.55; 4.97)	0.902	2.90 (-0.47; 6.37)	0.844	0.18 (-3.94; 4.47)	0.574
O_3								
2006-2010	0.16 (-6.57; 7.38)	1(Ref)	-1.26 (-7.90; 5.87)	1(Ref)	-0.53 (-7.77; 7.29)	1(Ref)	-3.32 (-12.52; 6.85)	1(Ref)
2011-2015	1.26 (-5.41; 8.39)	0.818	-4.92 (-11.18; 1.78)	0.422	-2.02 (-9.04; 5.56)	0.766	-2.28 (-11.40; 7.79)	0.869
2016-2020	-4.19 (-10.65; 2.75)	0.357	-6.56 (-12.90; 0.24)	0.253	-6.21 (-13.11; 1.23)	0.258	-14.20 (-23.17; -4.18)	0.091
NO								
2006-2010	0.04 (-1.63; 1.74)	1(Ref)	0.84 (-0.85; 2.56)	1(Ref)	0.50 (-1.39; 2.43)	1(Ref)	2.31 (-0.80; 5.52)	1(Ref)
2011-2015	-0.82 (-2.72; 1.12)	0.512	-0.52 (-2.46; 1.46)	0.305	-0.85 (-2.96; 1.31)	0.356	-0.22 (-3.53; 3.21)	0.281
2016-2020	1.52 (-0.32; 3.40)	0.246	1.12 (-0.69; 2.95)	0.827	1.58 (-0.42; 3.62)	0.446	2.26 (-0.96; 5.57)	0.980
NO_2								
2006-2010	1.04 (-3.43; 5.72)	1(Ref)	1.88 (-2.58; 6.55)	1(Ref)	1.52 (-2.99; 6.25)	1(Ref)	4.57 (-0.80; 10.22)	1(Ref)
2011-2015	2.63 (-2.11; 7.59)	0.634	2.18 (-2.50; 7.07)	0.928	2.79 (-2.04; 7.86)	0.706	2.60 (-3.12; 8.65)	0.623
2016-2020	5.11 (0.34; 10.11)	0.224	6.13 (1.31; 11.18)	0.206	6.27 (1.40; 11.37)	0.162	5.76 (-0.05; 11.91)	0.770

Abbreviations: CIs, confidence intervals; $PM_{2.5}$, 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: *, P<0.10; **, P<0.05; Percent changes were estimated based on the odds ratios using conditional logistic regression; [a] Estimates of interaction analyses; [b] P for interaction; [c] Seasons: warm seasons: May to October; cold seasons: November to April; [d] Air temperature: was divided by the tertiles values of air temperature.

sTable 10. Percent changes and 95% CIs in the odds of overall stroke events associated with each IQR increase in single-day lagged ambient air pollutant concentrations (over lag 5 and lag 6 days) in the two-pollutant models.

	Percent changes (95%CIs) in the odds of overall stroke events					
	$PM_{2.5}$	**PM_{10}**	**PM_{coarse}**	**O_3**	**NO**	**NO_2**
Lag 5						
Single	1.94 (-0.04; 3.95)*	2.36 (0.30; 4.46)**	2.22 (0.10; 4.39)**	-0.92 (-5.13; 3.47)	0.251 (-0.79; 1.31)	2.88 (0.07; 5.77)**
Adj. $PM_{2.5}$	-	-	1.66 (-0.62; 4.00)	1.06 (-3.66; 6.01)	-0.26 (-1.42; 0.92)	1.97 (-1.32; 5.36)
Adj. PM_{10}	-2.72 (-9.07; 4.07)	-	1.12 (-1.53; 3.91)	1.59 (-3.21; 6.62)	-0.43 (-1.62; 0.77)	1.53 (-1.84; 5.02)
Adj. PM_{coarse}	1.34 (-0.78; 3.51)	1.67 (-0.97; 4.37)	-	0.38 (-4.06; 5.03)	-0.16 (-1.28; 0.97)	2.03 (-1.01; 5.16)
Adj. O_3	2.14 (-0.04; 4.36)*	2.69 (0.40; 5.04)**	2.28 (0.06; 4.54)**	-	0.19 (-1.02; 1.41)	4.39 (0.63; 8.29)**
Adj. NO	2.15 (-0.05; 4.41)*	2.78 (0.42; 5.19)*	2.34 (0.07; 4.66)**	-	-	4.21 (0.50; 8.05)**
Adj. NO_2	1.19 (-1.12; 3.56)	1.71 (-0.78; 4.26)	1.60 (-0.70; 3.96)	3.54 (-2.24; 9.66)	-	-
Lag 6						
Single	1.93 (-0.02; 3.92)*	2.28 (0.21; 4.40)**	1.88 (-0.25; 4.06)*	-4.28 (-8.36; -0.02)**	0.54 (-0.51; 1.60)	3.35 (0.54; 6.24)**
Adj. $PM_{2.5}$	-	-	1.26 (-1.03; 3.61)	-3.07 (-7.62; 1.70)	0.10 (-1.07; 1.28)	2.61 (-0.67; 6.01)
Adj. PM_{10}	-1.63 (-8.08; 5.28)	-	0.66 (-2.05; 3.44)	-2.76 (-7.37; 2.08)	-0.03 (-1.22; 1.18)	2.35 (-1.04; 5.84)
Adj. PM_{coarse}	1.49 (-0.61; 3.64)	1.88 (-0.77; 4.59)	-	-3.51 (-7.80; 0.97)	0.23 (-0.89; 1.37)	2.81 (-0.25; 5.95)*
Adj. O_3	1.33 (-0.81; 3.53)	1.68 (-0.62; 4.04)	1.38 (-0.84; 3.65)	-	0.02 (-1.19; 1.24)	2.62 (-1.04; 6.41)
Adj. NO	1.84 (-0.33; 4.07)*	2.31 (-0.05; 4.73)*	1.71 (-0.58; 4.05)	-	-	4.15 (0.47; 7.97)**
Adj. NO_2	0.95 (-1.34; 3.29)	1.28 (-1.22; 3.84)	1.01 (-1.31; 3.38)	-1.71 (-7.18; 4.09)	-	-

Abbreviations: CIs, confidence intervals; $PM_{2.5}$, 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: *, $P<0.10$; **, $P<0.05$; Percent changes were estimated based on the odds ratios calculated using conditional logistic regression; The two-pollutant models were conducted for air pollutants with a correlation coefficient <0.7. The model was adjusted for the corresponding lagged days of air temperature and relative humidity.

sTable 11. Percent changes and 95% CIs in the odds of overall stroke events associated with each IQR increase in moving average lagged ambient air pollutant concentrations (over lag 5-6 and lag 0-6 days) in the two-pollutant models.

	percent changes (95%CIs) in the odds of overall stroke events					
	$PM_{2.5}$	**PM_{10}**	**PM_{coarse}**	**O_3**	**NO**	**NO_2**
Lag 5-6						
Single	2.11 (0.09; 4.17)**	2.55 (0.43; 4.71)**	2.50 (0.23; 4.82)**	-2.93 (-7.48; 1.84)	0.46 (-0.70; 1.63)	3.48 (0.61; 6.44)**
Adj. $PM_{2.5}$	-	-	1.83 (-0.64; 4.36)	-0.97 (-6.12; 4.46)	-0.13 (-1.45; 1.19)	2.62 (-0.82; 6.19)
Adj. PM_{10}	-3.15 (-10.09; 4.32)	-	1.26 (-1.64; 4.25)	-0.45 (-5.67; 5.07)	-0.33 (-1.67; 1.02)	2.19 (-1.35; 5.86)
Adj. PM_{coarse}	1.44 (-0.75; 3.69)	1.79 (-0.93; 4.58)	-	-1.56 (-6.38; 3.50)	-0.05 (-1.30; 1.23)	2.61 (-0.54; 5.85)
Adj. O_3	1.93 (-0.31; 4.21)*	2.46 (0.08; 4.89)**	2.28 (-0.09; 4.70)*	-	0.11 (-1.25; 1.49)	4.10 (0.27; 8.09)**
Adj. NO	2.22 (-0.06; 4.54)*	2.86 (0.40; 5.38)**	2.53 (0.07; 5.054)**	-	-	4.91 (1.03; 8.93)**
Adj. NO_2	1.05 (-1.37; 3.53)	1.56 (-1.07; 4.25)	1.61 (-0.88; 4.16)	1.55 (-4.74; 8.25)	-	-
Lag 0-6						
Single	1.77 (-0.50; 4.08)	1.69 (-0.65; 4.08)	0.63 (-2.17; 3.51)	-6.19 (-12.30; 0.36)*	1.51 (-0.36; 3.42)	4.33 (0.92; 7.87)**
Adj. $PM_{2.5}$	-	-	-0.46 (-3.57; 2.75)	-4.92 (-11.88; 2.59)	1.03 (-1.15; 3.26)	4.33 (0.04; 8.81)**
Adj. PM_{10}	3.11 (-6.05; 13.16)	-	-1.22 (-4.85; 2.54)	-5.14 (-12.16; 2.44)	1.10 (-1.14; 3.39)	4.73 (0.27; 9.39)**
Adj. PM_{coarse}	1.93 (-0.61; 4.54)	2.37 (-0.74; 5.57)	-	-6.40 (-12.86; 0.53)*	1.64 (-0.44; 3.77)	5.14 (1.24; 9.18)**
Adj. O_3	0.98 (-1.56; 3.57)	0.80 (-1.85; 3.52)	-0.29 (-3.23; 2.74)	-	0.77 (-1.44; 3.04)	3.81 (-0.54; 8.35)*
Adj. NO	1.12 (-1.50; 3.81)	0.93 (-1.86; 3.79)	-0.44 (-3.52; 2.74)	-	-	4.60 (-0.03; 9.45)*
Adj. NO_2	0.00 (-2.80; 2.88)	-0.41 (-3.40; 2.67)	-1.37 (-4.49; 1.81)	-1.62 (-9.79; 7.29)	-	-

Abbreviations: CIs, confidence intervals; $PM_{2.5}$, 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: *, P<0.10; **, P<0.05; Percent changes were estimated based on the odds ratios calculated using conditional logistic regression; The two-pollutant models were conducted for air pollutants with a correlation coefficient <0.7. The model was adjusted for the corresponding lagged days of air temperature and relative humidity.

sTable 12. Summary of cited epidemiological evidence on the associations between air pollution and strokes.

Years	First author	Titles	Study design	Air pollutants	Exposure windows	Outcomes	Findings
Systematic reviews / Meta-analysis							
2023	Erin R Kulick	Ambient Air Pollution and Stroke: An Updated Review	Systematic review	Short and long-term exposure to ambient air pollution	1 -24 hours	Stroke	Reduction in air pollutant concentrations represents a significant population-level opportunity to reduce risk of cerebrovascular disease
2022	Jeroen de Bont	Ambient air pollution and cardiovascular diseases: An umbrella review of systematic reviews and meta-analyses	Umbrella review	$PM_{2.5}$, PM_{10}, NOx	Short-term (no data)	Cardiovascular disease (CVDs)	Short-term exposures to $PM_{2.5}$, PM_{10} and NOx were consistently associated with increased risks of stroke (fatal and nonfatal).
2023	Wenjian Lin	Short-term Exposure to Air Pollution and the Incidence and Mortality of Stroke: A Meta-Analysis	Meta-analysis	PM_{10}, $PM_{2.5}$, NO_2, SO_2, CO, and O_3	Short-term	Incidence and mortality of strokes	Short-term exposure to PM_{10}, $PM_{2.5}$, NO_2, SO_2, and O_3 was associated with increased stroke incidence; Short-term exposures to PM_{10}, $PM_{2.5}$, NO_2, SO_2 were correlated with increased mortality from stroke.
Original study							
2018	Andrew F W Ho (Singapore)	The Relationship Between Ambient Air Pollution and Acute Ischemic Stroke: A Time-Stratified Case-Crossover Study in a City-State With Seasonal Exposure to the Southeast Asian Haze Problem	Time-stratified case-crossover study	Pollutant Standards Index	Maximum of lag 5 days	Ischemic stroke	A short-term elevated risk of ischemic stroke after exposure to air pollution
2017	B K Butland (UK)	Air pollution and the incidence of ischaemic and haemorrhagic stroke in the South London Stroke Register: a case-cross-over analysis	Time-stratified case-cross-over study	PM_{10}, $PM_{2.5}$, NO_2, NOx, and O_3	Maximum of lag 6 days	Ischemic and hemorrhagic stroke	No evidence of a positive association between outdoor air pollution and incident stroke or its subtypes; A negative association with PM_{10} suggestive of a 14.6% fall in risk of hemorrhagic stroke per 10 μg/m^3 increase in PM_{10}
2023	Britney Gaines (Israel)	Particulate Air Pollution Exposure and Stroke among Adults in Israel	Retrospective cohort study	$PM_{2.5}$	Lag 0,1,2 days	Ischemic stroke, intracerebral hemorrhage or	$PM_{2.5}$ exposure was associated with a higher ischemic stroke risk, with larger effect estimates at

						transient ischemic attack (TIA)	higher exposure levels. Vulnerability to the air pollution effects differed by age, sex, ethnicity, and comorbidities.
2020	Cai Chen (China)	Effect of air pollution on hospitalization for acute exacerbation of chronic obstructive pulmonary disease, stroke, and myocardial infarction	Generalized additive models (GAM)	$PM_{2.5}$, PM_{10}, SO_2, NO_2, and O_3	Maximum of lag 5 days	Hospitalization for acute exacerbation of chronic obstructive pulmonary disease, stroke, and MI.	The hospitalization risk for stroke with hypertension due to SO_2 and NO_2 was greater than that of stroke without hypertension. The risk of hospitalization for stroke with hypertension as a comorbidity due to O_3 was lower than without hypertension. SO_2 and O_3 appeared protective for stroke patients with coronary atherosclerosis.
2024	Dongxia Jiang (China)	Short-term effects of ambient oxidation, and its interaction with fine particles on first-ever stroke: A national case-crossover study in China	Case-crossover study	NO_2, O_3, and their combined oxidation (Owt)	Maximum of lag 7 days	First-ever stroke	A significant association between ambient NO_2 exposure at lag0 day with first-ever stroke; A significant interaction between NO_2 and $PM_{2.5}$; Physical inactivity enhanced the detrimental effects of O_3 and Owt exposure, while smoking and TIA history enhanced the detrimental effects of NO_2 exposure; However, TIA history appeared to mitigate the adverse effects of O_3 exposure.
2017	Fangfang Huang (China)	Gaseous Air Pollution and the Risk for Stroke Admissions: A Case-Crossover Study in Beijing, China	Bidirectional case-crossover study	NO_2, SO_2, CO, $PM_{2.5}$, O_3	Maximum of lag 2 days	Hospital admissions for stroke	NO_2 and SO_2 were positively associated with stroke admissions, with stronger effects in warm seasons and with patients >65 years.

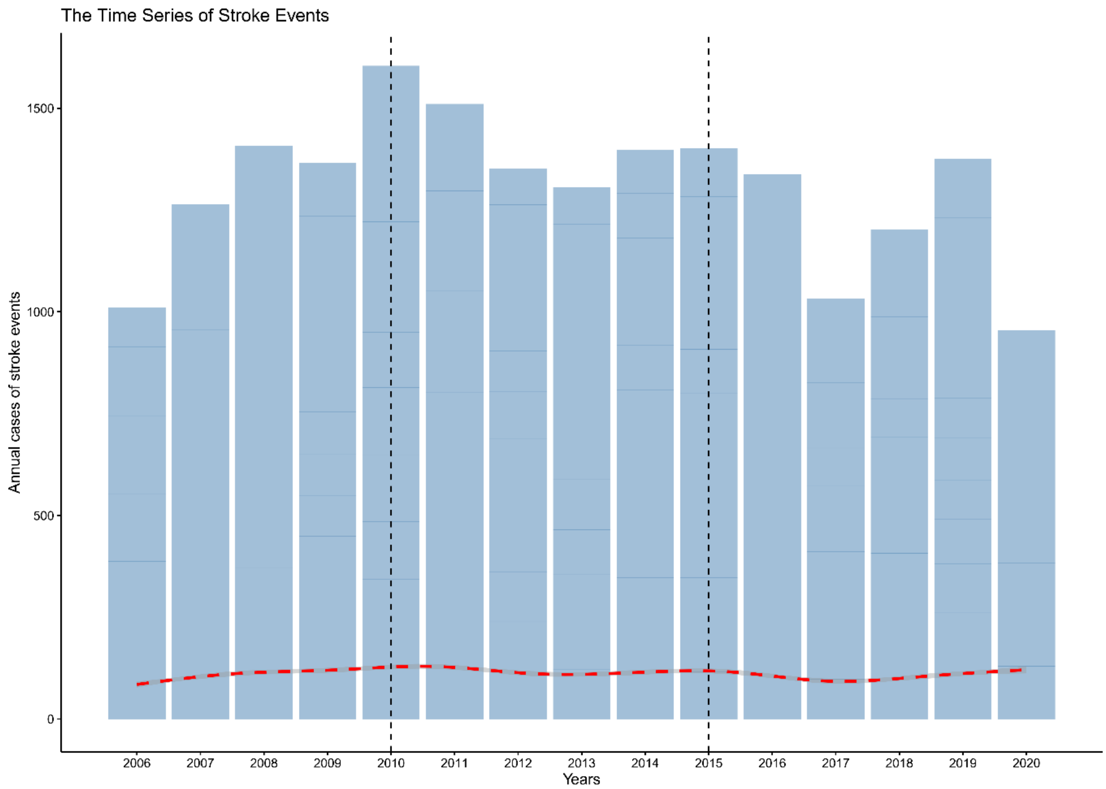
							The associations of CO and O_3 with stroke admissions differed across seasons
2022	Hao Chen (China)	Ambient Air Pollution and Hospitalizations for Ischemic Stroke: A Time Series Analysis Using a Distributed Lag Nonlinear Model in Chongqing, China	Original study: DLNM	$PM_{2.5}$, PM_{10}, SO_2, NO_2, O_3	Maximum of lag 7 days	Ischemic Stroke	Short-term exposure to $PM_{2.5}$, PM_{10}, SO_2, NO_2, O_3 contributes to more ischemic stroke hospitalization
2017	Hui Liu (China)	Association between ambient air pollution and hospitalization for ischemic and hemorrhagic stroke in China: A multicity case-crossover study	Time-stratified case-crossover analysis	PM_{10}, NO_2, SO_2, CO, and O_3	Maximum of lag 5 days	Ischemic stroke and hemorrhagic stroke hospitalizations	Air pollution was positively associated with ischemic stroke (6-day average levels). For hemorrhagic stroke, we observed the only significant association in relation to nitrogen dioxide on the current day
2023	Iván Gutiérrez-Avila (Mexico)	Short-term exposure to $PM_{2.5}$ and 1.5 million deaths: a time-stratified case-crossover analysis in the Mexico City Metropolitan Area	Case-crossover study	$PM_{2.5}$	Maximum of lag 6 days	Broad-category and cause-specific mortality outcomes hemorrhagic stroke	A 10-µg/m^3 $PM_{2.5}$ higher cumulative exposure over one week (lag0-6) was associated with higher cause-specific mortality outcomes: hemorrhagic stroke; No differences in effect size of associations were observed between age, sex and SES strata
2023	Jamie L Humphrey (US)	Disentangling impacts of multiple pollutants on acute cardiovascular events in New York city: A case-crossover analysis	Case-crossover study	NO_2, $PM_{2.5}$, SO_2, and O_3	Maximum of lag 6 days	Acute CVD event, ischemic heart disease, heart failure, stroke, ischemic stroke, acute myocardial infarction	Our results indicate immediate, robust effects of combustion-related pollution on CVD risk (stroke), by sub-diagnosis. Though acute impacts differed minimally by age, sex, or race, the much younger age-at-event for Black New Yorkers calls attention to cumulative social susceptibility
2017	Jeffrey J Wing (US)	Short-term exposures to ambient air pollution and risk of recurrent ischemic stroke	Time-stratified case-crossover study	$PM_{2.5}$, O_3	Lag 2 and lag 3 days	Recurrent ischemic stroke	No evidence of associations between previous-day air

							pollution levels and recurrent ischemic stroke
2022	Kohei Hasegawa (Japan)	Short-term associations of ambient air pollution with hospital admissions for ischemic stroke in 97 Japanese cities	GAM with a quasi-Poisson regression	SO_2, NO_2, Ox, CO, and $PM_{2.5}$	Maximum of lag 2 days	Hospital admissions for ischemic stroke	Short-term exposure to ambient air pollution was associated with increased hospital admissions for ischemic stroke, and medication use and season may modify the association
2024	Kun Fang (China)	Hourly effect of atmospheric reactive nitrogen species on the onset of acute ischemic stroke: Insight from the Shanghai Stroke Service System Database	Time-stratified case-crossover study	Hourly concentrations of PM_{10}, $PM_{2.5}$, O_3, SO_2, CO, NO_2, and nitrous acid (HONO)	Maximum of 72 lag hours	Acute ischemic stroke	Acute exposure to PM_{10}, $PM_{2.5}$, SO_2, NO_2, and HONO was found to be associated with acute ischemic stroke onset, respectively.
2008	Lynda D Lisabeth (US)	Ambient air pollution and risk for ischemic stroke and transient ischemic attack	Poisson regression	$PM_{2.5}$, O_3	Maximum of lag 5 days	Ischemic strokes/TIAs	Borderline associations between recent $PM_{2.5}$ and O_3 exposure and ischemic stroke/TIA risk, even in this community with relatively low pollutant levels
2023	Meijun Li (China)	Air pollution and stroke hospitalization in the Beibu Gulf Region of China: A case-crossover analysis	Time-stratified case-crossover study	$PM_{2.5}$, PM_{10}, NO_2, SO_2, O_3 and CO	Lag 0-1 days	Hospitalizations of stroke and its subtypes	Short-term increase in NO_2, SO_2, and PM_{10} might be important triggers of stroke hospitalization. All seven air pollutants were associated with ischemic stroke hospitalization, while only CO was associated with hemorrhagic stroke hospitalization
2023	Panumas Surit (Thailand)	Association between air quality index and effects on emergency department visits for acute respiratory and cardiovascular diseases	Retrospective study	Air Quality Index (AQI) of $PM_{2.5}$	Maximum of lag 6 days	Emergency Department visits, and hospitalizations, and unexpected deaths due to acute respiratory disease, acute coronary syndrome, acute heart failure, and stroke	No positive association between PM-related quality index and stroke was found, though positive associations were found for other CVDs
2012	Paul J Villeneuve (Canada)	Short-term effects of ambient air pollution on stroke: who is most vulnerable?	Time-stratified case-crossover study	NO_2, $PM_{2.5}$, CO, O_3, and SO_2	Lag 0, 1, and 3 days	Ischemic or hemorrhagic stroke, TIAs	Positive associations were observed between ischemic stroke and air pollution

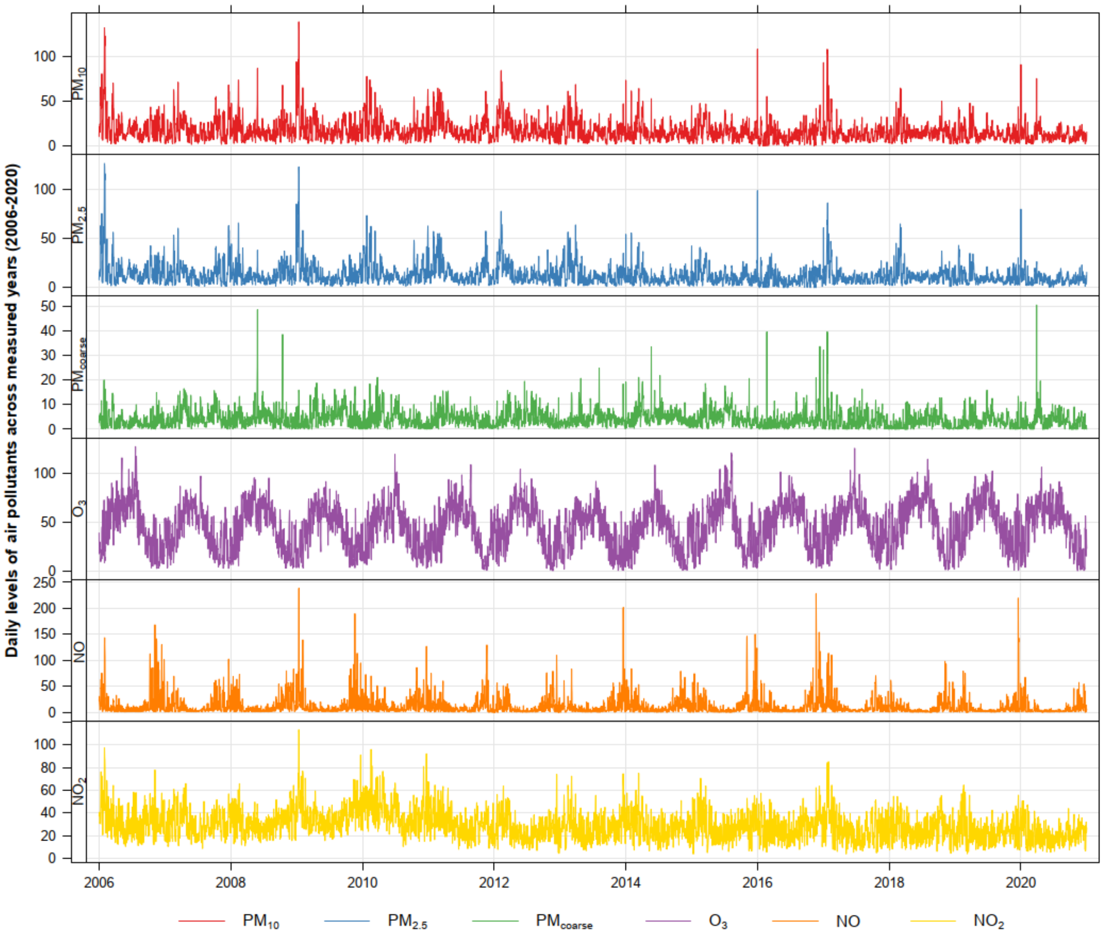
							during the 'warm' season (April through September), but no associations were evident with the other stroke subtypes. Air pollution was not associated with hemorrhagic stroke or transient ischemic attacks
2023	Peng Wang (China)	Cleaner outdoor air diminishes the overall risk of intracerebral hemorrhage but brings differential benefits to subpopulations: a time-stratified case-crossover study	Time-stratified case-crossover study	$PM_{2.5}$, PM_{10}, SO_2, NO_2, CO, and O_3	Maximum of lag 5 days	Intracerebral hemorrhage	The elevation of daily $PM_{2.5}$, SO_2, and CO was associated with increased Intracerebral hemorrhage risk in the first group and was not positively associated with risk escalation in the second group.
2017	Pi Guo (China)	Ambient Air Pollution and Risk for Ischemic Stroke: A Short-Term Exposure Assessment in South China	Time-series Poisson regression model	$PM_{2.5}$, SO_2, NO_2, O_3	Maximum of lag 5 days	Ischemic Stroke	A borderline significant association between NO_2 exposure, modeled as an averaged lag effect, and ischemic stroke risk.
2024	Radosław Czernych (Poland)	Air Pollution Increases Risk of Occurrence of Intracerebral Haemorrhage but Not of Subarachnoid Haemorrhage: Time-Series Cross-Sectional Study	Time-Series Cross-Sectional Study	SO_2, NO, NO_2, NOx, CO, $PM_{2.5}$, PM_{10}, and O_3	Maximum of lag 3 days	hemorrhagic stroke	Transient elevations in ambient NO2, NO, and CO are associated with a higher relative risk of intracerebral but not subarachnoid hemorrhage
2012	Ravi Maheswaran (UK)	Outdoor air pollution and incidence of ischemic and hemorrhagic stroke: a small-area level ecological study	A small-area level ecological study design	PM_{10}, NOx	Maximum of lag 2 days	Ischemic and hemorrhagic strokes	Although there was no significant association between outdoor air pollutants and ischemic stroke incidence for all ages combined, there was a suggestion of increased risk among people aged 65 to 79 years. There was no evidence of increased incidence in hemorrhagic stroke.

2018	Rosa Maria Vivanco-Hidalgo (Spain)	Short-term exposure to traffic-related air pollution and ischemic stroke onset in Barcelona, Spain	Time-stratified case-crossover study	$PM_{2.5}$, Black Carbon (BC)	Maximum of lag 3 days	Ischemic stroke	No association was found between $PM_{2.5}$ and BC exposure and acute ischemic stroke risk. By stroke subtype, large-artery atherosclerotic stroke could be triggered by daily increases in BC
2021	Runhua Zhang (China)	Association between short-term exposure to ambient air pollution and hospital admissions for transient ischemic attacks in Beijing, China	Time-series study	$PM_{2.5}$, PM_{10}, CO, SO_2, NO_2, and O_3	Maximum of lag 2 days	Hospital admissions for TIAs	This research contributes evidence on the association between air pollution and admissions for TIA in the low- and middle-income countries and may promote related public health policy development
2019	Shengzhi Sun (China)	Short-term exposure to air pollution and incidence of stroke in the Women's Health Initiative	Original study: time-stratified case-crossover	$PM_{2.5}$, PM_{10}, NO_2, NOx, SO_2, and O_3	Maximum of lag 6 days	Ischemic or hemorrhagic stroke	Daily NO_2 and NOx were associated with higher risk of hemorrhagic stroke, but ambient levels of four other air pollutants were not associated with higher risk of total stroke, ischemic stroke, or ischemic stroke subtypes
2022	So Young Kim (South Korea)	Short- and long-term exposure to air pollution increases the risk of stroke	Population cohort study	SO_2, NO_2, O_3, CO, and PM_{10}	Maximum of lag 7 days (short-term)	Stroke hospitalizations	Both short- and long-term exposure to CO were related to stroke
2023	Tao Liu (China)	Joint Associations of Short-Term Exposure to Ambient Air Pollutants with Hospital Admission of Ischemic Stroke	Time-stratified case-crossover study	$PM_{2.5}$, NO_2, SO_2, O_3 and CO	Maximum of lag 3 days	Ischemic stroke	Short-term exposures to $PM_{2.5}$, maximum day 8 hour- O_3, NO_2, SO_2, and CO were positively associated with increased risks of hospital admission for ischemic stroke. The joint associations of air pollutants with ischemic stroke might be overestimated using single-pollutant models
2018	Wei Zeng (China)	Ambient fine particulate pollution and daily morbidity of stroke in Chengdu, China	Time series analysis-GAM	$PM_{2.5}$, PMcoarse and PM_{10}	Maximum of lag 5 days	Daily morbidity of stroke	Short-term exposure to $PM_{2.5}$ within 1 day is

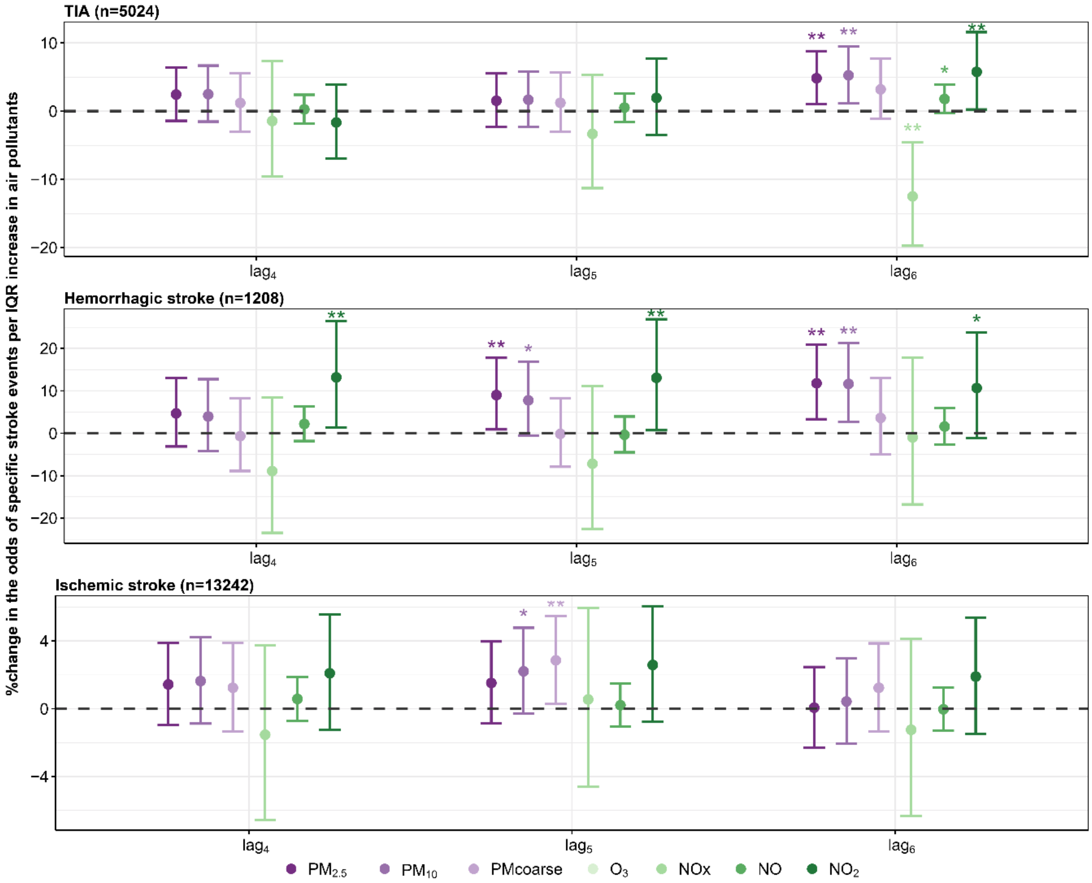
							associated with the onset of stroke. The younger people (age<65) and females are more sensitive than older people and males.
2024	Xin Lv (China)	Hourly Air Pollution Exposure and Emergency Hospital Admissions for Stroke: A Multicenter Case-Crossover Study	Case-Crossover Study	PM_{10}, $PM_{2.5}$, NO_2, SO_2, CO, and O_3	Maximum of lag 2 days	Emergency hospital admissions for stroke	Hourly exposure to PM_{10}, $PM_{2.5}$, NO_2, SO_2 was associated with an increased risk of hospital admissions for total stroke and ischemic stroke. The risk was more pronounced among male patients or those aged <65 years old.
2020	Yanfang Guo (China)	Short-term associations between ambient air pollution and stroke hospitalizations: time-series study in Shenzhen, China	Time-series analysis	$PM_{2.5}$, NO_2 and O_3	Maximum of lag 3 days	Stroke hospitalizations	Short-term exposure to $PM_{2.5}$, NO_2 and O_3 may induce stroke morbidity
2018	Yaohua Tian (China)	Association between ambient air pollution and daily hospital admissions for ischemic stroke: A nationwide time-series analysis	Poisson time-series regression models	$PM_{2.5}$, O_3, NO_2, SO_2, CO	Maximum of lag 2 days	Daily hospital admissions for ischemic stroke	A transient increase in air pollution levels may increase the risk of ischemic stroke
2022	Yuhan Zhao (China)	Associations between ambient air pollution, meteorology, and daily hospital admissions for ischemic stroke: a time-stratified case-crossover study in Beijing	Time-stratified case-crossover study	$PM_{2.5}$, PM_{10}, SO_2, NO_2, CO, O_3	Maximum of lag 21 days	Daily hospital admissions for ischemic stroke	Particulate pollutants could increase the risk of ischemic stroke, and the elderly were more sensitive to it, while the results of gaseous pollutants are still discordant



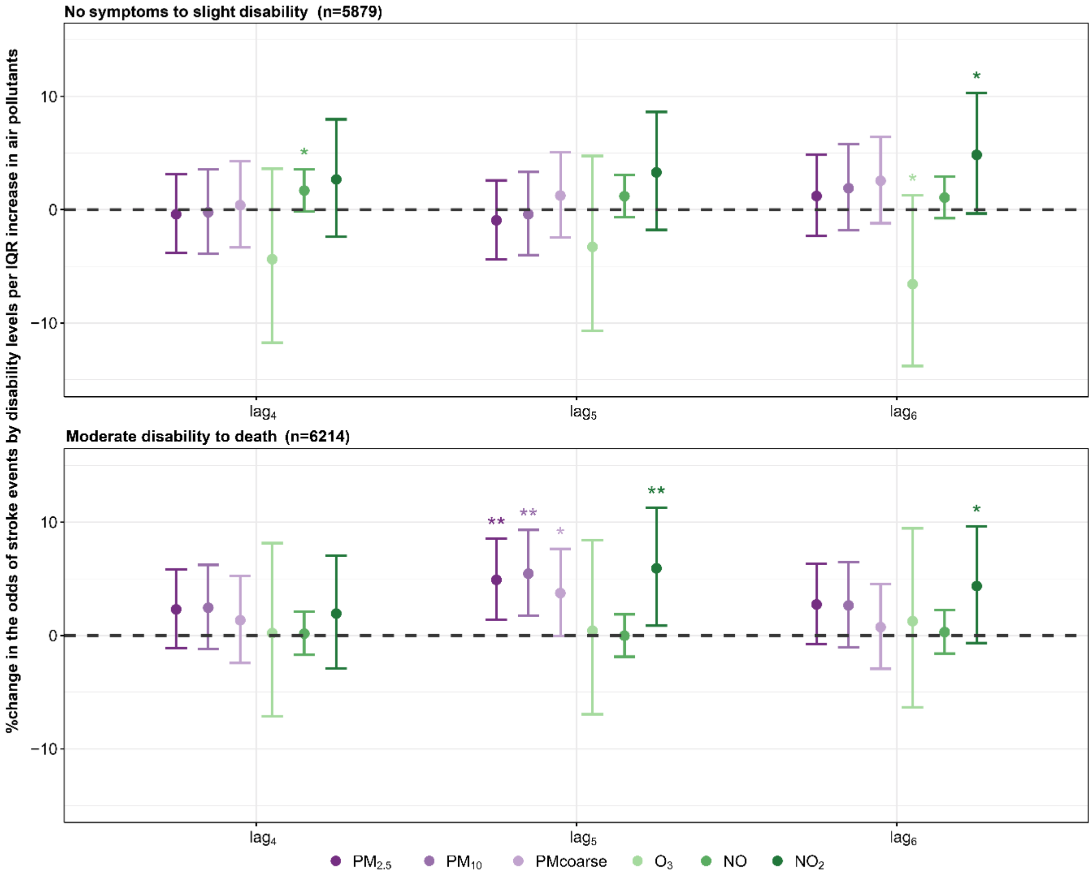
sFig 1. The time series of annual cases of overall stroke events from Augsburg, Germany, from 2006 to 2020. Note: The red dashed line represents the smooth curve of stroke cases across years.



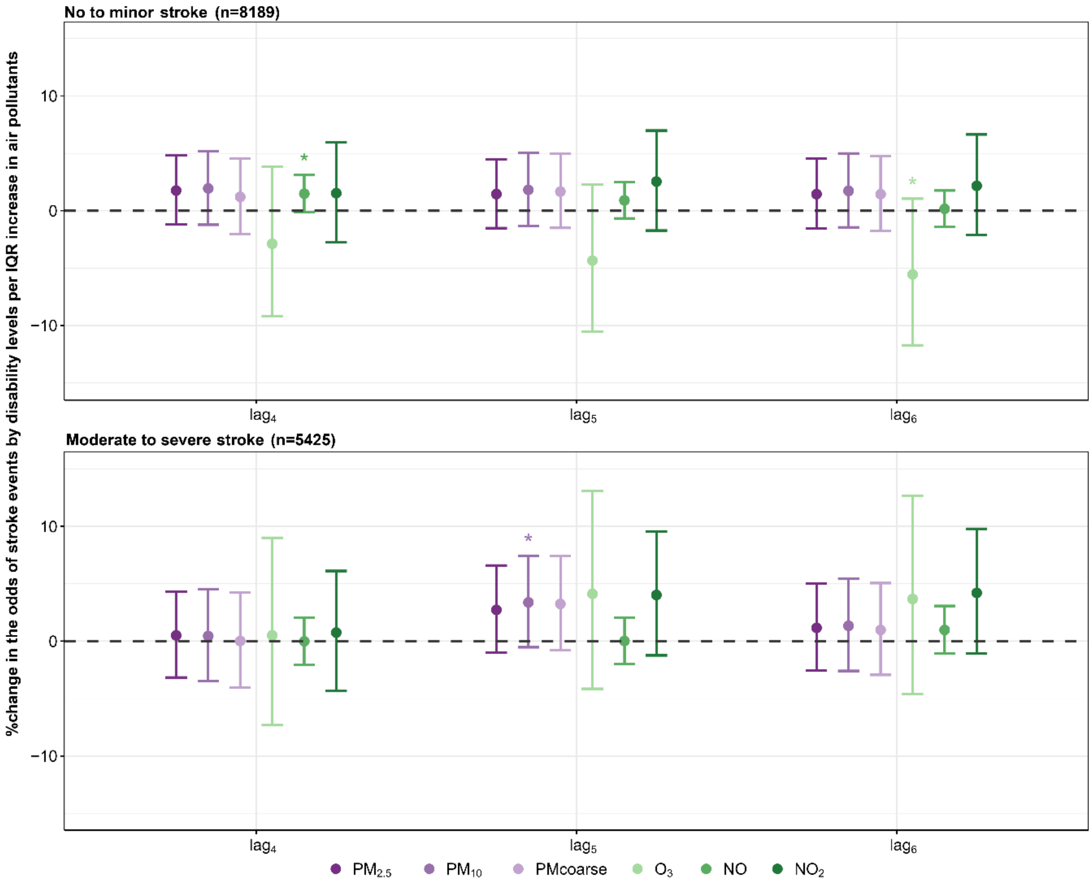
sFig 2. The daily average concentrations of six air pollutants from Augsburg, Germany, from 2006 to 2020.



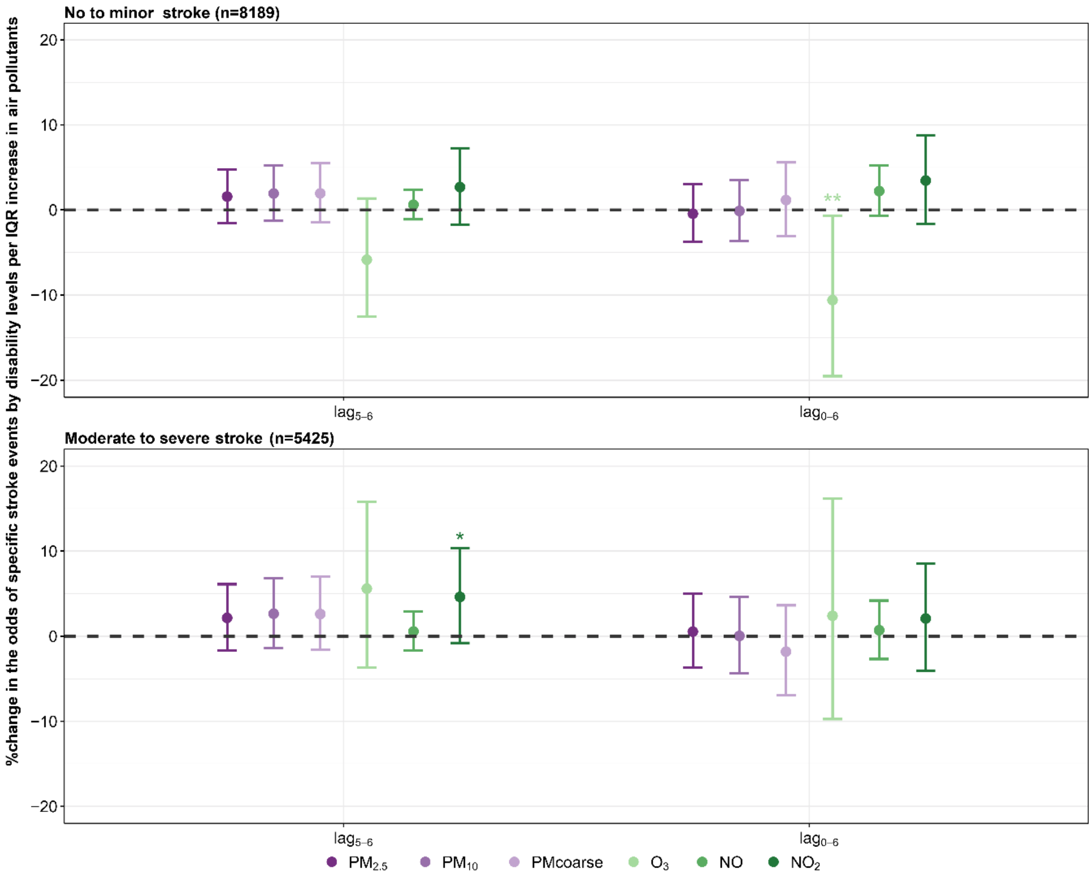
sFig 3. Subgroup percent changes (95% CIs) in the odds of stroke events in each interquartile range (IQR) increase in single-day lagged air pollutants by three subtypes. **Note**: *, *P*<0.10; **, *P*<0.05.



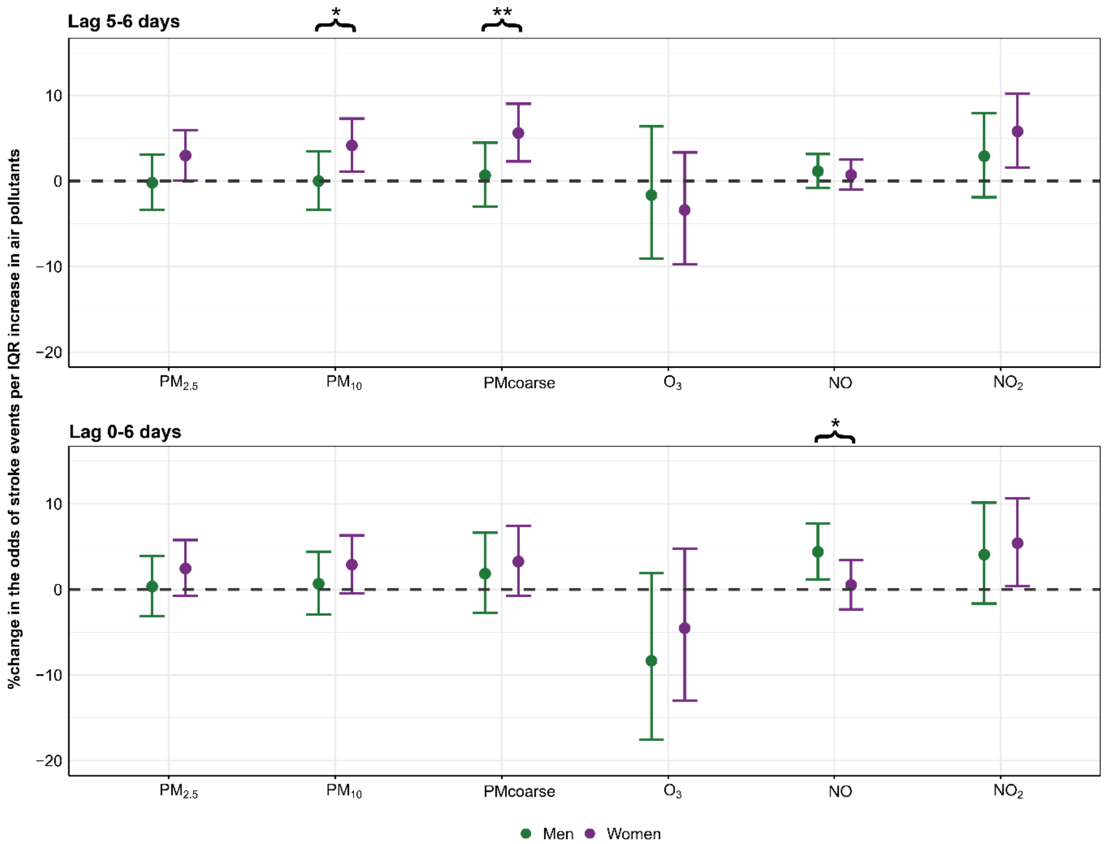
sFig 4. Stratified percent change (95% CI) in the overall stroke events in each interquartile range (IQR) increase in single-day lagged air pollutants by disability levels. **Note**: *, *P*<0.10; **, *P*<0.05.



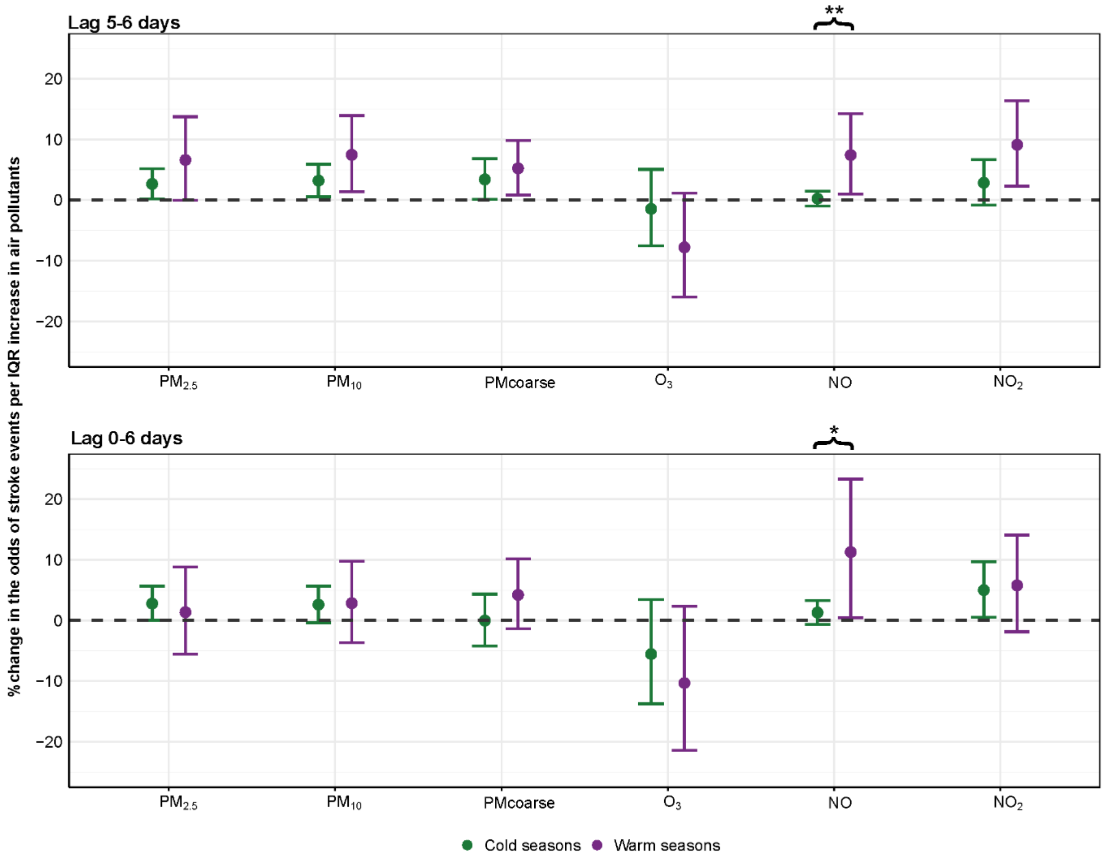
sFig 5. Stratified percent change (95% CI) in the overall stroke events in each interquartile range (IQR) increase in single-day lagged air pollutants by severity levels. **Note**: *, *P*<0.10; **, *P*<0.05.



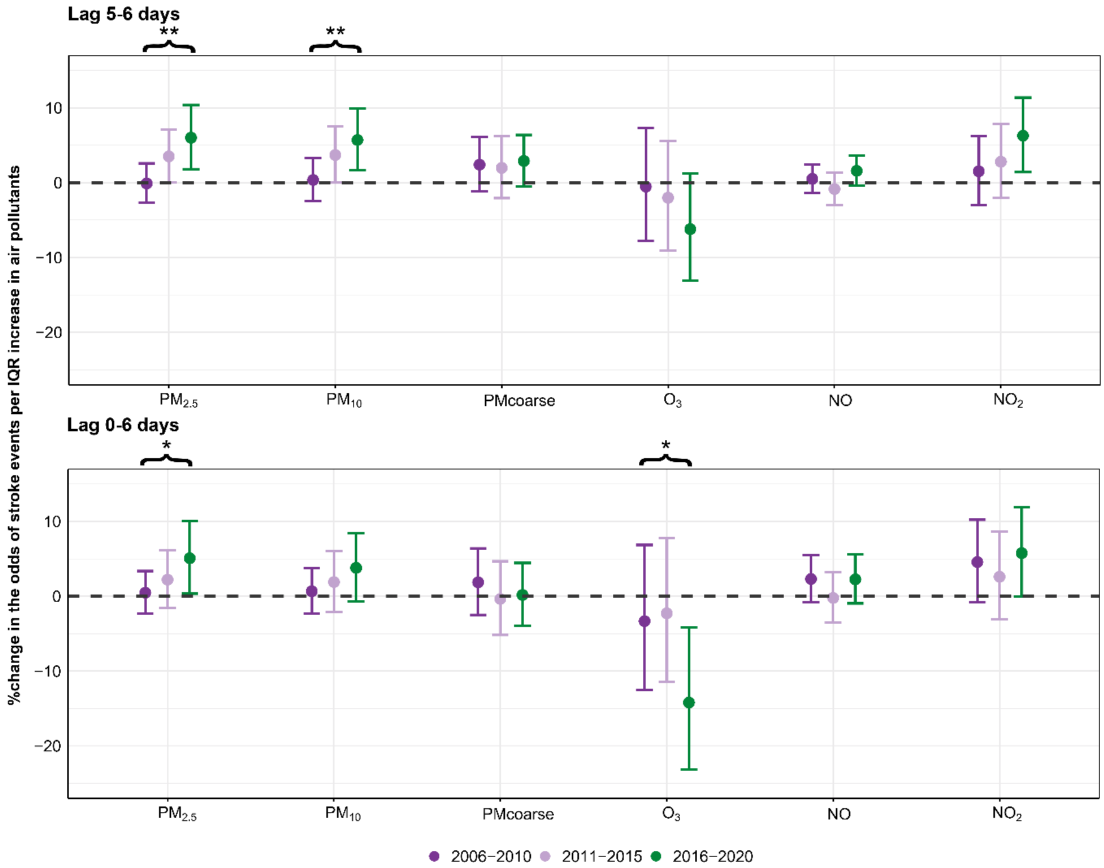
sFig 6. Stratified percent change (95% CI) in the overall stroke events in each interquartile range (IQR) increase in moving average air pollutants by severity levels. **Note**: *, *P*<0.10; **, *P*<0.05.



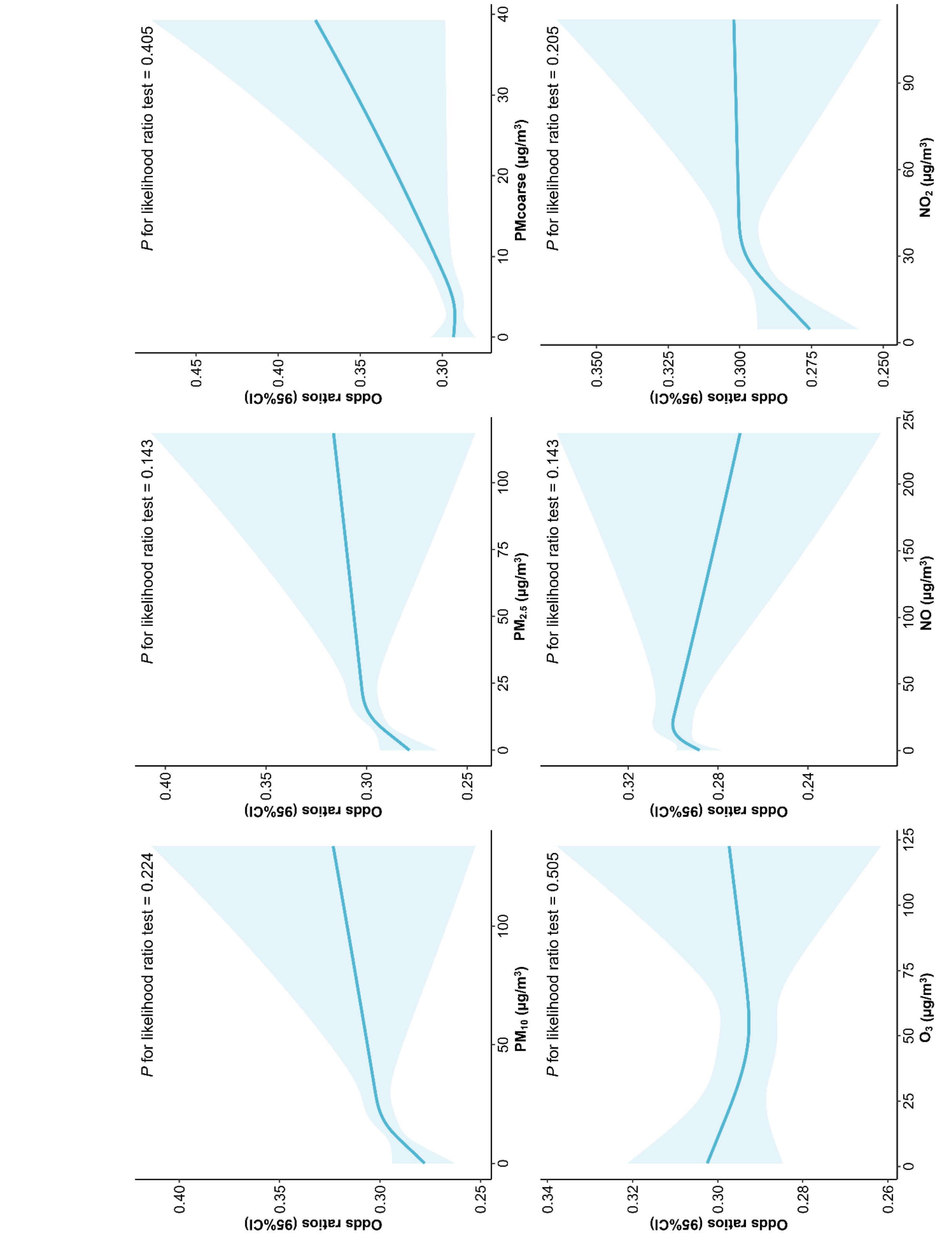
sFig 7. Percent changes (95% CIs) in the odds of overall stroke events in each interquartile range (IQR) increase in lag5-6 and 0-6 days of air pollutants modified by sex. **Note**: *, *P*<0.10; **, *P*<0.05.



sFig 8. Percent changes (95% CIs) in the odds of daily overall stroke events in each interquartile range (IQR) increase in lag5-6 and 0-6 days of air pollutants modified by seasons. **Note**: *, *P*<0.10; **, *P*<0.05.



sFig 9. Percent changes (95% CIs) in the odds of daily overall stroke events in each interquartile range (IQR) increase in lag5-6 and 0-6 days of air pollutants modified by 5-year periods. **Note**: *, *P*<0.10; **, *P*<0.05.



sFig 10. The exposure-response analysis between six air pollutants and the odds of overall stroke events at lag5-6 days using the restricted cubic splines.

Appendix: Paper III

Title:	Short-term effects of ultrafine particles on stroke events: An assessment using four different exposure metrics
Authors:	Minqi Liao, Siqi Zhang, Maximilian Schwarz, Cheng He, Susanne Breitner-Busch, Josef Cyrys, Markus Naumann, Lino Braadt, Claudia Traidl-Hoffmann, Gertrud Hammel, Annette Peters, Michael Ertl, Alexandra Schneider
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Note: The following manuscript and supplementary materials reflect the version initially submitted to the journal and have not been revised subsequently. The additional results concerning particles in the 10–500 nm range, as presented in the dissertation, are not included here but will be incorporated into the final version.

Short-term effects of ultrafine particles on stroke events: An assessment using four different exposure metrics

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Abstract

Background: The effects of different ultrafine particle (UFP) metrics on strokes are unclear. This case-crossover study investigated the association between short-term exposure to four size-segregated UFP metrics and stroke occurrence.
Methods: From 2006 to 2020, we included 19,518 stroke cases from the University Hospital Augsburg, Germany, a less polluted area. Meanwhile, daily averages of four size-segregated UFP metrics, including particle number (PNC), mass (PMC), length (PLC), and surface area (PSC) concentrations, were collected from fixed monitoring sites in Augsburg. Conditional logistic regression was employed to assess the association between UFP metrics and stroke risk. Potential individual vulnerability and effect modification were examined using the stratified and interaction analyses, respectively.
Results: Short-term UFP exposures were associated with increased stroke risk, with the odd ratios (95% confidence intervals) of strokes for each interquartile range increase in lag 0-6 days of UFPs being 4.76% (1.06; 8.60) for PNC, 3.99% (0.93; 7.13) for PMC, 4·52% (1·11; 8.05) for PLC, and 4.14% (1.00; 7.38) for PSC. More attention should be given to the particles within the size fractions of 10-100 nm and 30-100 nm. The cumulative effects of UFP were more pronounced for ischemic strokes and minor strokes with less severe severity. Cold spells might exaggerate the effects of UFPs.
Conclusion: UFP metrics like particle length and surface area concentration, in addition to particle number, may provide valuable insights into particle properties relevant to stroke risk. Expanding real-time, size-segregated monitoring of UFPs represents an effective strategy to mitigate the health impacts of traffic-related air pollution.

Keywords: Ultrafine particle; Particle number concentration; Particle length concentration; Particle surface area concentration; Particle mass concentration; Cold spells

1. Introduction

According to the Health Effects Institute, air pollution accounted for 8.1 million deaths in 2021, making it the second-largest risk factor of death worldwide [1]. Increasing epidemiological evidence has indicated the short-term adverse health impacts of ambient particulate matter (PM) exposure, such as increased hospital admissions [2] and mortality [3], particularly for cardiovascular and respiratory diseases [4-6]. Ultrafine particles (UFPs), which have an aerodynamic diameter ≤ 0.01μm, are typically generated as by-products of fossil fuel combustion and emissions from motor vehicles [7]. The small size of UFPs endows them with enhanced capabilities in depositing in the lung and translocating to other organs [7]. Additionally, their large active surface makes them more threatening by absorbing greater quantities of hazardous metals and organic compounds [8]. These unique physical properties allow them to exert higher toxicity than larger particles [7,8]. UFPs are mainly measured as particle number concentration (PNC, number of particles/cm^3), as they constitute 85% or more of the total number of fine particulate matter (e.g., with a diameter of ≤ 2.5 µm; $PM_{2.5}$) [9], but contribute little to the particle mass concentrations (PMC, µg/m^3) in ambient air [7]. In addition, particle surface area concentration (PSC, $\mu m^2/cm^3$) considers the absorption and retention of toxic substances and plays an important role in determining the biological activity of nanoparticles [10].

Studies have shown an association between short-term exposure to UFPs and adverse health effects, such as myocardial infarction (MI) risk [11-14], cardiovascular hospitalizations [15], and even mortality [15-19]. The difference in physical properties of various UFP-related metrics may influence their health effects; however, evidence on the impact of different UFP metrics on well-being has remained insufficient. A case-crossover study reported that daily UFP exposure, measured using PNC, over the previous four days (0-4) was associated with increased hospital admissions for ischemic stroke in Copenhagen, Denmark [20]. Another case-crossover study in New York State, U.S., also noticed an association between UFP exposure, measured using PSC, and elevated stroke risk, with PSC showing to be a more sensitive indicator than PNC [15]. Furthermore, compared to PNC, the particle length concentration (PLC, mm/cm^3) was found to be a UFP metric being more closely associated with blood inflammatory biomarkers in blood [21] and the risk of MI in Augsburg, Germany [11].

Within the conventional range in aerodynamic diameter (≤100 nm), the size fractions of UFPs in urban environments can be related to the nature of the fuel and the processes by which they are typically formed, specifically the primary particles emitted directly from the engine (>30 nm). In particular, the secondary particles (newly formed nucleation mode, <30 nm) are a considerable number of very small particles formed after cooling and condensation of exhaust gases [22], and the Aitken mode (30-100 nm) is typically associated with combustion sources [23]. Both modes contribute to the concentration of traffic-related peaks during rush hour [23]. The accumulation mode (100-1000 nm) commonly results from the emissions of fine particles and dynamic events, including condensation and coagulation [24]. Epidemiological evidence, however, focusing on the pathogenic effects of size-segregated UFP metrics is limited. In addition, our previous research has revealed that nocturnal heat exposure is related to elevated stroke risk [25]. Similarly, cold spells were associated with an increased risk of hospitalization for MI [26]. Furthermore, studies unveil that heat waves interact synergistically with $PM_{2.5}$, increasing mortalities of MI [27] and strokes [28]. No evidence exists for the potential influence of extreme temperature events (ETEs), including heat waves and cold spells, on the association between UFPs and strokes.

Using four UFP metrics of different size fractions, this study aims to distinguish the association between various UFPs and stroke events using daily hospitalization data collected over a study period of 15 years in Augsburg, Germany, in which monitoring stations were designed for the collection of several physical and chemical particulate characteristics [21]. Additionally, we estimated the effects across stroke subtypes, disabilities, and severities and explored the potential modification effect by time-invariant factors (sex assigned at birth, age), seasons, time trends, and ETEs.

2. Materials and methods

2.1 Study population

We used the first stroke events that occurred during the study period (between January 1st, 2006, and August 31st, 2020) at the University Hospital Augsburg. This is one of the biggest stroke centers in Germany and is responsible for more than 750,000 inhabitants in the region [25]. This study was performed following the Declaration of Helsinki. Ethical approval was waived in the present study according to the Bavarian Hospital Act.

2.2 Outcome and covariates

Based on the records from this comprehensive stroke care facility, we collected demographic characteristics (sex and age) and basic clinical data of patients (subtypes of strokes, disability, and severity) at admission. The following three main subtypes of strokes were defined according to the International Statistical Classification of Diseases and Related Health Problems, 10th version (ICD-10 codes): transient ischemic attacks (TIAs) (G45), hemorrhagic strokes (I60, I61, I62), and ischemic strokes (I63). Following the occurrence of a stroke, we measured functional independence using the Modified Rankin Scale (mRS), a 7-level scale ranging from 0 (no symptoms) to 6 (death) [29,30]. Besides, a severe stroke was represented by a higher score on the National Institutes of Health Stroke Scale (NIHSS), a scale of 0 to 42 that assessed the stroke severity [30]. To simplify the analysis, we defined “Disability due to strokes” by combining an mRS score of 0-2 as “No symptoms to slight disability” with an mRS score of 3-6 as “Moderate disability to death”. Furthermore, we calculated the "Stroke severity" by combining the NIHSS scores of 0-3 and 4-42 as "No symptoms to minor stroke” and “Moderate to severe stroke”, respectively.

2.3 Exposures

2.3.1 Air pollution and meteorological data

The UFP measurements have been conducted since 2004 at a fixed urban background site on the premises of the Fachhochschule Augsburg (FH, University of Applied Sciences Augsburg) in Augsburg, Germany, and were available for the whole study period. The daily average concentrations of the four metrics of UFPs, including particle number (PNC), mass (PMC), length (PLC), and surface area (PSC) concentrations, were obtained from this aerosol monitoring station located 1 km southeast of the city center, with the nearest major road in the northeast at a distance of 100 m [31]. The supplemental materials section I explains details regarding the devices for collecting and the calculation methods for the four different UFP metrics.

Based on the particle behavior, origin, and deposition in the respiratory tract [17], we mainly focused on four metrics within the size of 10-100 nm, the typical range of UFPs by convention [32]. In addition, we further subdivided the particle size distribution into the following ranges: 10-30 nm (nucleation mode) and 30-100 nm (Aitken mode) due to their likely deposition in the lung [11]. Given that the probability of an increase in measurement uncertainty increases substantially for the particles below 10 nm in size [33], we thus excluded the extremely small UFPs of 3-10 nm from our analysis. Smaller particles of 100-500 nm are more likely to deposit in the lung than those of >500 nm, which tend to deposit more in the upper respiratory tract [34]. Particles in the range of 100-500 nm (accumulation mode) were also included in the analysis to further explore the effect of UFPs in larger sizes.

In addition to UFPs, classic air pollutants were routinely measured at different monitoring sites for specific study periods [35], owing to different operating periods across monitoring sites. In detail, the continuous levels of PM with an aerodynamic diameter of $\leq$10 μm (PM_{10}) and $PM_{2.5}$ and meteorological parameters (ambient air temperature and relative humidity) were obtained from the FH measuring site throughout the whole study period (2006-2020). The 24-hour average nitrogen oxides (NO_2, NO) were obtained from an urban background monitoring site at Bourgesplatz (BP), located approximately 1.5 km north of the city center of Augsburg [35]. The daily average ozone (O_3) level was measured at the monitoring site operated by the Bavarian Environment Agency (LfU), which is located 4 km south of the city center [35]. Specifically, missing PM_{10} and $PM_{2.5}$ values were imputed from existing LfU or BP data, while missing NO and NO_2 values were imputed from measurements at the LfU.

2.3.2 ETE definitions

Considering that ambient air temperature plays a role in concentrations of UFP, from the perspective of PNC [22], we defined the ETEs (heat waves or cold spells) with a combination of intensity and duration of extreme air temperatures according to the relative threshold approach [27,28]. We then calculated the specific cutoffs of air temperature for heat waves (95.0th and 97.5th percentiles) and cold spells (2.5th and 5.0th percentiles). Days with air temperature equaling or exceeding any of the heat wave cutoffs were considered heat waves, whereas days with air temperature equaling or below any of the cold spell cutoffs were considered cold spells. In each definition of ETEs, the heat waves and the cold spells were coded as "1" and "2", respectively, while the remaining non-ETE days with normal air temperature were coded as "0" [27,28]. The details of air temperature thresholds and the number of ETE days in different ETE definitions are provided in sTable 1 in the supplementary materials-section II.

2.4 Statistical analysis

A time-stratified case-crossover design was applied to explore the association between four UFP concentration metrics and stroke events. The case day referred to the date of hospital admission owing to stroke events, and the corresponding control days were defined as dates on the identical day of the week and in the same calendar month as the case day, with each patient serving as his or her own control [36]. The case-crossover study design controls for time-invariant confounding (e.g., sex, age, family history, and genetic variations) by making within-subject comparisons within reference windows [36]. In addition, choosing the control days close to the case days enabled us to control for various time-varying variables, such as seasonality and long-term trends in air pollution and stroke events [36].

Conditional logistic regression models were implemented by applying a linear term for the four size-segregated UFP metrics during different lag periods in separate models. Effect estimates were reported as the percent changes (PCs) in the odds ratios (ORs) and their corresponding 95% confidence intervals (CIs) associated with per interquartile range (IQR) increases in UFPs. After excluding the days with missing values of UFP metrics, we explored UFP effects across different exposure windows: i) the single-day lags: current day (lag 0) and up to six days before the events (lag 1-lag 6); ii) the moving average lags: multi-days preceding the events representing immediate (lag 0-1) and delayed (lag 2-4, 5-6); and iii) the cumulative effects (lag 0-6). Using a natural cubic spline with three degrees of freedom (df), our main model further adjusted for the same lag day of ambient air temperature and relative humidity to control for potentially remaining confounding factors.

To identify whether specific subgroups exhibit differential susceptibility, stratified analyses were conducted by fitting separate models by subtypes of strokes (TIAs, hemorrhagic, and ischemic strokes), stroke-induced disability (No symptoms to slight disability [mRS 0-2] *vs*. Moderate disability to death [mRS 3-6]), and severity of stroke (No symptoms to minor stroke [NIHSS 0-3] *vs.* Moderate to severe stroke [NIHSS 4-42]). The nonspecific types of strokes were excluded from the stratified analysis.

To explore potential effect modifications on the associations between UFP exposures and stroke risk, we further included interaction terms in the model, including sex (men *vs.* women), age (<65.0 years *vs.* ≥65.0 years), seasons (warm seasons [from May to October] *vs.* cold seasons [from November to April]), and five-year periods of admission (2006-2010, 2011-2015, 2016-2020), which were divided due to their similar time durations and comparable total number of cases. To further assess the potential modification effects of two types of ETEs, the interaction models were also built for heat waves during the warm seasons (non-ETE days *vs.* heat waves) and cold spells during the cold seasons (non-ETE days *vs.* cold spells), respectively.

A series of sensitivity analyses were carried out to test the robustness of our results: i) we fitted the two-pollutant models for investigating the potential independence of the UFP effects by additionally controlling for the same lag day of routinely measured air pollutants ($PM_{2.5}$, PM_{10}, NO, and NO_2), which were selected if they had a Spearman correlation coefficient (rs) <0.70 and a variance inflation factor (VIF) < 5 to avoid collinearity [37]; ii) to assess the potential influence of missing values, the main analysis was repeated after missing values were imputed using the average value of the non-missing values for the same date in the neighboring 1-week (one week before and after); iii) we excluded patients who admitted to the hospital after the beginning of the COVID-19 pandemic (February 2020) to avoid the potential fluctuation in ambient air pollution concentrations due to the "lock-down" in Germany; v) according to Stafoggia M, *et al.*, [38], we separately adjusted for high and low temperatures, which were defined as the average temperature on the current and previous 1 day before the event (lag 0-1) above the median annual temperature and the average temperature on the previous 6 days (lag 1-6) below the median annual temperature, respectively. The optimal degree for natural cubic splines was set at 3 to allow better comparability when entering different temperatures; v) we plotted the exposure-response curve by introducing a restricted cubic spline function (df=3) for UFPs in the main model to check the linearity of the association between UFP metrics and the odds of stroke events.

All data management and statistical analyses were conducted using R software (Version 4.1.2). Statistical tests were two-sided, with a significance level (α) set at 0.05 and a marginal significance at 0.10.

3. Results

3.1 Descriptive statistics

The basic characteristics of the study population by subtypes of strokes are shown in Table 1. Over 15 years, 19,518 patients were admitted to the hospital for a stroke, including 5,024 (25.7%) TIAs, 1,208 (6.2%) hemorrhagic strokes, and 13,242 (67.8%) ischemic strokes, with the remaining 44 (0.2%) events of unknown stroke type. The mean (SD) age of all patients was 70.9 (13.3) years, with 8,585 (44.0%) being women. A substantial proportion of patients were ≥65.0 years of age (14,030; 73.1%), and a larger part of them were diagnosed with a "Moderate disability to death [mRS 3-6] (31.8%) or "No symptoms to minor stroke [NIHSS 0-3]" (42.0%). Stroke events occurred more often during the cold seasons (60.4%), the period between 2011 and 2015 (35.7%), than during the other periods of similar length. The distribution of strokes between heat waves (4.7%) and cold spells (4.9%) was even.

The daily means of the four UFP metrics in four size fractions throughout the study period are displayed in Table 2. At the size of 10-100 nm, the mean (SD) estimated exposure concentrations were 7,411.5 (4,370.0) particles/cm^3 for PNC, 0.7 (0.5) μg/m^3 for PMC, 283,123.1 (17,5247.6) mm/cm^3 for PLC and 46.0 (29.8) μm^2/cm^3 for PSC, respectively. Especially, within the ultrafine range (10-100 nm), a larger contribution from the Aitken mode (30-100 nm) than from the nucleation mode (10-30 nm) was observed among the four UFP metrics. The mean concentrations of PMC and PSC in the accumulation mode (100-500 nm) were notably higher than those of other size fractions. As sTable 2 presents, the distribution of UFPs after imputation was quite similar to the original data. sTable 3 provides the mean levels of the current-day UFP metrics by different definitions of ETEs. Notably, the daily averages of four UFP metrics appeared to be higher during cold spells than during heat waves.

The Spearman correlation coefficients between the four UFPs in four size ranges and two meteorological parameters are shown in sTable 4. Overall, daily UFPs within different size fractions displayed positive correlations with each other (Spearman *rs* = 0.37 to 0.99) but were predominantly inversely related to ambient air temperature and relative humidity. For each specific UFP metric within the size of 10-100 nm, their correlations with four traditionally measured ambient air pollutant parameters ($PM_{2.5}$, PM_{10}, NO, and NO_2) are provided in sTable 5. In general, there were weak positive correlations (Spearman *rs* = 0.03 to 0.11) between all four UFP metrics and classical air pollutants.

3.2 Association between daily UFPs and overall stroke events

Figure 1 describes the associations between daily UFPs within the size of 10-100 nm and the occurrence of overall stroke events across different exposure windows, with the single-day model showing the 3 days transient effects and the lagged moving average model indicating the 2-4 days delayed and 0-6 days cumulative adverse health effects of UFPs on strokes. Particles within the size ranges of 30-100 nm and 100-500 nm also showed similar results, however, the effect of the smallest particles (10-30 nm) tended to occur later (sFigs 1-3).

For the single-day lags, elevated risk of stroke events was consistently seen for the exposure window of lag 3 days, across all four UFP metrics. An IQR increase in four UFP metrics (10-100nm) at lag 3-day was associated with an increase in the odds of 2.45% (0.14; 4.81), 2.54% (0.26; 4.87), 2.57% (0.27; 4.92), and 2.57% (0.29; 4.90), respectively. Compared to the smaller particles in the nucleation mode (10-30 nm), the effect estimates from the Aitken mode (30-100nm) were larger and more consistently observed across four metrics (see sTable 6). For the moving average lags, we noticed a delayed effect (2-4 days) and a cumulative effect (0-6 days) of all four UFP metrics within the range of 10-100 nm on stroke events. Across four UFP metrics, we found for lag 0-6 the strongest impact of PNC_{10-100} on strokes (PC = 4.76% [1.06; 8.60]), followed by PLC_{10-100} (PC = 4.52% [1.11;

8.05]), and PSC_{10-100} (PC = 4.14% [1.00; 7.38]), with the weakest impact being found for PMC_{10-100} (PC = 3.99% [0.93; 7.13]) (see sTable 7).

As most of the effects across the four metrics were consistently observed at the lag of 3 and 0-6 days, these exposure windows were consequently used as the main lag periods for secondary analyses. When comparing the four size-fractioned UFPs in association with strokes, we noticed that the patterns of associations were similar and comparable across the four metrics (Figure 2). Within the ultrafine range (10-100 nm), it is noteworthy that the effects of particles from the Aitken mode (30-100 nm) were more robust than the smaller particles from the nucleation mode (10-30 nm) between the two exposure windows. The effects of large particles in the accumulation mode (100-500 nm) were less stable than particles in other size ranges (data are available in sTables 6&7).

3.3 Stratified analyses

When dividing stroke patients by their sub-types, the adverse health effects of UFPs on strokes were mostly found for patients with ischemic strokes, which were significantly associated with the cumulative 0-6 days of PMC_{10-100} (3.83% [0.15; 7.64]), PLC_{10-100} (PC = 4.16% [0.08; 8.42]), and PSC_{10-100} (PC = 3.91% [0.13; 7.83]). Aside from the UFPs (10-100 nm), ischemic stroke patients were more vulnerable to PMC, PLC, and PSC from the Aitken mode (30-100 nm) than UFPs in other sizes in the exposure window of lag 0-6 days (Figure 3, sFigs 4-6). Numeric data are available in sTable 8.

The stratification by stroke-induced disability revealed that the effect of lagged moving average 0-6 days of PNC_{10-100} was more pronounced among patients with slight disability levels (No symptoms to slight disability) (see sFig 7 & sTable 9). Comparable patterns were identified for the stratification by stroke severity, with the effect estimates for lag 0-6 days of PNC_{10-100} and PLC_{10-100} being stronger among patients with milder stroke severity (No symptoms to minor stroke). In particular, we noticed that the effects of all UFP metrics from the nucleation mode (10-30 nm) were larger among patients with a milder disability or severity than their more severe counterparts (see sFig 8 & sTable 10).

3.4 Effect modification

Generally, as presented in sTables 11-13, the association between four UFP metrics (10-100 nm) in two exposure windows did not vary across sex, age, seasons, and five-year periods, but the cold spells of ETEs seem to modify the effect of UFPs on strokes. Although no significant effect modification was noticed for seasons or ETEs, the adverse effects of UFPs (10-100 nm) in triggering stroke events were stronger during cold spells within the cold seasons (sTable 12). Under the definitions of P5.0_2d or P5.0_4d of the cold spells, the lag 3-day exposures to PMC_{10-100}, PLC_{10-100}, and PSC_{10-100} displayed stronger effects on stroke events compared to the days with normal air temperature (*P*-interaction < 0.10) (Figure 4), with the modification effect of the P5.0 threshold of cold spells being attenuated with longer durations. In contrast, we did not observe any modification effect of cold spells on the effects of four metrics for lag 0–6 days (sFig 9), and no modification effect was observed for exposure to heat waves under different definitions during warm seasons, regardless of exposure windows (sFigs 10-11, sTable 13).

3.5 Sensitivity analyses

In the two-pollutant models, the results of lag 0-6 days UFPs (10-100 nm) remained stable after additional adjustment for selected co-pollutants. By contrast, the effects of UFP exposures at a lag of 3 days were slightly attenuated after the adjustments for NO_2, which shares similar sources with UFPs [39] (see sFigs 12-13 & sTable 14). In addition, the significant associations between overall stroke events and UFPs (10-100 nm) at the lag 3 day and lag 0-6 days persisted in the models that used the imputed data, excluded patients diagnosed with strokes after the beginning of COVID-19 pandemic, as well as adjusted for high and low temperatures (sFigs 14-15 & sTable 15).

The exposure-response functions between the four metrics (10-100 nm) and overall stroke events during the lag 3 day and 0-6 days are illustrated in sFigs 16 & 17. Based on the likelihood ratio test, no deviation from linearity was observed for all four metrics in the two exposure windows, with the likelihood ratio test consistently indicating no differences between linear and non-linear models (all P-values for the likelihood ratio test > 0.05).

4. Discussion

In this 15-year population-based study, we unveiled the delayed and cumulative adverse effects of UFP metrics (10-100 nm) on strokes, with the effect estimates for IQR increases in four metrics being comparable. Particles in the Aitken mode (30-100 nm) showed more consistent and positive associations with strokes than in the nucleation mode (10-30 nm). Furthermore, UFPs were more likely to adversely affect patients with ischemic and minor strokes. The UFP effects might be amplified during days with extremely low temperatures.

These results were consistent with supporting evidence of the detrimental health effects of UFPs, such as increased hospital admissions for diseases in the respiratory, cardiovascular, and neurological systems [39-41]. There might be potential crosstalk between the heart and brain by sharing the same pathophysiological mechanisms [42]. However, in comparison to literature linking short-term exposure to ambient UFP with heart diseases [11-14], the evidence regarding strokes is sparse. So far, an early study in Helsinki, Finland (1998-2004) underscored a positive but insignificant association between the previous-day level of UFP and stroke mortality (8.5% [-1.2; 19.1]) [43]. Subsequently, another study in Copenhagen, Denmark (2003-2006) found that IQR increases in UFP at lag 4 days increased the risk of mild stroke by 14.0% (4.0; 25.0) and the risk of ischemic strokes without atrial fibrillation by 9.0% (1.0; 17.0) [20]. There is even less evidence focusing on different UFP metrics. The increased MI risks in response to hourly exposures to PLC and PSC were larger than for PNC, within the ultrafine range of 10-100 nm [11]. Another study found that PSC might be a more sensitive indicator than PNC regarding the association with hospital admissions for cardiovascular diseases in New York State, U.S. (2013-2018) [15]. Contrarily, we saw comparable effects across four UFP metrics across particle size distribution. This means that, aside from commonly used metrics (PNC and PMC), the physical characteristics of UFPs (PLC and PSC) might be additional indicators measuring the health impairment of UFPs. We hypothesize that particle toxicity and the biological pathways linking UFPs to strokes might be driven more by intrinsic properties (e.g., chemical composition) rather than size-specific characteristics (sizes or metrics), but we were unable to clarify this due to the unavailability of particulate chemical composition data. Notably, the strong correlations between the UFP metrics prevented us from separating their individual effects or assessing whether the high PNC in the 10–30 nm range compensated for lower PMC, PLC, and PSC, leading to similar overall results. Of note, the health effects of PMC warrant further investigation, as only a limited fraction of PMC can be measured within the conventional size threshold of 100 nm [24]. This measurement constraint hampers a comprehensive assessment of their potential impact on stroke risk. More studies are needed to further distinguish their effects and assess whether PMC, PSC, and PLC can fully capture the health-relevant aspects of UFPs.

Some studies have detected the variations in health effects of UFP metrics due to size fractions, but their findings have remained inconclusive. For instance, a time-series study in the Ruhr Area, Germany, showed that size-specific PNC (100-750 nm) and lung-deposited PSC had similar immediate and delayed associations with increased natural and cardiovascular mortalities, with PNC (100-500 nm) having the strongest effect on natural mortality [44]. Larger PNC, especially particles in the ranges of 30-100 nm and 100-800 nm, had stronger effects on hospital admissions for heart diseases, cardiovascular and respiratory diseases, compared to smaller size fractions (10-30 nm) [45]. The effects of larger PNC on cardiovascular or respiratory hospital admissions were consistently reported by the observations in Prague, Czech Republic (≥346 nm vs. <346 nm) [46] and in Beijing, China (100-300 nm vs. <100 nm) [47]. However, a study in Augsburg, Germany, noticed a more precise positive association with MI for UFPs (30-100 nm), compared to the particles in the smaller or larger size range [11]. Our size-fractioned analyses showed that the 10-100 nm and 30-100 nm ranges were consistently more pathogenic than other modes across all four UFP metrics. The heterogeneity in findings across studies may be attributed to variations in the methodological issues and emission sources across study areas [7,34]. The diffusion coefficients and measurement uncertainty of particle size distribution measurement below 30 nm are high [34]. This means that the bulk of the daily average UFP was detected in the size range above 30 nm, which yielded higher exposure levels and more precise effect estimates in the Aitken mode than those in the nucleation mode. Daily variation of particles of this size cannot be ruled out because of their association with fresh and aged traffic emissions, which showed a noticeable peak during morning rush hour, as well as the distance from measurement locations to roadways [34,48]. Despite this, particles within the range of 10-100 nm mainly reflect emissions from the diesel-driven motor vehicles in Augsburg [34], but massive amounts of airborne particles in the range of 100-500 nm are associated with stationary combustion, which is influenced by the use of residential heating facilities [48]. These may partly explain the inconsistent results from this size range. In addition to particle size distribution, we noticed the effect of particle size fraction (30-100 nm) in both delayed mode (lag 3) and cumulative mode (lag 0-6), with larger effects being found in the accumulation mode. The effect of the smallest particles (10-30 nm) was only found at lag 0-6 days, suggesting that larger particles in the Aitken mode may exert effects after shorter exposure lags than their smaller counterpart in the nucleation mode. This finding needs to be interpreted with caution due to the methodological difficulties in measuring particles in this size fraction of UFPs.

There are direct and indirect pathways of UFPs being thought to trigger acute cerebrovascular stroke. Direct pollutant effects are hypothesized because inhaled UFPs are unique in their small size and high concentration, which enables them to deposit and retain in the distal airways and alveoli, penetrate the alveolar-capillary barrier, or cross the blood-brain barrier and subsequently gain access to the central nervous system, thus causing platelet aggregation and neuroinflammation [41,49-51]. After being exposed to UFPs for a longer period, the cumulative toxic effect may be evoked as UFPs can cross the alveolar membranes and release toxins into the bloodstream upon depositing on the vascular endothelium, then modify the integrity of vascular tissue by eliciting a surge in local oxidative stress and inflammation and facilitating plaque instability and thrombosis [41,50]. Convincing evidence has been presented that UFP exposure could access to blood cells, elicit elevated blood levels of pro-inflammatory cytokines, initiate the hepatic synthesis of acute-phase proteins [52]. The UFP-triggered oxidative stress would further promote vascular dysfunction and increase mitochondrial reactive oxygen species (ROS) formation and lipid oxidation [41]. Excess ROS formation can influence blood pressure, accelerate atherosclerosis, and contribute to strokes [41,50]. By indirect pathways, the toxic effects of UFPs may be strengthened as their chemical constituent can cause not only vascular activation via producing circulating stress hormones and vasoconstrictors but also neuronal activation through autonomic lung arc reflexes or by a spill-over of local inflammation into systemic inflammation [50].

The risk of strokes associated with UFPs may vary depending on their subtypes and severity levels, with adverse effects predominantly found for ischemic strokes and minor strokes with lower severity levels. There is supportive evidence of the positive association between short-term exposure to particulate air pollutants and ischemic stroke risk [53], which are typically caused by the narrowing of vessels due to atherosclerosis or systemic embolism [54]. Furthermore, our findings are in line with another study stating that strokes associated with UFP exposures were at the mild end of the stroke spectrum and probably resulted from blockages of small vessels [20]. This may also be related to the "ceiling effect" that additional UFP exposure may not produce a detectable incremental effect when those with advanced disease may have reached a plateau in disease progression [55]. Given that the existing evidence on the biological mechanisms of particles in TIAs and hemorrhagic strokes remains insufficient, more investigations should attempt to elucidate their associations with UFPs.

The interaction model showed that the cold spells might modify the association, with the detrimental effects of UFPs on strokes being stronger in days with extreme cold air temperature, especially on the coldest 5.0% of days lasting two or four days. As highlighted in previous research, the cold air temperature may amplify the adverse health effects of UFPs on the cardiovascular system, such as PSC-related hospitalizations [15] and PNC-related mortality [56]. In particular, we noticed that the daily averages of four UFP metrics tended to increase during cold spells, as the levels increased when the cold spell cutoffs became more rigorous. We hypothesize that the excess risk of strokes in response to UFPs during cold spells may be attributed to elevated emissions of UFP from vehicles [57], enhanced particle formation, and slower atmospheric dispersion under low air temperatures [7,58]. Likewise, as temperatures drop near ground level at night, stable atmospheric layers of air form, thus trapping primary pollutants near their emissions sources [7,59], thus amplifying their adverse health effects. No modification effect was observed for heat waves, so future studies are still needed to elucidate the effect of two sides of ETEs on strokes, especially under a changing climate.

This is the first study comparing the effects of four UFP metrics in different size fractions on stroke events. Besides, the validated and complete registration for strokes over 15 years enables us to systematically investigate the association of UFP exposure with strokes and their subtypes with sufficient statistical power. Moreover, the application of the case-crossover study design provides us with opportunities to control time-invariant factors. However, our study suffers from several limitations. First, the measurement of UFPs in our study relied on one fixed measuring site. However, short-term health effect studies are usually not biased by potential spatial variation, and a carefully selected monitoring site could be considered adequate for UFP because of the high temporal correlations of PNC across the city area of Augsburg [31]. For clinicians, conducting local analyses might provide a more precise picture of what matters. Second, it is challenging for us to differentiate the health effects of the four UFP metrics because they are highly correlated with each other. In general, the four UFP metrics exhibit largely consistent associations with strokes, indicating a certain level of comparability among these metrics. Third, there may be potential misclassification of reported TIAs, as their diagnosis is often challenging; transient symptoms may resolve quickly and are not always confirmed by imaging, meaning they might not result from a cerebral ischemic event. However, this would only cause reduced precision of associations in response to UFPs rather than blurring the real adverse effects. Finally, the generalizability of our findings to other populations is limited due to the potentially different demographic and socioeconomic characteristics and emission sources across study areas.

5. Conclusions

Short-term exposure to UFP may be associated with the occurrence of strokes, with similar effects of the four UFP metrics, suggesting that PNC, PLC, and PSC may serve as promising indicators capturing the properties of UFPs. The detrimental impacts of UFPs were more pronounced for ischemic strokes and minor strokes with a lower severity. Particular attention should be directed toward particles within the conventional ultrafine range (10–100 nm) and those classified under the Aitken mode (30–100 nm). Notably, cold spells may amplify the damage of UFPs. More efforts are needed to monitor UFPs and to set up control levels, especially during days with extremely low air temperatures, thus alleviating the stroke burden.

Declaration of interests statement

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.

CRediT authorship contribution statement

Alexandra Schneider, Michael Ertl: Conceptualization, Methodology; **Minqi Liao**: Validation, Formal analysis, Visualization, Writing – Original Draft; **Siqi Zhang**: Software, Validation, Formal analysis; **Maximilian Schwarz, Cheng He**: Formal analysis, Visualization; **Siqi Zhang, Maximilian Schwarz, Cheng He, Susanne Breitner-Busch, Markus Naumann, Lino Braadt, Claudia Traidl-Hoffmann, Gertrud Hammel, Annette Peters, Michael Ertl, Alexandra Schneider**: Writing-Reviewing and Editing; **Annette Peters, Alexandra Schneider:** Supervision.

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Data availability

Data will be made available on request.

Table Legends

Table 1. Description of stroke patients hospitalized in the study areas of Augsburg, Germany, from 2006 to 2020.

Table 2. Basic descriptive statistics of daily levels of four size-fractioned ultrafine particle metrics in the study areas of Augsburg, Germany, from 2006 to 2020.

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Tables

Table 1. Description of stroke patients hospitalized in the study areas of Augsburg, Germany, from 2006 to 2020.

Characteristics	Overall strokes	TIAs [a]	Hemorrhagic strokes [a]	Ischemic strokes [a]
N (%)	19518	5024 (25.7)	1208 (6.2)	13242 (67.8)
Age (y), continuous	70.9±13.3	69.06 ±13.20	71.61 ±13.54	71.53 ±13.27
Age (y), categorical				
<65.0	5488 (28.1)	1634 (32.5)	314 (26.0)	3532 (26.7)
≥65.0	14030 (71.9)	3390 (67.5)	894 (74.0)	9710 (73.3)
Sex				
Men	6290 (32.2)	1535 (30.6)	416 (34.4)	4328 (32.7)
Women	8585 (44.0)	2176 (43.3)	537 (44.5)	5859 (44.2)
Missing	4643 (23.8)	1313 (26.1)	255 (21.1)	3055 (23.1)
Disability due to strokes (by mRS score)				
No symptoms to slight disability [b]	5879 (30.1)	2358 (86.2)	146 (22.1)	3374 (38.8)
Moderate disability to death [c]	6214 (31.8)	378 (13.8)	516 (77.9)	5316 (61.2)
Missing	7425 (38.0)	2288 (45.5)	546 (45.2)	4552 (34.4)
Stroke severity (by NIHSS score)				
No symptoms to minor stroke [d]	8189 (42.0)	2837 (93.5)	271 (35.6)	5070 (51.7)
Moderate to severe stroke [e]	5425 (27.8)	196 (6.5)	490 (64.4)	4733 (48.3)
Missing	5904 (30.2)	1991 (39.6)	447 (37.0)	3439 (26.0)
Seasons [f]				
Warm seasons	9667 (50.0)	2558 (50.9)	581 (48.1)	6512 (49.2)
Cold seasons	9851 (50.0)	2466 (49.1)	627 (51.9)	6730 (50.8)
Extreme temperature events (ETE)				
Heat waves [g]	912 (4.7)	255 (5.1)	32 (2.6)	622 (4.7)
Cold spells [h]	953 (4.9)	240 (4.8)	68 (5.6)	641 (4.8)
Non-ETE days	17653 (90.4)	4529 (90.1)	1108 (91.7)	11979 (90.5)
5-year periods [i]				
2006-2010	6649 (34.1)	1825 (36.3)	437 (36.2)	4351 (32.9)
2011-2015	6966 (35.7)	1767 (35.2)	434 (35.9)	4757 (35.9)
2016-2020	5903 (30.2)	1432 (28.5)	337 (27.9)	4134 (31.2)

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 symptoms to minor stroke"; [e] NIHSS score of 4-42 is "Moderate to severe stroke"; [f] Seasons: determined by the official time of heating time in Germany, warm seasons: May to October; cold season: November to April; [g] Heat waves are defined as the days with air temperature equaling to or exceeding the 95.0th or 97.5th percentiles; [h] Cold spells are defined as the days with air temperature equaling to or lowering than the 2.5th or 5.0th percentiles; [i] 5-year periods: the year of admission.

Abbreviations: TIA, Transient ischemic attacks; 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).

Table 2. Basic descriptive statistics of daily levels of four size-fractioned ultrafine particle metrics in the study areas of Augsburg, Germany, from 2006 to 2020.

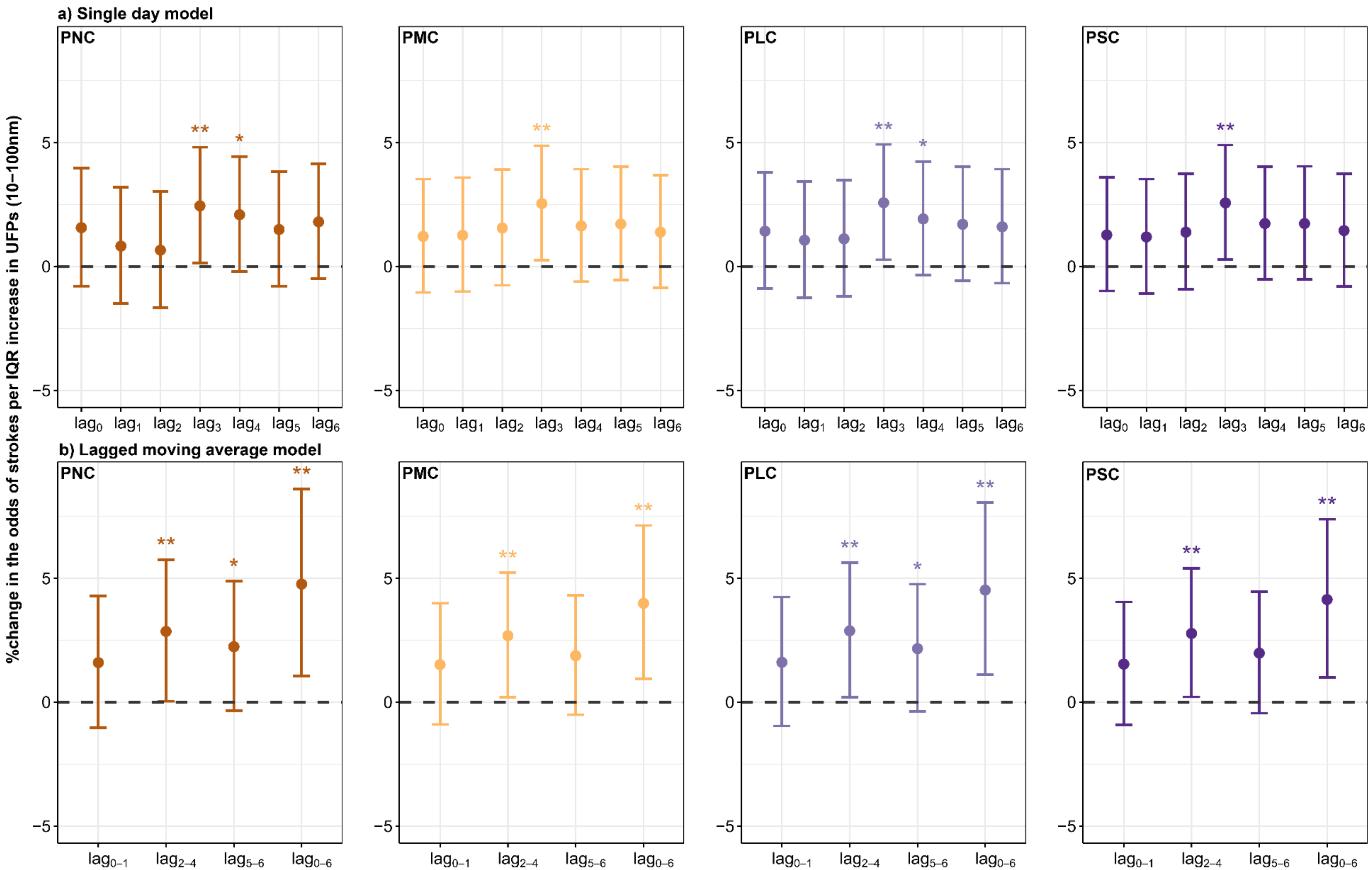
	Mean ± SD	Min	P25	Median	P75	Max	IQR
PNC (particles/cm^3)							
PNC $_{10\text{-}100}$	7411.5±4370.0	504.4	4469.6	6416.7	9021.1	48386.9	4551.5
PNC $_{10\text{-}30}$	3438.5±2083.6	279.8	2103.7	2968.4	4230.6	42526.3	2126.9
PNC $_{30\text{-}100}$	3973.0±2623.1	224.7	2299.3	3373.6	4866.4	26932.0	2567.1
PNC $_{100\text{-}500}$	1490.0±990.0	0.0	843.7	1282.7	1851.5	10562.8	1007.8
PMC (μg/m^3)							
PMC $_{10\text{-}100}$	0.7±0.5	0.1	0.4	0.6	0.9	5.1	0.5
PMC $_{10\text{-}30}$	0.0±0.0	0.0	0.0	0.0	0.0	0.4	0.0
PMC $_{30\text{-}100}$	0.7±0.5	0.0	0.4	0.6	0.9	5.0	0.5
PMC $_{100\text{-}500}$	10.1±7.9	0.0	5.1	8.3	12.8	98.8	7.7
PLC (mm/cm^3)							
PLC $_{10\text{-}100}$	283123.1±175247.6	19149.8	168233.5	243513.2	346557.4	1710893.0	178323.9
PLC $_{10\text{-}30}$	66055.2±40376.0	5122.0	40110.3	56962.3	81370.0	961207.8	41259.7
PLC $_{30\text{-}100}$	217067.9±143871.5	13461.7	124547.4	184315.4	266416.4	1528987.0	141869.0
PLC $_{100\text{-}500}$	258871.0±175416.6	0.0	146015.9	222491.3	321293.0	1990223.0	175277.1
PSC (μm^2/cm^3)							
PSC $_{10\text{-}100}$	46.0±29.8	3.3	26.6	39.2	56.7	311.9	30.1
PSC $_{10\text{-}30}$	4.3±2.7	0.3	2.6	3.7	5.3	71.1	2.7
PSC $_{30\text{-}100}$	41.7±27.8	2.7	23.7	35.4	51.4	299.1	27.7
PSC $_{100\text{-}500}$	165.9±118.7	0.0	90.1	140.8	207.0	1430.6	116.9

Note: All air pollutants and meteorology were consecutively measured between 2006 and 2020. The values were calculated based on the original UFP data excluding missing values (missing rate=8.29%).

Abbreviations: SD, standard deviation; IQR, interquartile range; PNC, particle number concentration; PMC, particle mass concentration; PLC, particle length concentration; PSC, particle surface concentration; 10-100, from 10 to 100 nm mobility diameter; 10-30, from 10 to 30 nm mobility diameter; 30-100, from 30 to 100 nm mobility diameter; 100-500, from 100 to 500 nm mobility diameter.

Figures and figure legends

Figure 1. Percent change (95%CI) in the odds of overall stroke events per interquartile range (IQR) increase in the a) single-day and b) lagged moving average UFP metrics (10-100 nm). Note: * *P*<0.10; ** *P*<0.05.



18

Figure 2. Percent change (95%CI) in the odds of overall stroke events per interquartile range (IQR) increase in four sizes of a) lag 3 and b) 0-6 days of UFP metrics. Note: * *P*<0.10; ** *P*<0.05.

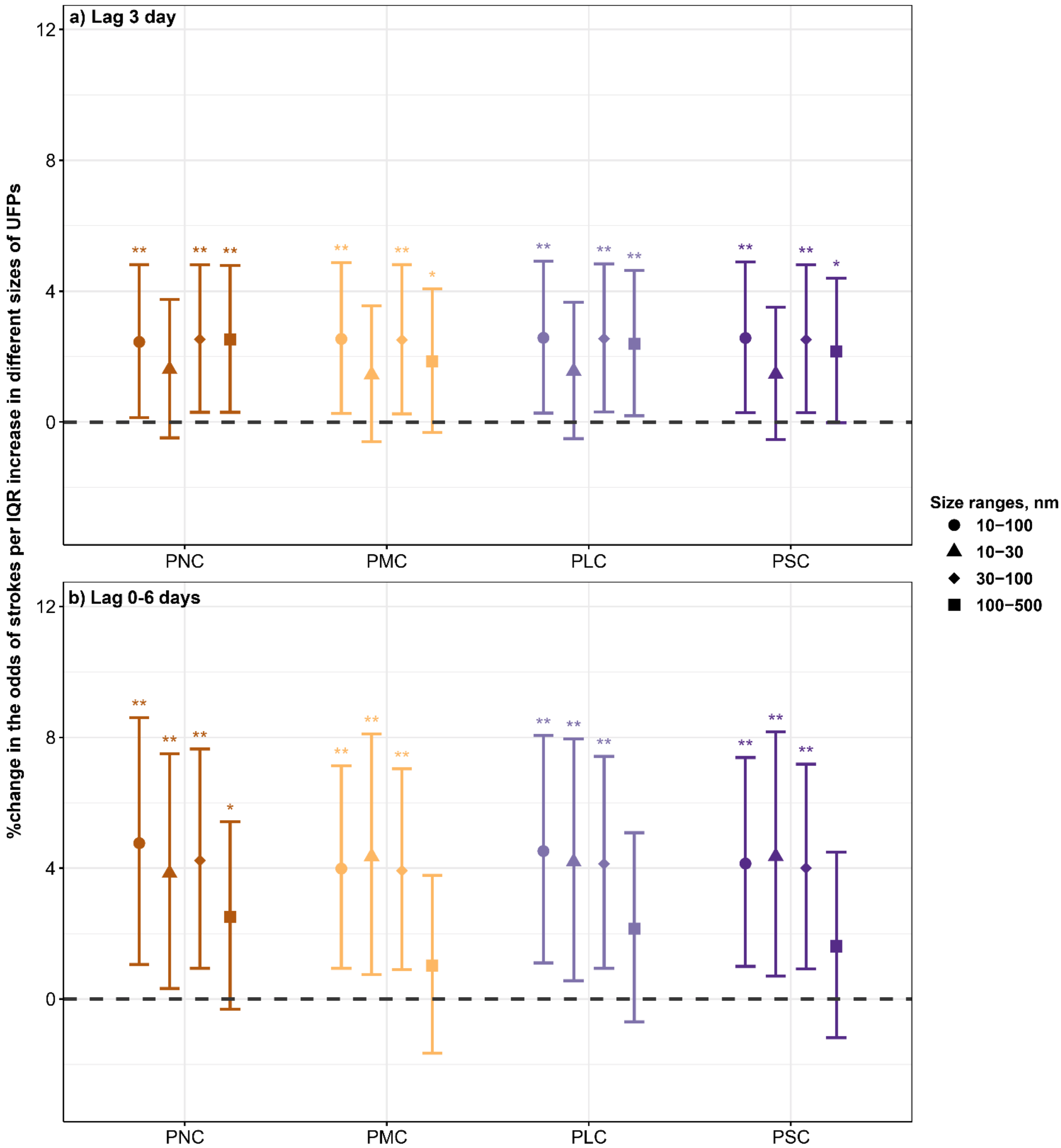


Figure 3. Percent change (95%CI) in the odds of three stroke subtypes per interquartile range (IQR) increase in lag 3 and 0-6 days of UFP metrics (10-100 nm). Note: * *P*<0.10; ** *P*<0.05.

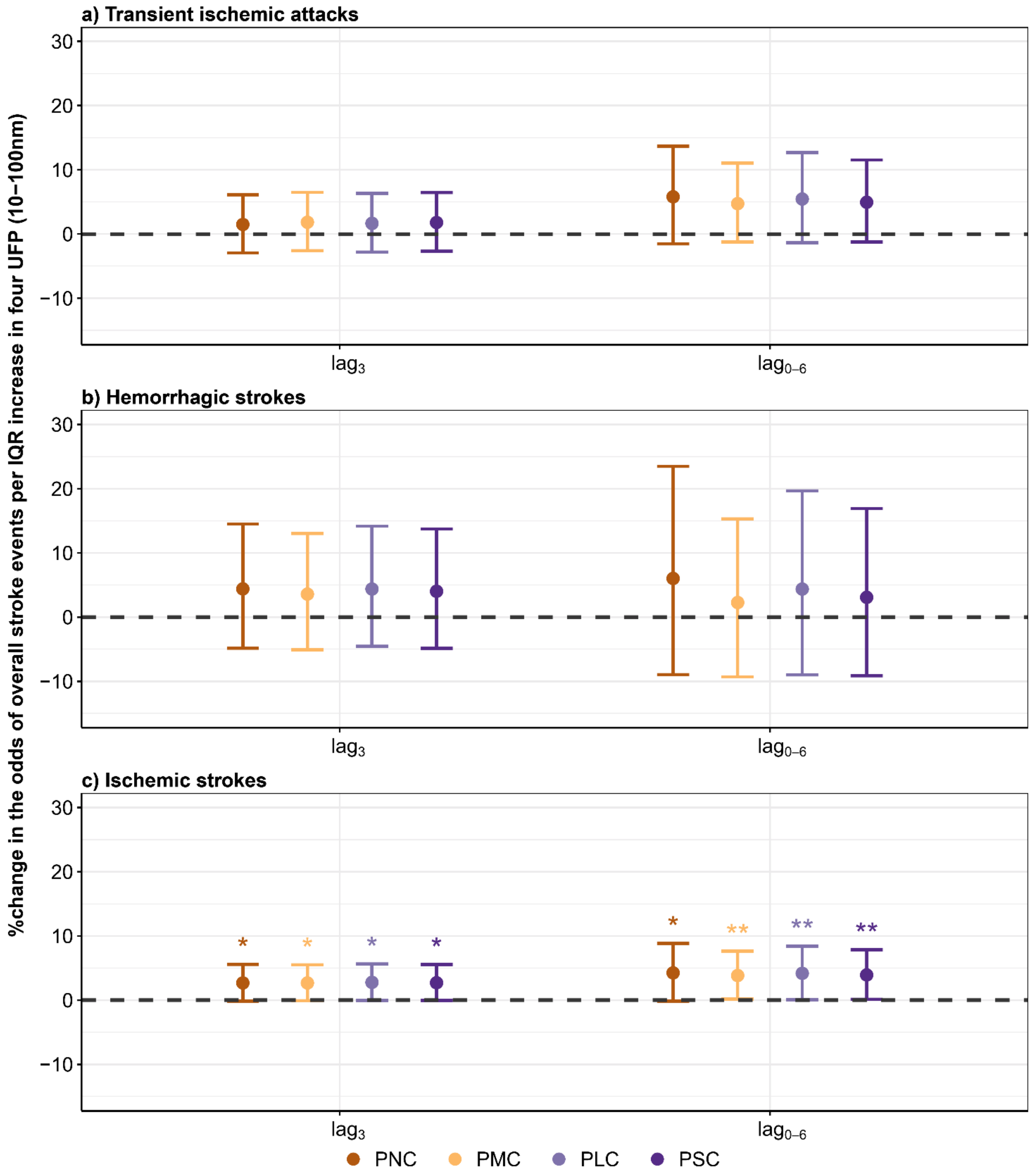
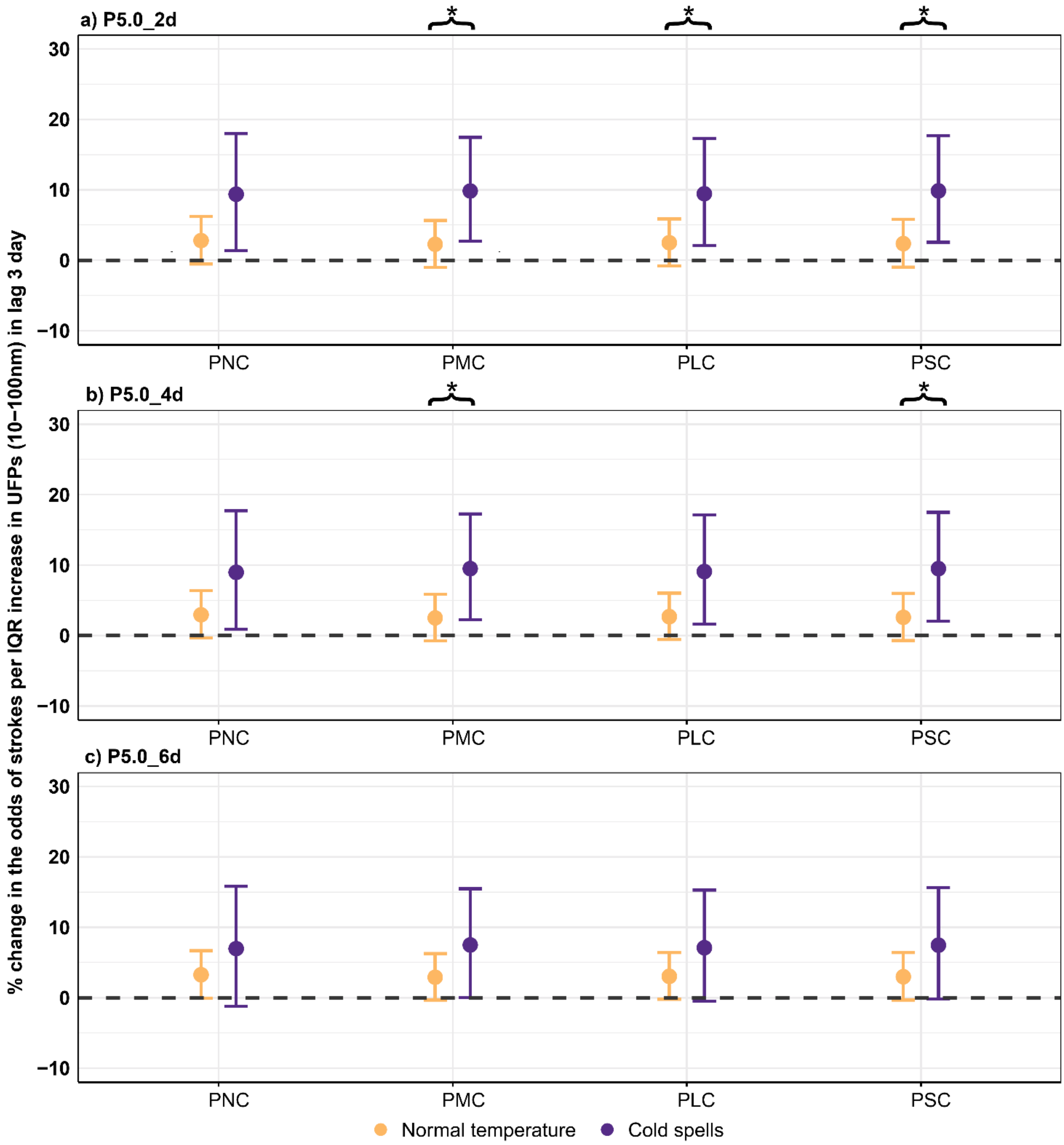


Figure 4. Effect modification by the consecutive a) 2 days, b) 4 days and c) 6 days of P5.0 thresholds of cold spells on the association between lag 3 days of UFP metrics (10-100 nm) and the percent changes in the odds of overall stroke events. Note: * *P*-interaction <0.10.



Short-term effects of ultrafine particles on stroke events: Assessment using four exposure metrics

(Supplementary materials)

Contents

I) Description of pollution measurement devices:

A Twin Differential Mobility Particle Sizer (TDMPS) system was used in conjunction with an aerodynamic particle sizer (APS, Model 3321, TSI Inc., U.S., size range 0.8 to 10 µm) to continuously measure particle size distribution (PSD) ranging from 3 nm to 10 µm [1-3].

The condensation particle counter (CPC) was used to measure total particle particulate number concentration (PNC) with sizes ranging from 3 nm to 3µm [3]. An electrical aerosol detector (EAD, model 3070A; TSI Inc., U.S.) was used to measure the length of particles (PLC) in sizes 10nm-1000µm in aerodynamic diameter (or 10 nm to 800 nm in mobility equivalent diameter, *Dp*), and the response of the EAD is almost proportional to the diameter, *Dp* [3]. A Diffusion Charging Particle Sensor (DCPS, model LQ1; Matter Aerosol AG, Switzerland) was utilized to obtain the total active (or Fuchs) surface of particles (PSC) in the size range <1 µm [3-5]. Measurement of particle mass concentration (PMC) was performed using two independent Tapered Element Oscillating Microbalances (TEOM, model 1400ab, Thermo Fisher Scientific Inc., U.S.) equipped with a Filter Dynamics Measurement System (FDMS model 8500b, Thermo Fisher Scientific Inc., U.S.) to correct the loss of volatile fractions from particulate mass [3-5].

To determine the physical properties of particles within the ultrafine range, total PLC in a given air volume is obtained by summing the particle diameters in a certain amount of time, and PSC equals the particle number concentration times the squared diameter of the particle within a certain size range[4]. (1)-(4) showed the calculation methods for PNC, PLC, PSC, and PMC based on the PSD data measured above [3].

$$NC(d_1 - d_2) = \sum_{d_1}^{d_2} NC_i \quad (1)$$

$$LC(d_1 - d_2) = \sum_{d_1}^{d_2} NC_i \times d_i \quad (2)$$

$$SC(d_1 - d_2) = \pi \sum_{d_1}^{d_2} NC_i \times {d_i}^2 \quad (3)$$

$$MC(d_1 - d_2) = \frac{1}{6} \rho\pi \sum_{d_1}^{d_2} NC_i \times {d_i}^3 \quad (4)$$

where d_1 and d_2 are the lower and upper edges of the size range, respectively. d_i is one of the size bins within the size range $d_1 - d_2$ and ρ is the particle density [3].

II) Definitions of Extreme temperature events (ETEs):

1. We calculated the cutoffs for heat waves, including the 95.0^{th} and 97.5^{th} percentiles of daily air temperature, then we defined the heat waves as the days with air temperature equaling or exceeding any of these thresholds for at least 2, 4, 6 consecutive days [6,7].
2. The cutoff values for cold spells were the 2.5^{th} and 5.0^{th} percentiles of daily air temperature, and the cold spells were defined as air temperature equal to or lower than any of these thresholds for at least 2, 4, 6 consecutive days [6,7].
3. As an example, "P97.5_4d" suggests a heat wave event that occurs at or above the 97.5^{th} percentile of AT for at least 4 consecutive days, whereas "P2.5_4d" indicates a cold spell event that occurs at or below the 2.5^{th} percentile of AT for at least 4 consecutive days.
4. These methods built 6 definitions for the heat waves or cold spells, respectively.

III) Tables

sTable 1. The definitions of different ETEs in Augsburg, Germany, from 2006 to 2020.

Model name	ETEs definition [a]			
	Percentile	Duration day	Threshold, °C	No. of ETEs [b]
Heat waves [c]				
P95.0_2d	≥95.0th percentile of apparent temperature	≥2 days	22.36	274
P95.0_4d		≥4 days	22.36	272
P95.0_6d		≥6 days	22.36	269
P97.5_2d	≥97.5th percentile of apparent temperature	≥2 days	23.79	137
P97.5_4d		≥4 days	23.79	136
P97.5_6d		≥6 days	23.79	135
Cold spells [d]				
P5.0_2d	≤5.0th percentile of apparent temperature	≥2 days	-2.37	274
P5.0_4d		≥4 days	-2.37	265
P5.0_6d		≥6 days	-2.37	251
P2.5_2d	≤2.5th percentile of apparent temperature	≥2 days	-4.28	137
P2.5_4d		≥4 days	-4.28	134
P2.5_6d		≥6 days	-4.28	130

Note:

[a] The ETEs were defined by the threshold of ambient air temperature (°C);

[b] The total number of ETE days in each definition during 2006-2020;

[c] Heat waves are defined as the days with apparent temperature equaling or exceeding the 95.0th or 97.5th percentiles for consecutive 2, 4, 6 days;

[d] Cold spells are defined as the days with apparent temperature equaling or lowering than the 2.5th or 5.0th percentiles for consecutive 2, 4, 6 days.

Abbreviations: ETEs, extreme temperature events.

sTable 2. Summary of 1-neighboring week values imputed daily levels of four size-fractioned ultrafine particle metrics in Augsburg, Germany, from 2006 to 2020.

	Mean ± SD	Min	P25	Median	P75	Max	IQR
PNC (particles/cm^3)							
PNC $_{10\text{-}100}$	7374.1±4250.8	504.4	4541.2	6401.7	8922.1	48386.9	4380.9
PNC $_{10\text{-}30}$	3413.5±2027.3	279.8	2129.8	2947.5	4199.7	42526.3	2069.9
PNC $_{30\text{-}100}$	3960.6±2551.1	224.7	2351.5	3401.1	4792.9	26932.0	2441.4
PNC $_{100\text{-}500}$	1481.2±959.2	0.0	871.9	1283.8	1819.8	10562.8	947.9
PMC (μg/m^3)							
PMC $_{10\text{-}100}$	0.7±0.5	0.1	0.4	0.6	0.9	5.1	0.5
PMC $_{10\text{-}30}$	0.0±0.0	0.0	0.0	0.0	0.0	0.4	0.0
PMC $_{30\text{-}100}$	0.7±0.5	0.0	0.4	0.6	0.9	5.0	0.5
PMC $_{100\text{-}500}$	10.0±7.6	0.0	5.2	8.3	12.6	98.8	7.4
PLC (mm/cm^3)							
PLC $_{10\text{-}100}$	282087.0±170409.7	19149.8	171480.3	245973.6	341368.0	1710893.0	169887.7
PLC $_{10\text{-}30}$	65565.9±39247.4	5122.0	40629.3	56588.3	80542.5	961207.8	39913.2
PLC $_{30\text{-}100}$	216521.1±139882.5	13461.7	128165.9	187196.6	262250.0	1528987.0	134084.1
PLC $_{100\text{-}500}$	257158.3±169953.1	0.0	150770.6	222959.8	315283.0	1990223.0	164512.4
PSC (μm^2/cm^3)							
PSC $_{10\text{-}100}$	45.9±28.9	3.3	27.6	39.9	55.7	311.9	28.1
PSC $_{10\text{-}30}$	4.3±2.6	0.3	2.7	3.7	5.3	71.1	2.6
PSC $_{30\text{-}100}$	41.6±27.0	2.7	24.6	36.0	50.5	299.1	25.9
PSC $_{100\text{-}500}$	164.7±114.9	0.0	92.7	141.7	203.6	1430.6	110.9

Note: All air pollutants and meteorology were consecutively measured between 2006 and 2020.

Abbreviations: CIs, confidence intervals; IQR, interquartile range; PNC, particle number concentration; PMC, particle mass concentration; PLC, particle length concentration; PSC, particle surface concentration; 10-100, from 10 to 100 nm mobility diameter; 10-30, from 10 to 30 nm mobility diameter; 30-100, from 30 to 100 nm mobility diameter; 100-500, from 100 to 500 nm mobility diameter.

sTable 3. Mean levels of four ultrafine particle metrics (10-100 nm) by different definitions of ETEs in Augsburg, Germany, from 2006 to 2020.

ETEs	The current day of four ultrafine particle metrics (10-100 nm) [a]			
	PNC (particles/cm^3)	**PMC (μg/m^3)**	**PLC (mm/cm^3)**	**PSC (μm^2/cm^3)**
Heat waves [b]				
P95.0_2d	7490.1±2805.9	0.9±0.3	308628.7±121696.6	52.7±21.0
P95.0_4d	7502.3±2813.8	0.9±0.3	309037.9±122104.6	52.8±21.0
P95.0_6d	7507.0±2828.9	0.9±0.3	309399.7±122767.1	52.9±21.1
P97.5_2d	7054.3±2133.7	0.8±0.2	292801.8±85007.3	50.5±14.8
P97.5_4d	7059.1±2141.8	0.8±0.2	293127.2±85277.4	50.6±14.9
P97.5_6d	7059.8±2150.6	0.8±0.3	293203.7±85624.8	50.6±14.9
Cold spells [c]				
P5.0_2d	10150.5±5862.4	1.1±0.7	412372.1±245270.1	70.0±42.3
P5.0_4d	9957.2±5590.1	1.1±0.7	402750.1±231707.5	68.2±39.8
P5.0_6d	9565.1±5280.6	1.1±0.6	384046.5±212588.2	64.8±35.8
P2.5_2d	11575.7±5987.3	1.3±0.7	472883.4±244759.9	80.6±41.7
P2.5_4d	11502.5±5922.5	1.3±0.7	468813.3±240700.5	79.7±40.8
P2.5_6d	11379.5±5796.8	1.3±0.6	462071.8±233344.1	78.4±39.3

Note:

[a] Data were presented as mean ± standard deviation;

[b] Heat waves are defined as the days with ambient air temperature equaling or exceeding the 95.0th or 97.5th percentiles for consecutive 2, 4, 6 days;

[c] Cold spells are defined as the days with ambient air temperature equaling or lowering than the 2.5th or 5.0th percentiles for consecutive 2, 4, 6 days.

Abbreviations: ETEs, extreme temperature events; PNC, particle number concentration; PMC, particle mass concentration; PLC, particle length concentration; PSC, particle surface concentration; 10-100, from 10 to 100 nm mobility diameter; P, percentile

sTable 4. Spearman correlation coefficients between daily levels of four size-fractioned ultrafine particle metrics and meteorological indicators in Augsburg, Germany, from 2006 to 2020.

	PNC_{10-30}	PNC_{10-100}	PNC_{30-100}	$PNC_{100-500}$	PLC_{10-30}	PLC_{10-100}	PLC_{30-100}	$PLC_{100-500}$	PSC_{10-30}	PSC_{10-100}	PSC_{30-100}	$PSC_{100-500}$	PMC_{10-30}	PMC_{10-100}	PMC_{30-100}	$PMC_{100-500}$	T (°C)	RH (%)
PNC_{10-30}	1.00																	
PNC_{10-100}	0.94	1.00																
PNC_{30-100}	0.81	0.96	1.00															
$PNC_{100-500}$	0.51	0.69	0.79	1.00														
PLC_{10-30}	1.00	0.95	0.83	0.53	1.00													
PLC_{10-100}	0.85	0.98	0.99	0.79	0.87	1.00												
PLC_{30-100}	0.77	0.94	1.00	0.83	0.80	0.99	1.00											
$PLC_{100-500}$	0.47	0.65	0.74	0.99	0.49	0.74	0.78	1.00										
PSC_{10-30}	0.99	0.96	0.85	0.54	1.00	0.89	0.82	0.50	1.00									
PSC_{10-100}	0.77	0.94	0.99	0.85	0.80	0.99	1.00	0.79	0.81	1.00								
PSC_{30-100}	0.74	0.91	0.99	0.86	0.76	0.98	1.00	0.81	0.78	1.00	1.00							
$PSC_{100-500}$	0.42	0.58	0.67	0.96	0.44	0.67	0.70	0.99	0.45	0.72	0.74	1.00						
PMC_{10-30}	0.99	0.97	0.87	0.55	1.00	0.90	0.83	0.51	1.00	0.83	0.79	0.46	1.00					
PMC_{10-100}	0.72	0.90	0.98	0.88	0.74	0.97	0.99	0.83	0.76	1.00	1.00	0.76	0.78	1.00				
PMC_{30-100}	0.70	0.89	0.97	0.88	0.73	0.96	0.99	0.83	0.75	0.99	1.00	0.76	0.76	1.00	1.00			
$PMC_{100-500}$	0.37	0.51	0.59	0.91	0.38	0.59	0.63	0.95	0.39	0.64	0.66	0.99	0.40	0.68	0.68	1.00		
T (°C)	-0.01	-0.01	0.00	0.00	-0.01	0.00	0.00	0.00	-0.01	0.00	0.01	-0.01	-0.01	0.01	0.01	-0.02	1.00	
RH (%)	0.01	0.01	0.00	0.03	0.01	0.00	0.00	0.05	0.01	0.00	0.00	0.07	0.01	0.00	0.00	0.08	-0.57	1.00

Note: All ultrafine particle metrics and meteorological indicators were consecutively measured between 2006 and 2020.

Abbreviations: PNC, particle number concentration; PLC, particle length concentration; PSC, particle surface concentration; PMC, particle mass concentration; 10-100, from 10 to 100 nm mobility diameter; 10-30, from 10 to 30 nm mobility diameter; 30-100, from 30 to 100 nm mobility diameter; 100-500, from 100 to 500 nm mobility diameter; T, air temperature; RH, relative humidity.

sTable 5. Spearman correlation coefficients between daily levels of four UFP metrics (10-100 nm) and routinely measured air pollutants in Augsburg, Germany, from 2006 to 2020.

	PNC_{10-100}	PLC_{10-100}	PSC_{10-100}	PMC_{10-100}	PM_{10}	$PM_{2.5}$	NO	NO_2
PNC_{10-100}	1.00							
PLC_{10-100}	0.98	1.00						
PSC_{10-100}	0.94	0.99	1.00					
PMC_{10-100}	0.90	0.97	1.00	1.00				
PM_{10}	0.04	0.04	0.04	0.03	1.00			
$PM_{2.5}$	0.07	0.07	0.06	0.05	0.94	1.00		
NO	0.06	0.05	0.05	0.04	0.54	0.56	1.00	
NO_2	0.11	0.10	0.09	0.08	0.65	0.65	0.81	1.00

Note: All ultrafine particle metrics and meteorological indicators were consecutively measured between 2006 and 2020.

Abbreviations: 10-100, from 10 to 100 nm mobility diameter; PNC, particle number concentration; PMC, particle mass concentration; PLC, particle length concentration; PSC, particle surface concentration; $PM_{2.5}$, particulate matter with aerodynamic diameter below 2.5 µm; PM_{10}, particulate matter with aerodynamic diameter below 10 µm; NO, Nitric oxide; NO_2, nitrogen dioxide.

sTable 6. Percent changes and 95% CIs in the odds of overall stroke events associated with per IQR increase in the single-lagged day of four size-fractioned ultrafine particle metrics over lag 0 to lag 6 days.

	Percent changes (95% CIs)						
	Lag 0	**Lag 1**	**Lag 2**	**Lag 3**	**Lag 4**	**Lag 5**	**Lag 6**
PNC (particles/cm^3)							
PNC $_{10-100}$	1.56 (-0.79; 3.98)	0.82 (-1.49; 3.19)	0.66 (-1.66; 3.03)	2.45 (0.14; 4.81)**	2.09 (-0.21; 4.44)*	1.49 (-0.79; 3.83)	1.80 (-0.49; 4.14)
PNC $_{10-30}$	1.48 (-0.71; 3.72)	0.35 (-1.73; 2.48)	-0.02 (-2.09; 2.11)	1.61 (-0.48; 3.74)	1.91 (-0.19; 4.06)*	0.79 (-1.31; 2.93)	1.69 (-0.39; 3.82)
PNC $_{30-100}$	1.22 (-1.01; 3.51)	1.04 (-1.21; 3.34)	1.12 (-1.14; 3.43)	2.53 (0.30; 4.81)**	1.67 (-0.52; 3.92)	1.74 (-0.46; 4.00)	1.39 (-0.81; 3.64)
PNC $_{100-500}$	-0.02 (-2.16; 2.16)	0.13 (-2.04; 2.35)	1.70 (-0.53; 3.98)	2.52 (0.30; 4.79)**	1.82 (-0.37; 4.06)	1.10 (-1.08; 3.34)	1.00 (-1.18; 3.23)
PMC (μg/m^3)							
PMC $_{10-100}$	1.22 (-1.05; 3.53)	1.26 (-1.01; 3.59)	1.55 (-0.76; 3.91)	2.54 (0.26; 4.87)**	1.63 (-0.61; 3.93)	1.71 (-0.54; 4.02)	1.39 (-0.86; 3.69)
PMC $_{10-30}$	1.65 (-0.52; 3.87)	0.29 (-1.79; 2.42)	0.40 (-1.68; 2.51)	1.45 (-0.59; 3.55)	2.21 (0.20; 4.25)**	0.98 (-1.12; 3.12)	1.51 (-0.53; 3.60)
PMC $_{30-100}$	1.18 (-1.07; 3.48)	1.27 (-0.99; 3.59)	1.56 (-0.74; 3.91)	2.51 (0.25; 4.81)**	1.56 (-0.66; 3.83)	1.70 (-0.54; 3.98)	1.35 (-0.88; 3.63)
PMC $_{100-500}$	-1.23 (-3.29; 0.88)	-0.45 (-2.57; 1.73)	0.80 (-1.35; 3.00)	1.86 (-0.31; 4.07)*	1.26 (-0.88; 3.44)	0.86 (-1.29; 3.05)	0.84 (-1.28; 3.01)
PLC (mm/cm^3)							
PLC $_{10-100}$	1.42 (-0.89; 3.79)	1.06 (-1.26; 3.43)	1.12 (-1.20; 3.49)	2.57 (0.27; 4.92)**	1.92 (-0.34; 4.24)*	1.70 (-0.58; 4.03)	1.60 (-0.67; 3.93)
PLC $_{10-30}$	1.60 (-0.60; 3.84)	0.34 (-1.74; 2.47)	0.17 (-1.90; 2.28)	1.56 (-0.50; 3.66)	2.12 (0.01; 4.27)**	0.87 (-1.23; 3.01)	1.65 (-0.44; 3.77)
PLC $_{30-100}$	1.20 (-1.05; 3.51)	1.15 (-1.11; 3.46)	1.28 (-0.99; 3.60)	2.55 (0.30; 4.84)**	1.63 (-0.59; 3.90)	1.75 (-0.47; 4.03)	1.37 (-0.85; 3.64)
PLC $_{100-500}$	-0.42 (-2.52; 1.73)	-0.06 (-2.20; 2.13)	1.50 (-0.70; 3.74)	2.39 (0.19; 4.63)**	1.75 (-0.43; 3.96)	1.04 (-1.11; 3.23)	0.99 (-1.18; 3.20)
PSC (μm^2/cm^3)							
PSC $_{10-100}$	1.28 (-0.99; 3.59)	1.19 (-1.09; 3.52)	1.38 (-0.92; 3.74)	2.57 (0.29; 4.90)**	1.73 (-0.51; 4.03)	1.73 (-0.52; 4.04)	1.45 (-0.80; 3.75)
PSC $_{10-30}$	1.64 (-0.54; 3.87)	0.32 (-1.75; 2.43)	0.30 (-1.73; 2.36)	1.47 (-0.54; 3.51)	2.22 (0.14; 4.34)**	0.91 (-1.15; 3.02)	1.57 (-0.49; 3.68)
PSC $_{30-100}$	1.18 (-1.07; 3.48)	1.23 (-1.04; 3.54)	1.43 (-0.85; 3.76)	2.52 (0.28; 4.81)**	1.59 (-0.63; 3.86)	1.73 (-0.50; 4.02)	1.36 (-0.87; 3.64)
PSC $_{100-500}$	-0.86 (-2.95; 1.27)	-0.26 (-2.39; 1.91)	1.19 (-0.99; 3.40)	2.16 (-0.02; 4.39)*	1.56 (-0.60; 3.77)	0.96 (-1.19; 3.16)	0.94 (-1.21; 3.13)

Note: *, P<0.10; **, P<0.05.

The model was adjusted for the corresponding lagged days of air temperature and relative humidity.

Abbreviations: CIs, confidence intervals; IQR, interquartile range; PNC, particle number concentration; PMC, particle mass concentration; PLC, particle length concentration; PSC, particle surface concentration; 10-100, from 10 to 100 nm mobility diameter; 10-30, from 10 to 30 nm mobility diameter; 30-100, from 30 to 100 nm mobility diameter; 100-500, from 100 to 500 nm mobility diameter.

sTable 7. Percent changes and 95% CIs in the odds of overall stroke events associated with per IQR increase in the lagged moving average four size-fractioned ultrafine particle metrics over lag 0 to lag 6 days.

	Percent changes (95% CIs)			
	Lag 0-1	**Lag 2-4**	**Lag 5-6**	**Lag 0-6**
PNC (particles/cm^3)				
PNC $_{10\text{-}100}$	1.59 (-1.02; 4.28)	2.85 (0.03; 5.75)**	2.24 (-0.34; 4.88)*	4.76 (1.06; 8.60)**
PNC $_{10\text{-}30}$	1.29 (-1.15; 3.79)	2.15 (-0.55; 4.91)	1.84 (-0.56; 4.30)	3.85 (0.32; 7.49)**
PNC $_{30\text{-}100}$	1.45 (-1.01; 3.97)	2.74 (0.13; 5.43)**	2.01 (-0.41; 4.49)	4.23 (0.94; 7.64)**
PNC $_{100\text{-}500}$	0.03 (-2.17; 2.28)	2.64 (0.27; 5.07)**	1.14 (-1.08; 3.41)	2.51 (-0.31; 5.42)*
PMC (μg/m^3)				
PMC $_{10\text{-}100}$	1.51 (-0.90; 3.99)	2.68 (0.20; 5.22)**	1.88 (-0.51; 4.31)	3.99 (0.93; 7.13)**
PMC $_{10\text{-}30}$	1.42 (-1.10; 4.01)	2.61 (-0.11; 5.40)*	1.78 (-0.52; 4.14)	4.36 (0.75; 8.10)**
PMC $_{30\text{-}100}$	1.49 (-0.90; 3.94)	2.66 (0.18; 5.19)**	1.85 (-0.52; 4.27)	3.92 (0.90; 7.03)**
PMC $_{100\text{-}500}$	-0.99 (-3.14; 1.21)	1.64 (-0.66; 4.01)	0.90 (-1.30; 3.15)	1.03 (-1.66; 3.78)
PLC (mm/cm^3)				
PLC $_{10\text{-}100}$	1.61 (-0.96; 4.24)	2.88 (0.20; 5.63)**	2.16 (-0.37; 4.76)*	4.52 (1.11; 8.05)**
PLC $_{10\text{-}30}$	1.36 (-1.09; 3.88)	2.39 (-0.33; 5.17)*	1.86 (-0.55; 4.33)	4.20 (0.56; 7.96)**
PLC $_{30\text{-}100}$	1.47 (-0.96; 3.95)	2.69 (0.15; 5.30)**	1.95 (-0.44; 4.40)	4.13 (0.94; 7.42)**
PLC $_{100\text{-}500}$	-0.31 (-2.52; 1.95)	2.44 (0.08; 4.86)**	1.10 (-1.13; 3.39)	2.15 (-0.69; 5.08)
PSC (μm^2/cm^3)				
PSC $_{10\text{-}100}$	1.53 (-0.91; 4.04)	2.77 (0.21; 5.40)**	1.98 (-0.44; 4.45)	4.14 (1.00; 7.38)**
PSC $_{10\text{-}30}$	1.38 (-1.06; 3.87)	2.52 (-0.18; 5.29)*	1.84 (-0.54; 4.28)	4.36 (0.70; 8.16)**
PSC $_{30\text{-}100}$	1.49 (-0.93; 3.97)	2.66 (0.17; 5.22)**	1.91 (-0.48; 4.35)	4.00 (0.92; 7.18)**
PSC $_{100\text{-}500}$	-0.70 (-2.93; 1.59)	2.12 (-0.25; 4.54)*	1.04 (-1.22; 3.36)	1.61 (-1.18; 4.49)

Note: *, $P<0.10$; **, $P<0.05$.

The model was adjusted for the corresponding lagged moving average of air temperature and relative humidity.

Abbreviations: CIs, confidence intervals; IQR, interquartile range; PNC, particle number concentration; PMC, particle mass concentration; PLC, particle length concentration; PSC, particle surface concentration; 10-100, from 10 to 100 nm mobility diameter; 10-30, from 10 to 30 nm mobility diameter; 30-100, from 30 to 100 nm mobility diameter; 100-500, from 100 to 500 nm mobility diameter.

sTable 8. Subgroup percent changes and 95% CIs in the odds of stroke events associated with per IQR increase in the single lag 3 day and lagged moving average 0-6 days of four size-fractioned ultrafine particle metrics by subtypes of strokes.

	Percent changes (95% CIs)					
	Lag 3 days			Lag 0-6 days		
	Transient ischemic attacks	Hemorrhagic strokes	Ischemic strokes	Transient ischemic attacks	Hemorrhagic strokes	Ischemic strokes
PNC (particles/cm^3)						
PNC_{10-100}	1.50 (-2.94; 6.13)	4.38 (-4.84; 14.50)	2.67 (-0.15; 5.57)*	5.80 (-1.54; 13.68)	6.01 (-8.98; 23.46)	4.25 (-0.16; 8.85)*
PNC_{10-30}	0.83 (-3.04; 4.86)	3.20 (-5.38; 12.55)	1.90 (-0.70; 4.58)	4.91 (-2.18; 12.52)	6.98 (-7.53; 23.77)	3.23 (-0.96; 7.59)
PNC_{30-100}	1.70 (-2.69; 6.29)	4.19 (-4.57; 13.76)	2.64 (-0.05; 5.41)*	5.02 (-1.44; 11.90)	3.69 (-9.16; 18.35)	3.93 (-0.01; 8.03)*
$PNC_{100-500}$	2.66 (-1.69; 7.20)	2.66 (-5.57; 11.61)	2.45 (-0.26; 5.23)*	3.98 (-1.58; 9.85)	2.63 (-8.45; 15.05)	1.92 (-1.49; 5.45)
PMC (μg/m^3)						
PMC_{10-100}	1.84 (-2.61; 6.49)	3.57 (-5.10; 13.03)	2.67 (-0.09; 5.50)*	4.73 (-1.26; 11.07)	2.26 (-9.30; 15.29)	3.83 (0.15; 7.64)**
PMC_{10-30}	0.30 (-3.25; 3.98)	4.12 (-3.31; 12.12)	1.80 (-0.75; 4.41)	4.96 (-2.05; 12.48)	8.30 (-6.34; 25.22)	3.76 (-0.63; 8.34)*
PMC_{30-100}	1.86 (-2.57; 6.49)	3.44 (-5.17; 12.84)	2.65 (-0.09; 5.46)*	4.67 (-1.27; 10.98)	2.09 (-9.41; 15.06)	3.79 (0.14; 7.57)**
$PMC_{100-500}$	2.67 (-1.63; 7.15)	0.95 (-7.32; 9.95)	1.69 (-0.93; 4.38)	3.00 (-2.39; 8.69)	3.84 (-6.99; 15.93)	0.03 (-3.15; 3.32)
PLC (mm/cm^3)						
PLC_{10-100}	1.65 (-2.81; 6.32)	4.37 (-4.56; 14.15)	2.75 (-0.04; 5.63)*	5.45 (-1.33; 12.69)	4.35 (-9.00; 19.65)	4.16 (0.08; 8.42)**
PLC_{10-30}	0.58 (-3.12; 4.43)	3.81 (-4.42; 12.75)	1.94 (-0.71; 4.65)	5.11 (-2.13; 12.87)	7.52 (-7.11; 24.46)	3.57 (-0.77; 8.10)
PLC_{30-100}	1.79 (-2.65; 6.43)	3.95 (-4.78; 13.48)	2.66 (-0.05; 5.45)*	4.89 (-1.34; 11.50)	3.08 (-9.06; 16.84)	3.88 (0.05; 7.85)**
$PLC_{100-500}$	2.70 (-1.59; 7.18)	2.32 (-5.93; 11.30)	2.27 (-0.40; 5.02)*	3.76 (-1.85; 9.70)	3.22 (-7.98; 15.77)	1.42 (-2.01; 4.97)
PSC (μm^2/cm^3)						
PSC_{10-100}	1.79 (-2.69; 6.47)	4.01 (-4.88; 13.73)	2.70 (-0.05; 5.53)*	4.94 (-1.25; 11.53)	3.06 (-9.14; 16.90)	3.91 (0.13; 7.83)**
PSC_{10-30}	0.40 (-3.14; 4.07)	4.07 (-3.74; 12.52)	1.87 (-0.72; 4.53)	5.18 (-2.12; 13.04)	8.05 (-6.76; 25.20)	3.74 (-0.67; 8.33)*
PSC_{30-100}	1.83 (-2.59; 6.45)	3.67 (-4.97; 13.11)	2.64 (-0.06; 5.41)*	4.80 (-1.29; 11.28)	2.57 (-9.25; 15.93)	3.80 (0.10; 7.63)**
$PSC_{100-500}$	2.72 (-1.57; 7.19)	1.70 (-6.54; 10.66)	2.01 (-0.64; 4.74)	3.40 (-2.17; 9.29)	3.71 (-7.50; 16.28)	0.73 (-2.61; 4.19)

Note: *, $P<0.10$; **, $P<0.05$.

The model was adjusted for the corresponding lagged moving average of air temperature and relative humidity.

Abbreviations: CIs, confidence intervals; IQR, interquartile range; PNC, particle number concentration; PMC, particle mass concentration; PLC, particle length concentration; PSC, particle surface concentration; 10-100, from 10 to 100 nm mobility diameter; 10-30, from 10 to 30 nm mobility diameter; 30-100, from 30 to 100 nm mobility diameter; 100-500, from 100 to 500 nm mobility diameter.

sTable 9. Percent changes and 95% CIs in the odds of overall strokes associated with per IQR increase in the single lag 3 day and lagged moving average 0-6 days of four size-fractioned ultrafine particle metrics stratified by stroke-induced disability levels.

	Percent changes (95% CIs)			
	Lag 3 day		Lag 0-6 days	
	No symptoms to slight disability [a]	Moderate disability to death [a]	No symptoms to slight disability [a]	Moderate disability to death [a]
PNC (particles/cm^3)				
PNC_{10-100}	1.75 (-2.25; 5.92)	2.24 (-1.83; 6.49)	7.04 (0.36; 14.17)**	2.61 (-3.52; 9.12)
PNC_{10-30}	1.53 (-1.82; 5.00)	0.56 (-3.16; 4.43)	7.70 (1.25; 14.55)**	-0.55 (-6.43; 5.70)
PNC_{30-100}	1.34 (-2.76; 5.62)	3.34 (-0.78; 7.63)	4.71 (-1.24; 11.02)	4.52 (-1.20; 10.56)
$PNC_{100-500}$	3.09 (-0.96; 7.31)	1.62 (-2.28; 5.69)	1.86 (-3.02; 7.00)	3.90 (-1.09; 9.13)
PMC (μg/m^3)				
PMC_{10-100}	1.90 (-2.25; 6.22)	2.76 (-1.36; 7.06)	4.28 (-1.15; 10.01)	4.77 (-0.50; 10.33)*
PMC_{10-30}	0.25 (-2.75; 3.34)	1.62 (-2.10; 5.49)	7.41 (1.06; 14.16)**	0.03 (-5.85; 6.27)
PMC_{30-100}	1.91 (-2.20; 6.21)	2.75 (-1.36; 7.02)	4.14 (-1.25; 9.83)	4.86 (-0.40; 10.39)*
$PMC_{100-500}$	2.96 (-0.92; 6.99)	-0.48 (-4.33; 3.53)	-0.33 (-5.07; 4.64)	1.53 (-3.33; 6.63)
PLC (mm/cm^3)				
PLC_{10-100}	1.60 (-2.56; 5.94)	2.93 (-1.23; 7.26)	5.66 (-0.51; 12.22)*	4.06 (-1.81; 10.28)
PLC_{10-30}	0.96 (-2.30; 4.33)	1.04 (-2.68; 4.90)	7.86 (1.30; 14.84)**	-0.31 (-6.28; 6.05)
PLC_{30-100}	1.54 (-2.58; 5.83)	3.16 (-0.91; 7.40)	4.39 (-1.28; 10.39)	4.72 (-0.79; 10.53)*
$PLC_{100-500}$	3.07 (-0.92; 7.22)	1.17 (-2.70; 5.19)	1.14 (-3.76; 6.28)	3.49 (-1.57; 8.82)
PSC (μm^2/cm^3)				
PSC_{10-100}	1.73 (-2.47; 6.12)	2.98 (-1.19; 7.32)	4.68 (-1.00; 10.69)	4.65 (-0.88; 10.48)
PSC_{10-30}	0.53 (-2.59; 3.74)	1.37 (-2.31; 5.20)	7.69 (1.20; 14.59)**	-0.11 (-6.06; 6.22)
PSC_{30-100}	1.73 (-2.39; 6.03)	2.98 (-1.12; 7.24)	4.21 (-1.28; 10.00)	4.85 (-0.54; 10.53)*
$PSC_{100-500}$	3.03 (-0.92; 7.12)	0.43 (-3.43; 4.44)	0.33 (-4.58; 5.50)	2.67 (-2.40; 8.00)

Note: *, $P<0.10$; **, $P<0.05$.

The model was adjusted for the corresponding lagged moving average of air temperature and relative humidity.

[a] Disability due to stroke: No symptoms to slight disability (mRS=0-2), moderate disability to death (mRS=3-6).

Abbreviations: CIs, confidence intervals; IQR, interquartile range; PNC, particle number concentration; PMC, particle mass concentration; PLC, particle length concentration; PSC, particle surface concentration; 10-100, from 10 to 100 nm mobility diameter; 10-30, from 10 to 30 nm mobility diameter; 30-100, from 30 to 100 nm mobility diameter; 100-500, from 100 to 500 nm mobility diameter.

sTable 10. Percent changes and 95% CIs in the odds of overall strokes associated with per IQR increase in the single lag 3 day and lagged moving average 0-6 days of four size-fractioned ultrafine particle metrics stratified by stroke severity levels.

	Percent changes (95% CIs)			
	Lag 3 day		Lag 0-6 days	
	No symptoms to minor stroke [a]	Moderate to severe stroke [a]	No symptoms to minor stroke [a]	Moderate to severe stroke [a]
PNC (particles/cm^3)				
PNC_{10-100}	2.18 (-1.24; 5.72)	0.39 (-3.88; 4.85)	6.35 (0.74; 12.28)**	0.17 (-6.31; 7.11)
PNC_{10-30}	1.72 (-1.33; 4.88)	-1.02 (-5.00; 3.13)	6.81 (1.33; 12.60)**	-2.45 (-8.67; 4.19)
PNC_{30-100}	2.00 (-1.42; 5.53)	1.62 (-2.69; 6.11)	4.45 (-0.50; 9.64)*	2.16 (-3.83; 8.53)
$PNC_{100-500}$	1.61 (-1.77; 5.10)	1.78 (-2.34; 6.07)	2.34 (-1.90; 6.76)	1.73 (-3.50; 7.24)
PMC (µg/m^3)				
PMC_{10-100}	1.96 (-1.48; 5.51)	1.40 (-2.88; 5.87)	4.46 (-0.18; 9.31)*	2.62 (-3.00; 8.56)
PMC_{10-30}	0.72 (-1.97; 3.49)	0.16 (-3.70; 4.18)	6.19 (0.92; 11.74)**	-2.12 (-8.61; 4.83)
PMC_{30-100}	1.96 (-1.47; 5.51)	1.43 (-2.86; 5.90)	4.36 (-0.25; 9.18)*	2.70 (-2.87; 8.59)
$PMC_{100-500}$	1.47 (-1.82; 4.87)	-0.15 (-4.19; 4.06)	0.48 (-3.59; 4.72)	-0.98 (-5.91; 4.20)
PLC (mm/cm^3)				
PLC_{10-100}	2.07 (-1.41; 5.68)	1.18 (-3.15; 5.70)	5.29 (0.16; 10.69)**	1.59 (-4.54; 8.12)
PLC_{10-30}	1.30 (-1.66; 4.35)	-0.49 (-4.44; 3.62)	6.84 (1.27; 12.72)**	-2.31 (-8.60; 4.42)
PLC_{30-100}	1.99 (-1.40; 5.51)	1.57 (-2.69; 6.03)	4.35 (-0.42; 9.34)*	2.40 (-3.37; 8.52)
$PLC_{100-500}$	1.50 (-1.82; 4.93)	1.51 (-2.61; 5.80)	1.70 (-2.53; 6.11)	1.12 (-4.15; 6.68)
PSC (µm^2/cm^3)				
PSC_{10-100}	2.01 (-1.46; 5.60)	1.42 (-2.91; 5.94)	4.66 (-0.12; 9.68)*	2.33 (-3.50; 8.50)
PSC_{10-30}	0.97 (-1.89; 3.90)	-0.10 (-3.98; 3.94)	6.64 (1.12; 12.47)**	-2.16 (-8.45; 4.56)
PSC_{30-100}	1.97 (-1.42; 5.48)	1.51 (-2.76; 5.97)	4.34 (-0.34; 9.24)*	2.62 (-3.08; 8.65)
$PSC_{100-500}$	1.45 (-1.87; 4.89)	0.83 (-3.25; 5.09)	1.02 (-3.20; 5.43)	0.13 (-5.06; 5.60)

Note: *, P<0.10; **, P<0.05.

The model was adjusted for the corresponding lagged moving average of air temperature and relative humidity.

[a] Stroke severity: No symptoms to minor stroke (NIHSS=0-3), Moderate to severe stroke (NIHSS=4-42).

Abbreviations: CIs, confidence intervals; IQR, interquartile range; PNC, particle number concentration; PMC, particle mass concentration; PLC, particle length concentration; PSC, particle surface concentration; 10-100, from 10 to 100 nm mobility diameter; 10-30, from 10 to 30 nm mobility diameter; 30-100, from 30 to 100 nm mobility diameter; 100-500, from 100 to 500 nm mobility diameter.

sTable 11. The modification effects on the association of overall stroke events with per IQR increase in the single lag 3 day and lagged moving average 0-6 days of ultrafine particle metrics (10-100 nm).

	Lag 3 day		Lag 0-6 days	
	Percent changes (95%CIs) [a]	***P*** [b]	**Percent changes (95%CIs)** [a]	***P*** [b]
Sex				
PNC, particles/cm^3				
Men	2.94 (-0.84; 6.86)	Ref	6.53 (0.53; 12.88)	Ref
Women	3.28 (-0.16; 6.85)	0.89	3.27 (-2.04; 8.88)	0.42
PMC, µg/m^3				
Men	3.10 (-0.60; 6.93)	Ref	4.57 (-0.25; 9.63)	Ref
Women	2.34 (-0.97; 5.76)	0.76	3.42 (-0.89; 7.92)	0.72
PLC, mm/cm^3				
Men	2.87 (-0.87; 6.75)	Ref	5.60 (0.11; 11.39)	Ref
Women	3.08 (-0.31; 6.58)	0.93	3.50 (-1.39; 8.63)	0.57
PSC, µm^2/cm^3				
Men	2.93 (-0.77; 6.77)	Ref	4.86 (-0.17; 10.14)	Ref
Women	2.68 (-0.66; 6.13)	0.92	3.45 (-1.04; 8.15)	0.67
Age, years				
PNC, particles/cm^3				
<65.0	3.19 (-0.94; 7.49)	Ref	8.71 (1.99; 15.88)	Ref
≥65.0	2.16 (-0.51; 4.90)	0.68	3.27 (-0.93; 7.64)	0.17
PMC, µg/m^3				
<65.0	3.66 (-0.43; 7.92)	Ref	5.87 (0.60; 11.41)	Ref
≥65.0	2.10 (-0.51; 4.77)	0.52	3.19 (-0.24; 6.73)	0.39
PLC, mm/cm^3				
<65.0	3.49 (-0.63; 7.78)	Ref	7.47 (1.39; 13.92)	Ref
≥65.0	2.22 (-0.43; 4.93)	0.61	3.38 (-0.49; 7.41)	0.26
PSC, µm^2/cm^3				
<65.0	3.62 (-0.48; 7.89)	Ref	6.40 (0.87; 12.23)	Ref
≥65.0	2.17 (-0.45; 4.85)	0.55	3.26 (-0.31; 6.96)	0.34
Seasons [c]				
PNC, particles/cm^3				
Warm seasons	0.82 (-3.24; 5.06)	Ref	5.75 (-0.87; 12.81)	Ref
Cold seasons	3.10 (0.40; 5.87)	0.36	4.38 (0.10; 8.84)	0.73
PMC, µg/m^3				
Warm seasons	1.08 (-2.95; 5.27)	Ref	3.96 (-1.46; 9.69)	Ref
Cold seasons	3.13 (0.45; 5.87)	0.41	3.93 (0.41; 7.57)	0.99
PLC, mm/cm^3				
Warm seasons	1.24 (-2.85; 5.49)	Ref	5.30 (-0.91; 11.90)	Ref
Cold seasons	3.11 (0.42; 5.87)	0.45	4.23 (0.29; 8.32)	0.78
PSC, µm^2/cm^3				
Warm seasons	1.26 (-2.78; 5.47)	Ref	4.46 (-1.22; 10.46)	Ref
Cold seasons	3.10 (0.42; 5.85)	0.46	4.02 (0.37; 7.80)	0.90
Five-year periods				
PNC, particles/cm^3				
2006-2010	2.10 (-0.91; 5.21)	Ref	3.25 (-1.39; 8.10)	Ref
2011-2015	3.41 (-0.44; 7.41)	0.60	7.02 (0.66; 13.79)	0.34
2016-2020	1.46 (-4.47; 7.76)	0.85	6.46 (-3.07; 16.94)	0.56
PMC, µg/m^3				
2006-2010	1.72 (-1.09; 4.62)	Ref	2.21 (-1.48; 6.05)	Ref
2011-2015	4.49 (0.12; 9.06)	0.29	5.84 (0.42; 11.55)	0.26
2016-2020	2.70 (-2.52; 8.20)	0.75	7.43 (0.40; 14.94)	0.20
PLC, mm/cm^3				
2006-2010	1.83 (-1.03; 4.78)	Ref	2.68 (-1.47; 7.01)	Ref
2011-2015	4.35 (0.09; 8.78)	0.33	7.25 (1.05; 13.83)	0.22
2016-2020	2.47 (-3.11; 8.37)	0.84	7.61 (-0.86; 16.81)	0.31
PSC, µm^2/cm^3				
2006-2010	1.73 (-1.08; 4.63)	Ref	2.35 (-1.48; 6.32)	Ref
2011-2015	4.60 (0.21; 9.18)	0.27	6.46 (0.74; 12.50)	0.23
2016-2020	2.76 (-2.58; 8.39)	0.74	7.57 (0.06; 15.64)	0.22

Note:

[a] Estimates for interaction model;

[b] *P* for interaction;

[c] Seasons: warm seasons: May to October; cold seasons: November to April.

The model was adjusted for the corresponding lagged moving average of air temperature and relative humidity.

Abbreviations: CIs, confidence intervals; PNC, particle number concentration; PMC, particle mass concentration; PLC, particle length concentration; PSC, particle surface concentration; 10-100, from 10 to 100 nm mobility diameter.

sTable 12. The modification effects of 6 definitions of cold spells during the cold seasons on the association of overall stroke events with per IQR increase in the single lag 3 day and lagged moving average 0-6 days of ultrafine particle metrics (10-100 nm).

ETE definitions	Lag 3 day [a]		Lag 0-6 days [a]	
	Percent changes (95%CIs) [b]	***P*** [c]	Percent changes (95%CIs) [b]	***P*** [c]
PNC, particles/cm^3				
P5.0_2d				
Normal temperature days	2.80 (-0.53; 6.24)	Ref	3.43 (-2.01; 9.17)	Ref
Cold spells	9.37 (1.40; 17.97)	0.13	11.54 (0.80; 23.42)	0.16
P5.0_4d				
Normal temperature days	2.95 (-0.36; 6.37)	Ref	3.93 (-1.50; 9.66)	Ref
Cold spells	8.97 (0.87; 17.72)	0.17	9.77 (-0.88; 21.56)	0.31
P5.0_6d				
Normal temperature days	3.26 (-0.06; 6.68)	Ref	4.31 (-1.13; 10.05)	Ref
Cold spells	6.97 (-1.20; 15.81)	0.41	7.99 (-2.94; 20.15)	0.54
P2.5_2d				
Normal temperature days	3.22 (-0.03; 6.58)	Ref	4.02 (-1.30; 9.63)	Ref
Cold spells	8.27 (-2.13; 19.79)	0.37	10.09 (-3.74; 25.92)	0.42
P2.5_4d				
Normal temperature days	3.32 (0.07; 6.68)	Ref	4.58 (-0.75; 10.19)	Ref
Cold spells	7.76 (-2.73; 19.38)	0.44	6.37 (-7.28; 22.03)	0.81
P2.5_6d				
Normal temperature days	3.40 (0.15; 6.74)	Ref	4.71 (-0.63; 10.33)	Ref
Cold spells	7.34 (-3.47; 19.37)	0.50	5.65 (-7.95; 21.25)	0.90
PMC, µg/m^3				
P5.0_2d				
Normal temperature days	2.27 (-1.00; 5.65)	Ref	2.95 (-1.67; 7.78)	Ref
Cold spells	9.84 (2.73; 17.45)	0.05	9.31 (1.27; 18.00)	0.16
P5.0_4d				
Normal temperature days	2.50 (-0.74; 5.84)	Ref	3.56 (-1.03; 8.37)	Ref
Cold spells	9.49 (2.23; 17.27)	0.08	7.81 (-0.19; 16.45)	0.34
P5.0_6d				
Normal temperature days	2.90 (-0.34; 6.26)	Ref	3.97 (-0.62; 8.77)	Ref
Cold spells	7.49 (0.04; 15.49)	0.27	6.35 (-2.12; 15.54)	0.62
P2.5_2d				
Normal temperature days	2.92 (-0.24; 6.18)	Ref	3.63 (-0.80; 8.26)	Ref
Cold spells	8.42 (-0.95; 18.68)	0.28	7.38 (-2.87; 18.70)	0.51
P2.5_4d				
Normal temperature days	3.09 (-0.07; 6.35)	Ref	4.28 (-0.15; 8.90)	Ref
Cold spells	7.55 (-1.89; 17.90)	0.39	4.15 (-6.09; 15.51)	0.98
P2.5_6d				
Normal temperature days	3.18 (0.03; 6.42)	Ref	4.43 (-0.01; 9.07)	Ref
Cold spells	7.32 (-2.54; 18.18)	0.44	3.53 (-6.68; 14.86)	0.88
PLC (mm/cm^3)				
P5.0_2d				
Normal temperature days	2.49 (-0.78; 5.86)	Ref	3.22 (-1.84; 8.54)	Ref
Cold spells	9.44 (2.11; 17.30)	0.08	10.27 (1.05; 20.34)	0.16
P5.0_4d				
Normal temperature days	2.68 (-0.57; 6.02)	Ref	3.79 (-1.25; 9.09)	Ref
Cold spells	9.09 (1.61; 17.11)	0.12	8.65 (-0.52; 18.66)	0.34
P5.0_6d				
Normal temperature days	3.04 (-0.21; 6.39)	Ref	4.20 (-0.85; 9.50)	Ref
Cold spells	7.10 (-0.51; 15.28)	0.33	7.03 (-2.52; 17.52)	0.60
P2.5_2d				
Normal temperature days	3.02 (-0.16; 6.30)	Ref	3.87 (-1.04; 9.02)	Ref
Cold spells	8.18 (-1.41; 18.70)	0.32	8.51 (-3.30; 21.76)	0.48
P2.5_4d				
Normal temperature days	3.16 (-0.02; 6.44)	Ref	4.49 (-0.42; 9.64)	Ref
Cold spells	7.50 (-2.17; 18.12)	0.41	5.02 (-6.71; 18.23)	0.94
P2.5_6d				
Normal temperature days	3.24 (0.07; 6.50)	Ref	4.64 (-0.28; 9.80)	Ref
Cold spells	7.18 (-2.87; 18.27)	0.47	4.34 (-7.35; 17.51)	0.96
PSC, µm^2/cm^3				
P5.0_2d				
Normal temperature days	2.36 (-0.96; 5.80)	Ref	3.05 (-1.73; 8.06)	Ref
Cold spells	9.85 (2.55; 17.67)	0.06	9.60 (1.18; 18.72)	0.16
P5.0_4d				
Normal temperature days	2.58 (-0.72; 5.99)	Ref	3.65 (-1.11; 8.63)	Ref
Cold spells	9.50 (2.05; 17.49)	0.09	8.06 (-0.31; 17.13)	0.34
P5.0_6d				
Normal temperature days	2.98 (-0.32; 6.40)	Ref	4.05 (-0.70; 9.04)	Ref
Cold spells	7.46 (-0.16; 15.65)	0.29	6.54 (-2.26; 16.14)	0.62
P2.5_2d				
Normal temperature days	2.99 (-0.24; 6.32)	Ref	3.71 (-0.89; 8.53)	Ref

Cold spells	8.47 (-1.12; 18.97)	0.29	7.73 (-3.01; 19.66)	0.50
P2.5_4d				
Normal temperature days	3.15 (-0.08; 6.48)	Ref	4.35 (-0.25; 9.17)	Ref
Cold spells	7.65 (-2.00; 18.26)	0.39	4.41 (-6.30; 16.35)	0.99
P2.5_6d				
Normal temperature days	3.23 (0.02; 6.54)	Ref	4.51 (-0.11; 9.34)	Ref
Cold spells	7.39 (-2.69; 18.50)	0.45	3.76 (-6.92; 15.67)	0.90

Note:
[a] The modification effect by cold spells was explored restricted within the cold seasons (from November to April);
[b] Estimates for interaction models;
[c] *P* for interaction.
Abbreviations: ETEs, extreme temperature events; CIs, confidence intervals; PNC, particle number concentration; PMC, particle mass concentration; PLC, particle length concentration; PSC, particle surface concentration; 10-100, from 10 to 100 nm mobility diameter.

sTable 13. The modification effects of 6 definitions of heat waves during the warm seasons on the percent changes and 95% CIs in the odds of overall stroke events associated with per IQR increase in the single lag 3 day and lagged moving average 0-6 days of ultrafine particle metrics (10-100 nm).

ETE definitions	Lag 3 day [a]		Lag 0-6 days [a]	
	Percent changes (95%CIs) [b]	*P* [c]	Percent changes (95%CIs) [b]	*P* [c]
PNC, particles/cm^3				
P95.0_2d				
Normal temperature days	0.27 (-3.06; 3.71)	Ref	4.32 (-0.59; 9.48)	Ref
Heat waves	3.89 (-8.42; 17.85)	0.59	4.35 (-8.95; 19.59)	1.00
P95.0_4d				
Normal temperature days	0.27 (-3.06; 3.71)	Ref	4.36 (-0.55; 9.52)	Ref
Heat waves	4.05 (-8.29; 18.04)	0.57	4.20 (-9.07; 19.42)	0.98
P95.0_6d				
Normal temperature days	0.26 (-3.06; 3.70)	Ref	4.39 (-0.53; 9.55)	Ref
Heat waves	4.29 (-8.08; 18.31)	0.55	4.22 (-9.06; 19.45)	0.98
P97.5_2d				
Normal temperature days	0.54 (-2.75; 3.93)	Ref	4.55 (-0.34; 9.67)	Ref
Heat waves	-0.59 (-20.47; 24.26)	0.92	-0.89 (-20.13; 22.98)	0.63
P97.5_4d				
Normal temperature days	0.54 (-2.74; 3.93)	Ref	4.57 (-0.32; 9.69)	Ref
Heat waves	-0.22 (-20.17; 24.73)	0.95	-0.81 (-20.06; 23.06)	0.63
P97.5_6d				
Normal temperature days	0.57 (-2.71; 3.96)	Ref	4.56 (-0.32; 9.69)	Ref
Heat waves	-1.69 (-21.43; 22.99)	0.84	0.00 (-19.30; 23.93)	0.68
PMC, μg/m^3				
P95.0_2d				
Normal temperature days	0.78 (-2.45; 4.11)	Ref	3.21 (-0.72; 7.30)	Ref
Heat waves	-0.68 (-11.61; 11.60)	0.81	3.47 (-7.12; 15.27)	0.97
P95.0_4d				
Normal temperature days	0.77 (-2.45; 4.10)	Ref	3.21 (-0.71; 7.30)	Ref
Heat waves	-0.49 (-11.44; 11.80)	0.84	3.48 (-7.10; 15.27)	0.96
P95.0_6d				
Normal temperature days	0.76 (-2.46; 4.09)	Ref	3.23 (-0.70; 7.31)	Ref
Heat waves	-0.29 (-11.25; 12.03)	0.86	3.47 (-7.11; 15.27)	0.97
P97.5_2d				
Normal temperature days	0.86 (-2.30; 4.13)	Ref	3.26 (-0.60; 7.28)	Ref
Heat waves	-5.69 (-23.23; 15.86)	0.53	-1.05 (-18.16; 19.64)	0.66
P97.5_4d				
Normal temperature days	0.87 (-2.29; 4.14)	Ref	3.27 (-0.60; 7.29)	Ref
Heat waves	-5.60 (-23.14; 15.95)	0.53	-1.01 (-18.12; 19.66)	0.66
P97.5_6d				
Normal temperature days	0.90 (-2.26; 4.17)	Ref	3.26 (-0.61; 7.28)	Ref
Heat waves	-6.52 (-23.92; 14.86)	0.47	-0.37 (-17.51; 20.33)	0.71
PLC (mm/cm^3)				
P95.0_2d				
Normal temperature days	0.71 (-2.60; 4.12)	Ref	4.17 (-0.45; 9.01)	Ref
Heat waves	1.61 (-10.17; 14.92)	0.89	4.26 (-7.93; 18.06)	0.99
P95.0_4d				
Normal temperature days	0.70 (-2.60; 4.12)	Ref	4.20 (-0.43; 9.04)	Ref
Heat waves	1.79 (-10.01; 15.12)	0.87	4.19 (-7.98; 17.97)	1.00
P95.0_6d				
Normal temperature days	0.70 (-2.61; 4.12)	Ref	4.22 (-0.41; 9.06)	Ref
Heat waves	2.00 (-9.82; 15.37)	0.84	4.21 (-7.97; 17.99)	1.00
P97.5_2d				
Normal temperature days	0.89 (-2.37; 4.25)	Ref	4.31 (-0.26; 9.10)	Ref
Heat waves	-3.16 (-22.18; 20.50)	0.72	-1.11 (-19.97; 22.20)	0.62
P97.5_4d				
Normal temperature days	0.89 (-2.36; 4.26)	Ref	4.33 (-0.25; 9.11)	Ref
Heat waves	-2.90 (-21.97; 20.83)	0.73	-1.01 (-19.88; 22.30)	0.63
P97.5_6d				
Normal temperature days	0.93 (-2.33; 4.29)	Ref	4.32 (-0.26; 9.10)	Ref
Heat waves	-4.12 (-23.00; 19.39)	0.65	-0.12 (-19.06; 23.25)	0.69
PSC, μm^2/cm^3				
P95.0_2d				
Normal temperature days	0.84 (-2.43; 4.23)	Ref	3.58 (-0.59; 7.93)	Ref
Heat waves	0.15 (-11.19; 12.94)	0.91	3.74 (-7.34; 16.15)	0.98
P95.0_4d				
Normal temperature days	0.84 (-2.44; 4.23)	Ref	3.59 (-0.58; 7.94)	Ref
Heat waves	0.33 (-11.02; 13.14)	0.94	3.72 (-7.35; 16.12)	0.98
P95.0_6d				
Normal temperature days	0.83 (-2.44; 4.22)	Ref	3.61 (-0.56; 7.96)	Ref
Heat waves	0.54 (-10.84; 13.37)	0.96	3.73 (-7.35; 16.13)	0.99
P97.5_2d				
Normal temperature days	0.97 (-2.25; 4.29)	Ref	3.66 (-0.45; 7.94)	Ref

Heat waves	-4.92 (-23.23; 17.76)	0.59	-1.13 (-18.90; 20.54)	0.64
P97.5_4d				
Normal temperature days	0.97 (-2.24; 4.30)	Ref	3.67 (-0.44; 7.95)	Ref
Heat waves	-4.75 (-23.09; 17.95)	0.60	-1.06 (-18.84; 20.61)	0.65
P97.5_6d				
Normal temperature days	1.01 (-2.21; 4.33)	Ref	3.66 (-0.45; 7.94)	Ref
Heat waves	-5.80 (-23.97; 16.72)	0.53	-0.29 (-18.12; 21.42)	0.70

Note:
[a] The modification effect by Heat waves was explored restricted within the warm seasons (from May to October);
[b] Estimates for interaction models;
[c] *P* for interaction.
Abbreviations: ETEs, extreme temperature events; CIs, confidence intervals; PNC, particle number concentration; PMC, particle mass concentration; PLC, particle length concentration; PSC, particle surface concentration; 10-100, from 10 to 100 nm mobility diameter.

sTable 14. Percent changes and 95% CIs in the odds of overall stroke events associated with per IQR increase in the single lag 3 day and lagged moving average 0-6 days of four ultrafine particle metrics (10-100 nm) in the two-pollutant model.

	Percent changes (95% CIs)	
	Lag 3 day	**Lag 0-6 days**
PNC (particles/cm^3)		
+$PM_{2.5}$	2.05 (-0.33; 4.49)*	4.28 (0.41; 8.30)**
+PM_{10}	2.11 (-0.31; 4.59)*	4.38 (0.43; 8.49)**
+NO	2.11 (-0.61; 4.91)	2.52 (-2.14; 7.41)
+NO_2	1.72 (-1.15; 4.67)	4.24 (-0.28; 8.96)*
PMC (µg/m^3)		
+$PM_{2.5}$	2.05 (-0.43; 4.59)	3.68 (0.25; 7.22)**
+PM_{10}	2.21 (-0.33; 4.82)*	3.89 (0.36; 7.54)**
+NO	2.46 (-0.55; 5.55)	1.97 (-2.29; 6.41)
+NO_2	1.92 (-1.17; 5.11)	3.95 (-0.24; 8.32)*
PLC (mm/cm^3)		
+$PM_{2.5}$	2.13 (-0.29; 4.61)*	4.11 (0.43; 7.92)**
+PM_{10}	2.24 (-0.24; 4.77)*	4.27 (0.50; 8.18)**
+NO	2.39 (-0.48; 5.35)	2.43 (-2.12; 7.18)
+NO_2	1.94 (-1.06; 5.03)	4.30 (-0.12; 8.92)*
PSC (µm^2/cm^3)		
+$PM_{2.5}$	2.10 (-0.35; 4.60)*	3.79 (0.33; 7.38)**
+PM_{10}	2.24 (-0.27; 4.81)*	3.98 (0.42; 7.67)**
+NO	2.47 (-0.48; 5.50)	2.14 (-2.17; 6.64)
+NO_2	1.97 (-1.08; 5.11)	4.05 (-0.17; 8.45)*

Note: *, P<0.10; **, P<0.05.
The model was adjusted for the corresponding lagged days of air temperature and relative humidity.
Abbreviations: CIs, confidence intervals; IQR, interquartile range; PNC, particle number concentration; PMC, particle mass concentration; PLC, particle length concentration; PSC, particle surface concentration; 10-100, from 10 to 100 nm mobility diameter.

sTable 15. Percent changes and 95% CIs in the odds of overall stroke events associated with per IQR increase in the single lag 3 day and lagged moving average 0-6 days of ultrafine particle metrics over (10-100 nm) in specific sensitivity models.

	Percent changes (95% CIs)	
	Lag 3 day	**Lag 0-6 days**
PNC (particles/cm^3)		
Model 1 [a]	2.75 (0.55; 4.99)**	5.10 (1.64; 8.68)**
Model 2 [b]	2.51 (0.14; 4.94)**	4.55 (0.77; 8.46)**
Model 3 [c]	2.41 (0.11; 4.76)**	4.26 (0.69; 7.95)**
PMC (μg/m^3)		
Model 1 [a]	2.59 (0.49; 4.73)**	4.04 (1.22; 6.93)**
Model 2 [b]	2.66 (0.34; 5.04)**	3.98 (0.83; 7.24)**
Model 3 [c]	2.45 (0.21; 4.74)**	3.52 (0.59; 6.53)**
PLC (mm/cm^3)		
Model 1 [a]	2.78 (0.62; 4.98)**	4.72 (1.55; 7.99)**
Model 2 [b]	2.67 (0.32; 5.07)**	4.45 (0.92; 8.12)**
Model 3 [c]	2.52 (0.25; 4.85)**	4.04 (0.75; 7.44)**
PSC (μm^2/cm^3)		
Model 1 [a]	2.67 (0.56; 4.83)**	4.20 (1.32; 7.16)**
Model 2 [b]	2.67 (0.35; 5.05)**	4.11 (0.86; 7.46)**
Model 3 [c]	2.49 (0.25; 4.79)**	3.68 (0.66; 6.79)**

Note: *, *P*<0.10; **, *P*<0.05.

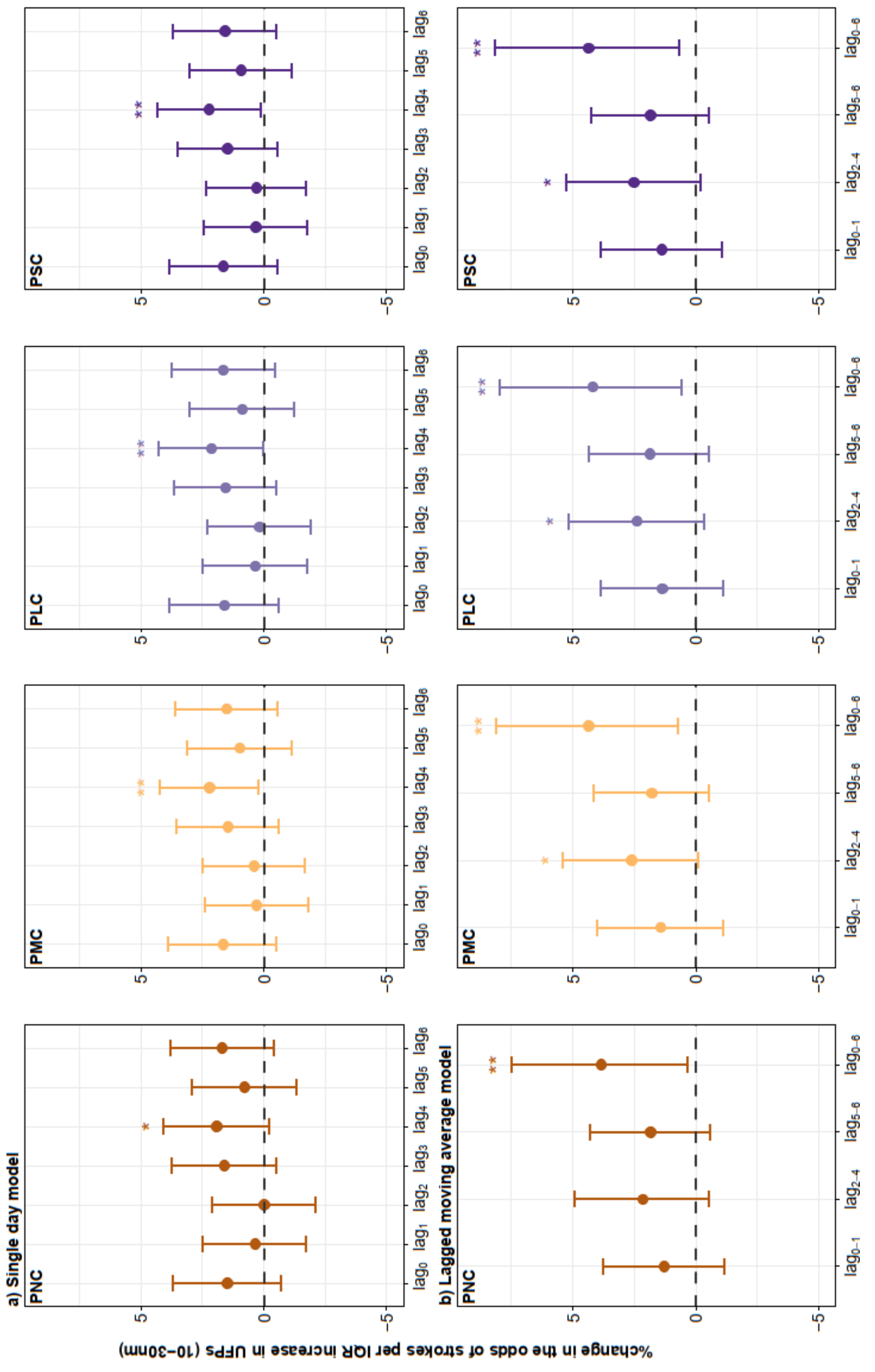
[a] Model 1 was conducted using the imputed data using 1-neighboring week values;

[b] Model 2 was conducted after excluding patients who were diagnosed after the beginning of the COVID-19 pandemic;

[c] Model 3 was adjusted for cold and warm air temperatures.

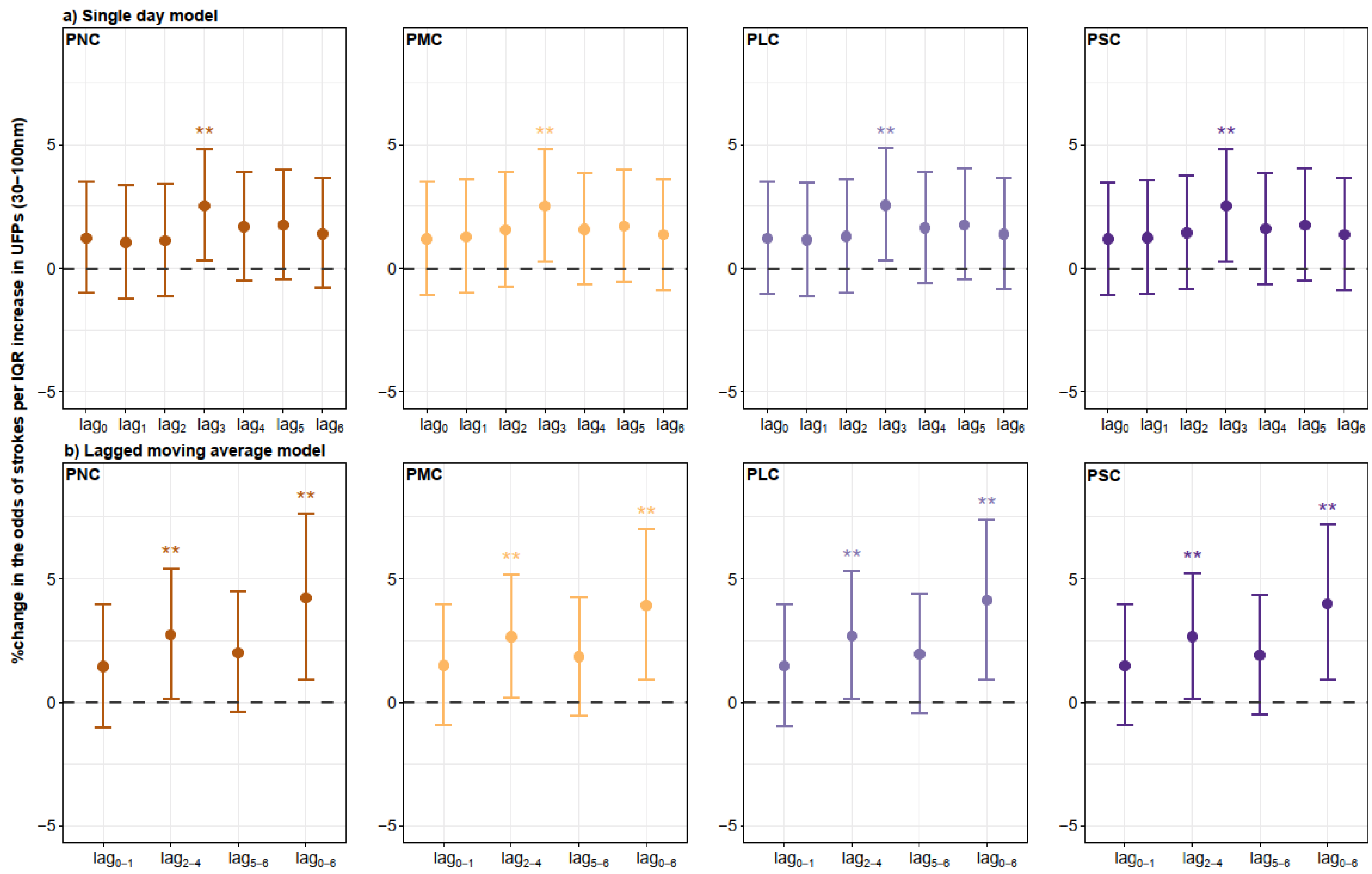
Abbreviations: CIs, confidence intervals; IQR, interquartile range; PNC, particle number concentration; PMC, particle mass concentration; PLC, particle length concentration; PSC, particle surface concentration; 10-100, from 10 to 100 nm mobility diameter.

IV) Figures



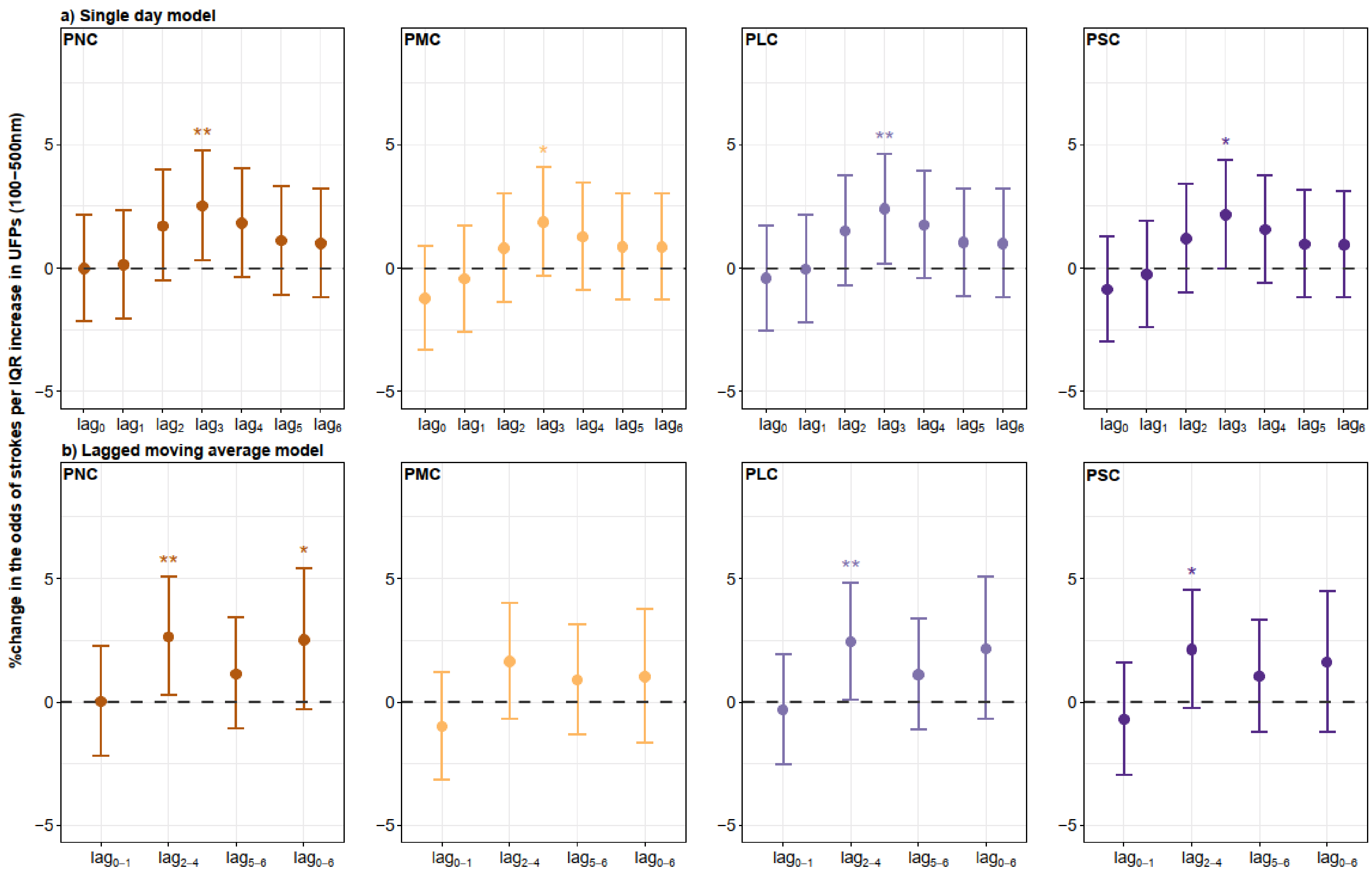
sFig 1. Percent change (95%CI) in the odds of overall stroke events per interquartile range (IQR) increase in the a) single-day and b) lagged moving average UFP metrics (10-30 nm). Note: * *P*<0.10; ** *P*<0.05.

24

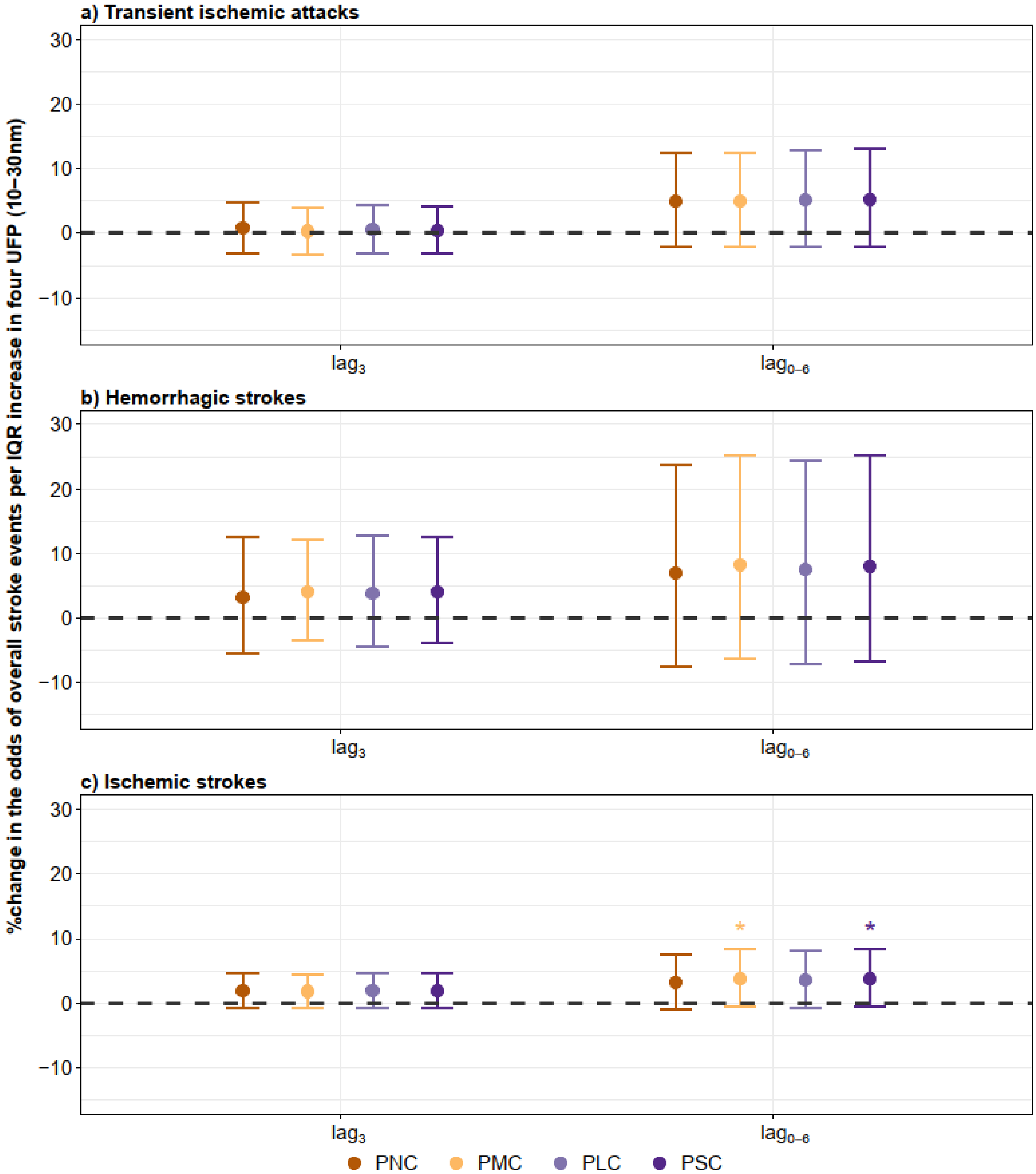


sFig 2. Percent change (95%CI) in the odds of overall stroke events per interquartile range (IQR) increase in the a) single-day and b) lagged moving average UFP metrics (30-100 nm). Note: * $P<0.10$; ** $P<0.05$.

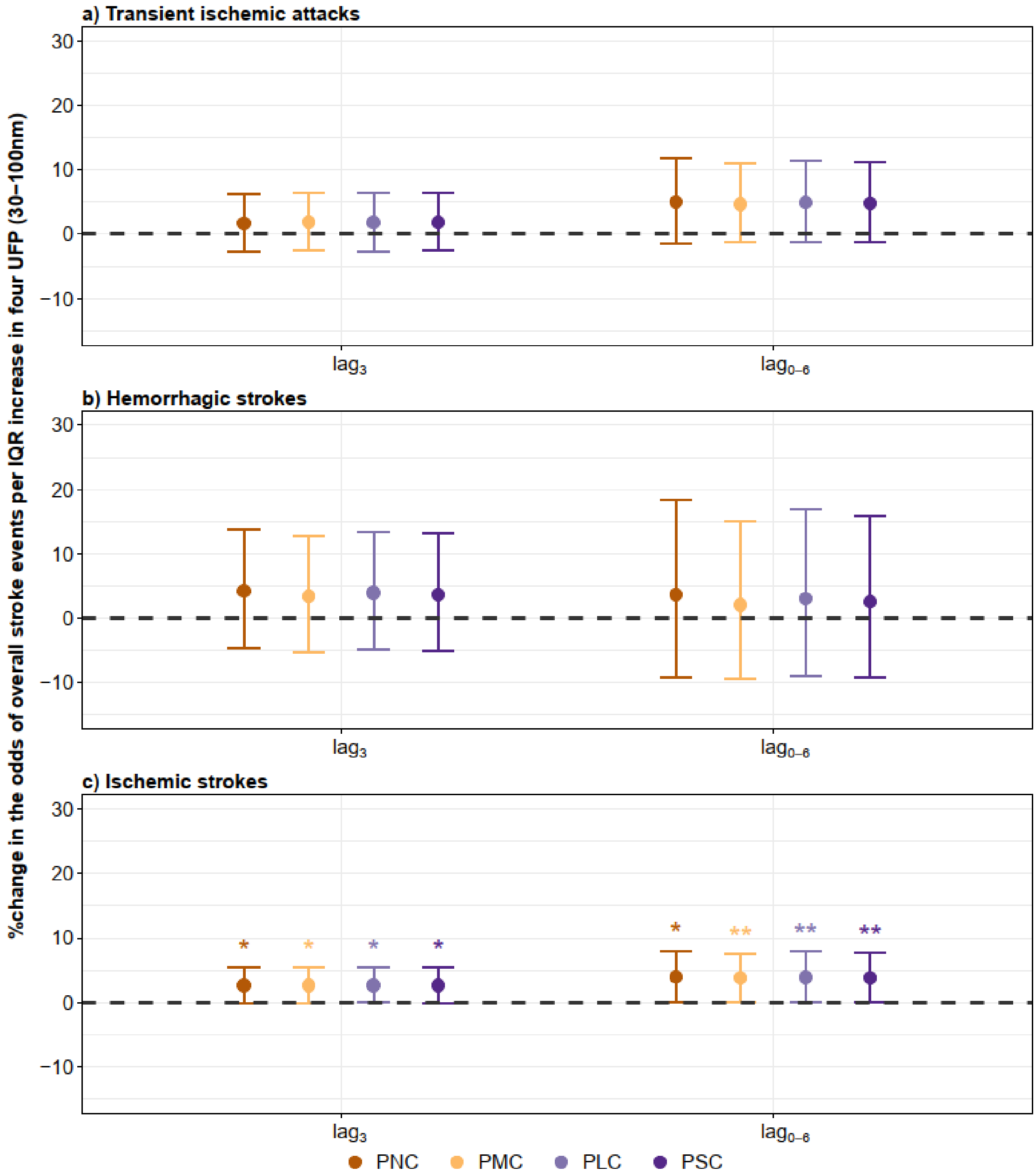
25



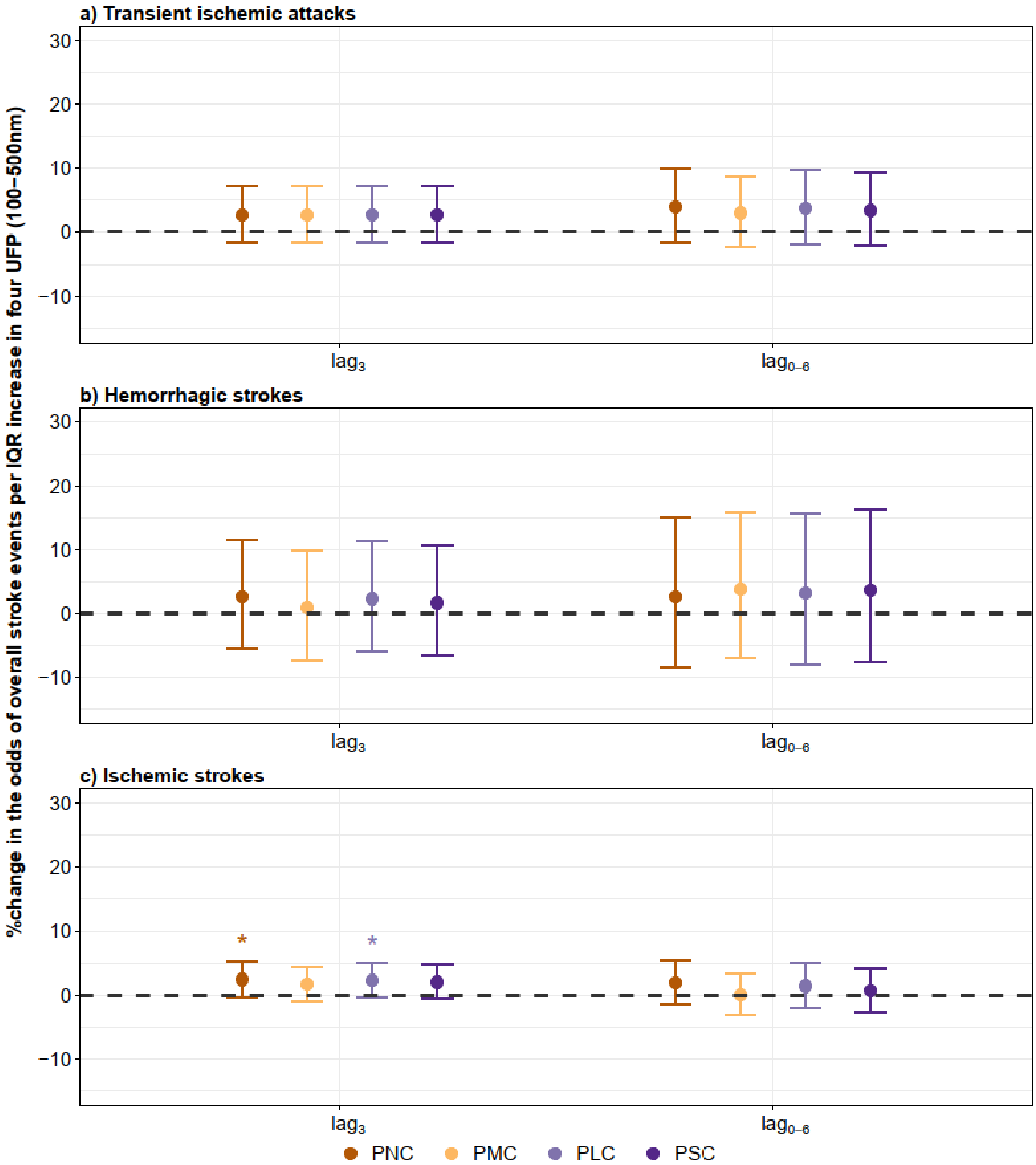
sFig 3. Percent change (95%CI) in the odds of overall stroke events per interquartile range (IQR) increase in the a) single-day and b) lagged moving average UFP metrics (100-500 nm). Note: * *P*<0.10; ** *P*<0.05.



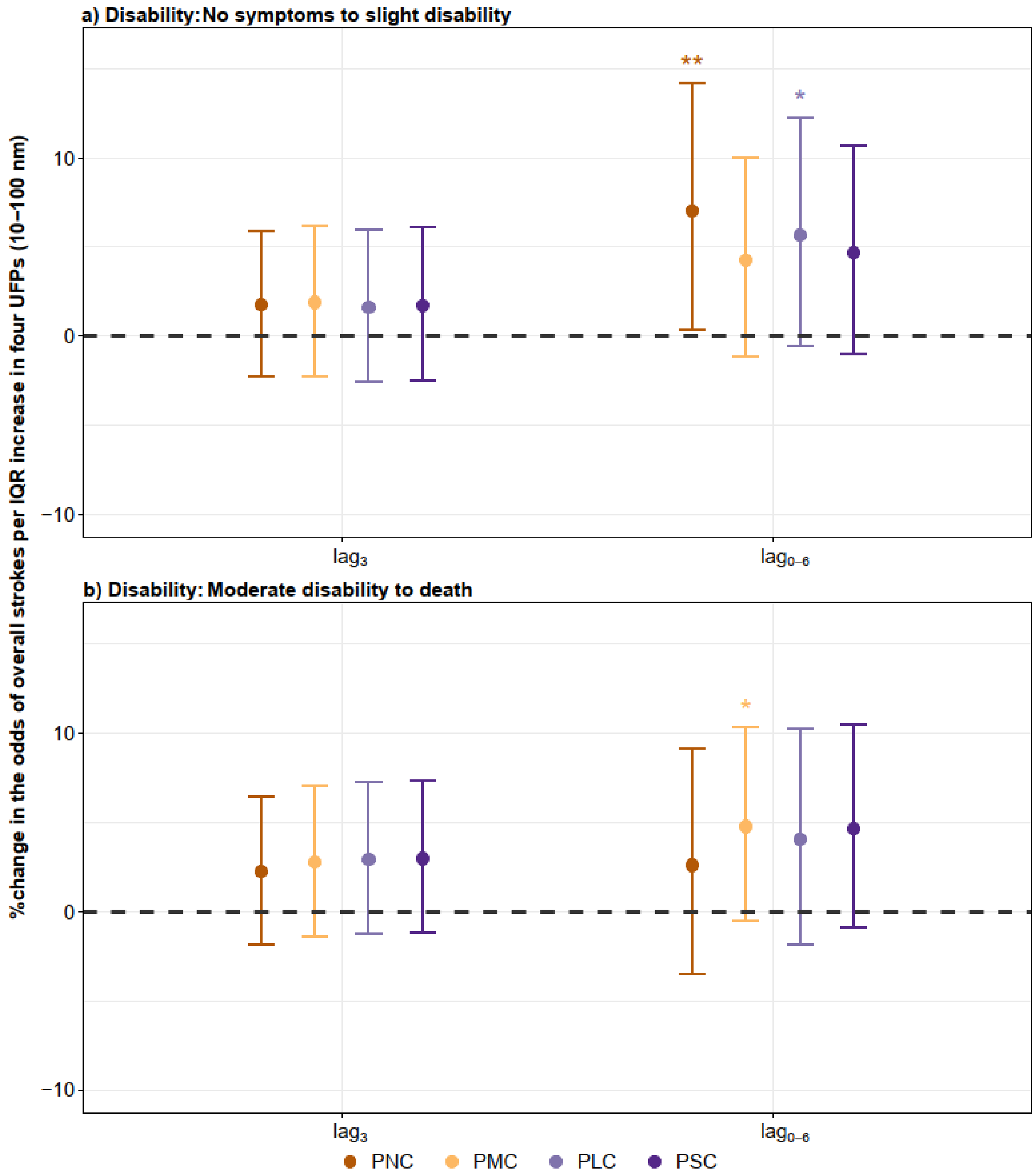
sFig 4. Percent change (95%CI) in the odds of three stroke subtypes per interquartile range (IQR) increase in single 3 day and moving average 0-6 days of UFP metrics (10-30 nm). Note: * *P*<0.10.



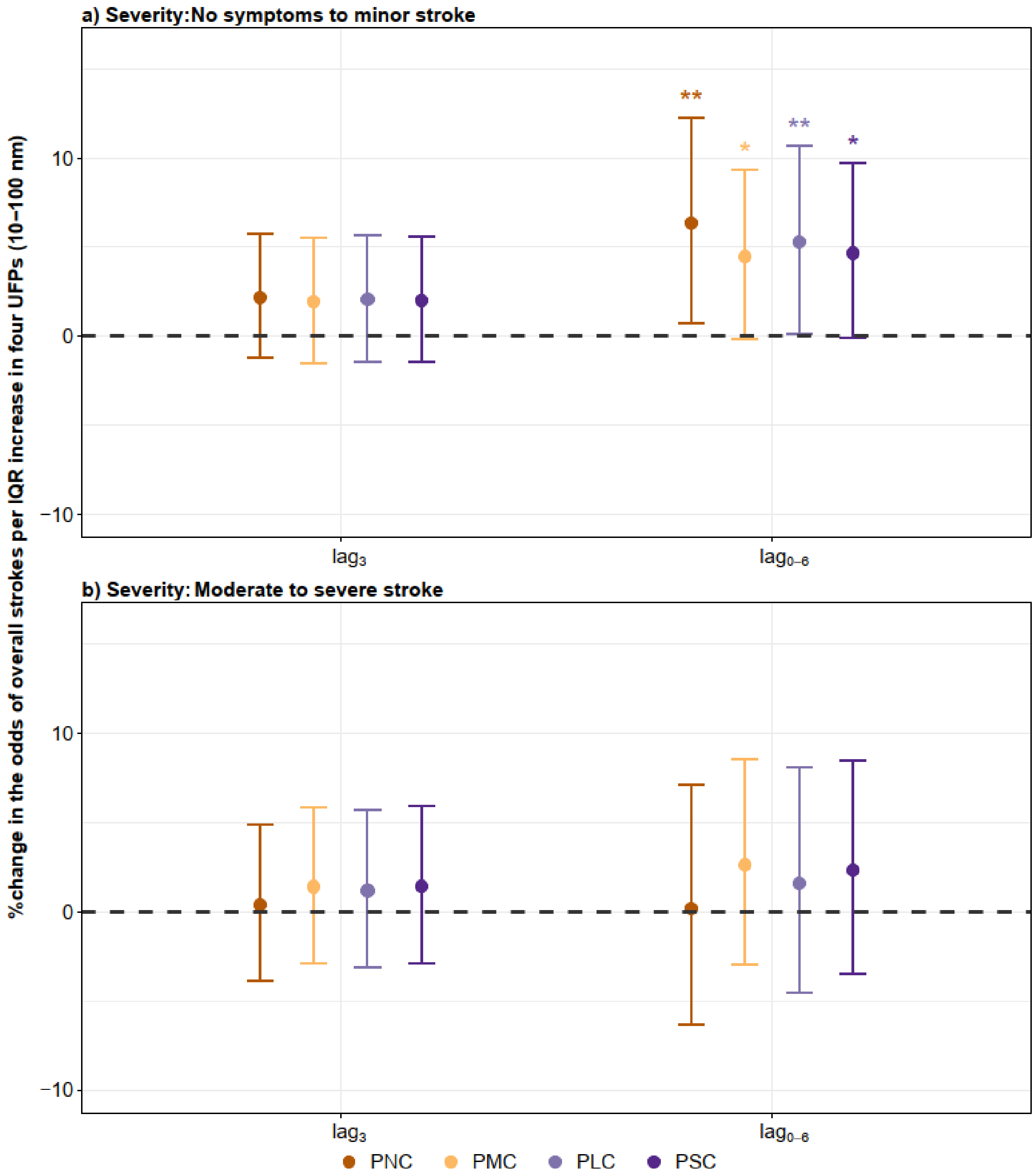
sFig 5. Percent change (95%CI) in the odds of three stroke subtypes per interquartile range (IQR) increase in single 3 day and moving average 0-6 days of UFP metrics (30-100 nm). Note: * *P*<0.10; ** *P*<0.05.



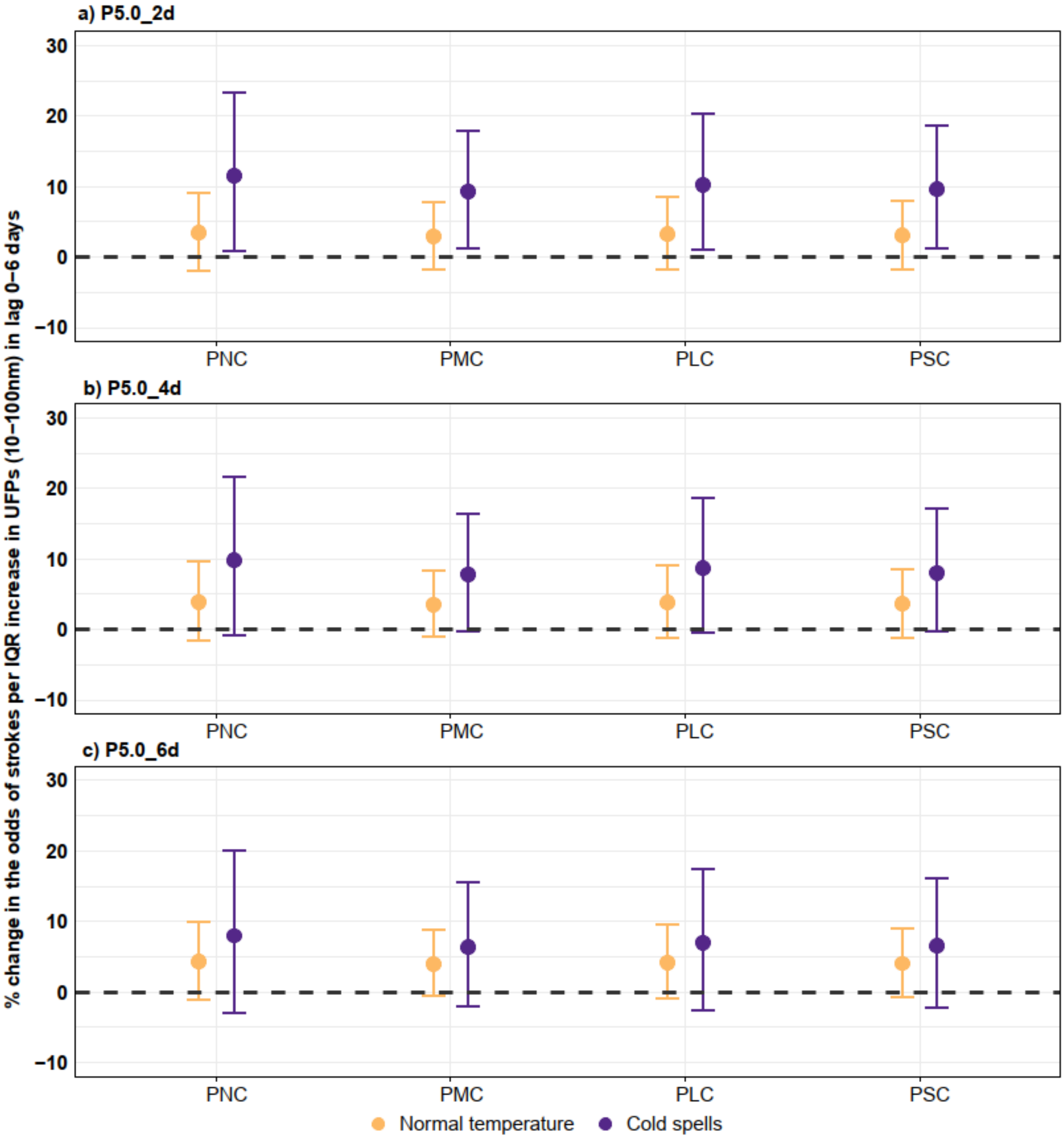
sFig 6. Percent change (95%CI) in the odds of three stroke subtypes per interquartile range (IQR) increase in single 3 day and moving average 0-6 days of UFP metrics (100-500 nm). Note: * *P*<0.10.



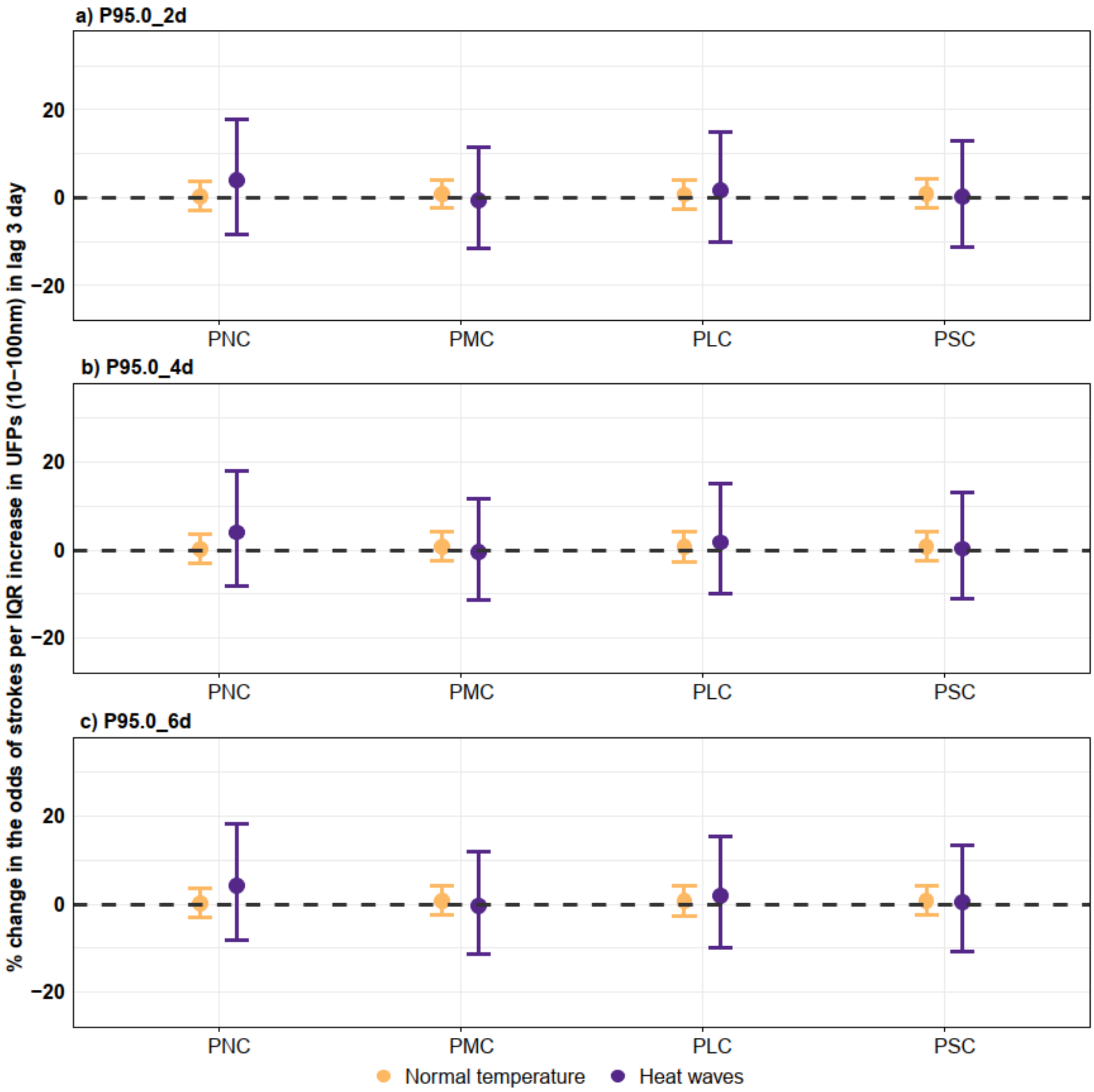
sFig 7. Stratified percent change (95%CI) in the odds of overall stroke events by two stroke-related disability levels per IQR increase in single 3 day and moving average 0-6 days of UFP metrics (10-100 nm). Note: * *P*<0.10; ** *P*<0.05.



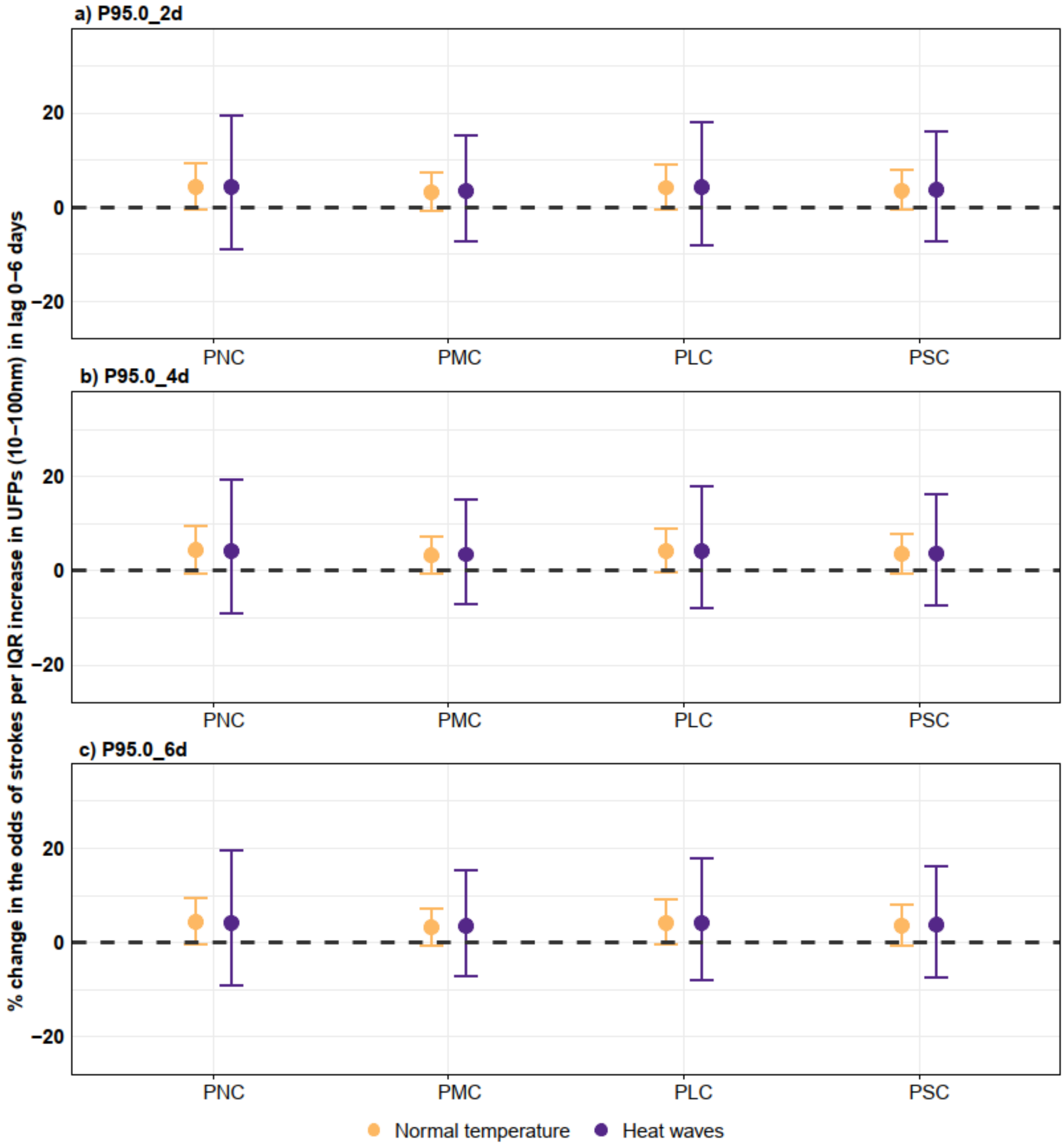
sFig 8. Stratified percent change (95%CI) in the odds of overall stroke events by two stroke severity levels per IQR increase in single 3 day and moving average 0-6 days of UFP metrics (10-100 nm). Note: * *P*<0.10; ** *P*<0.05.



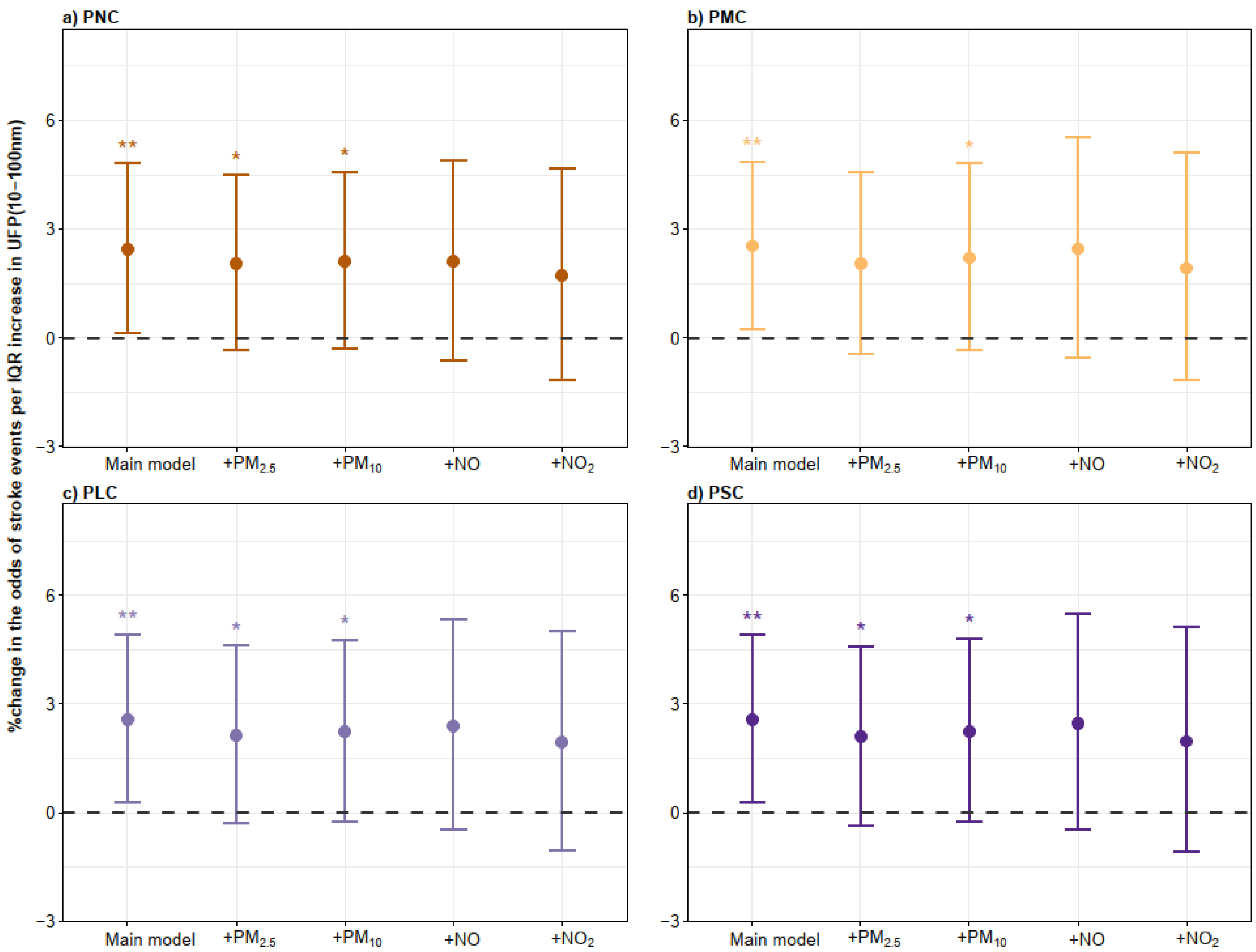
sFig 9. Effect modification by the consecutive a) 2 days, b) 4 days and c) 6 days of P5.0 thresholds of cold spells on the association between lag 0-6 days of UFP metrics (10-100 nm) and the percent changes in the odds of overall stroke events.



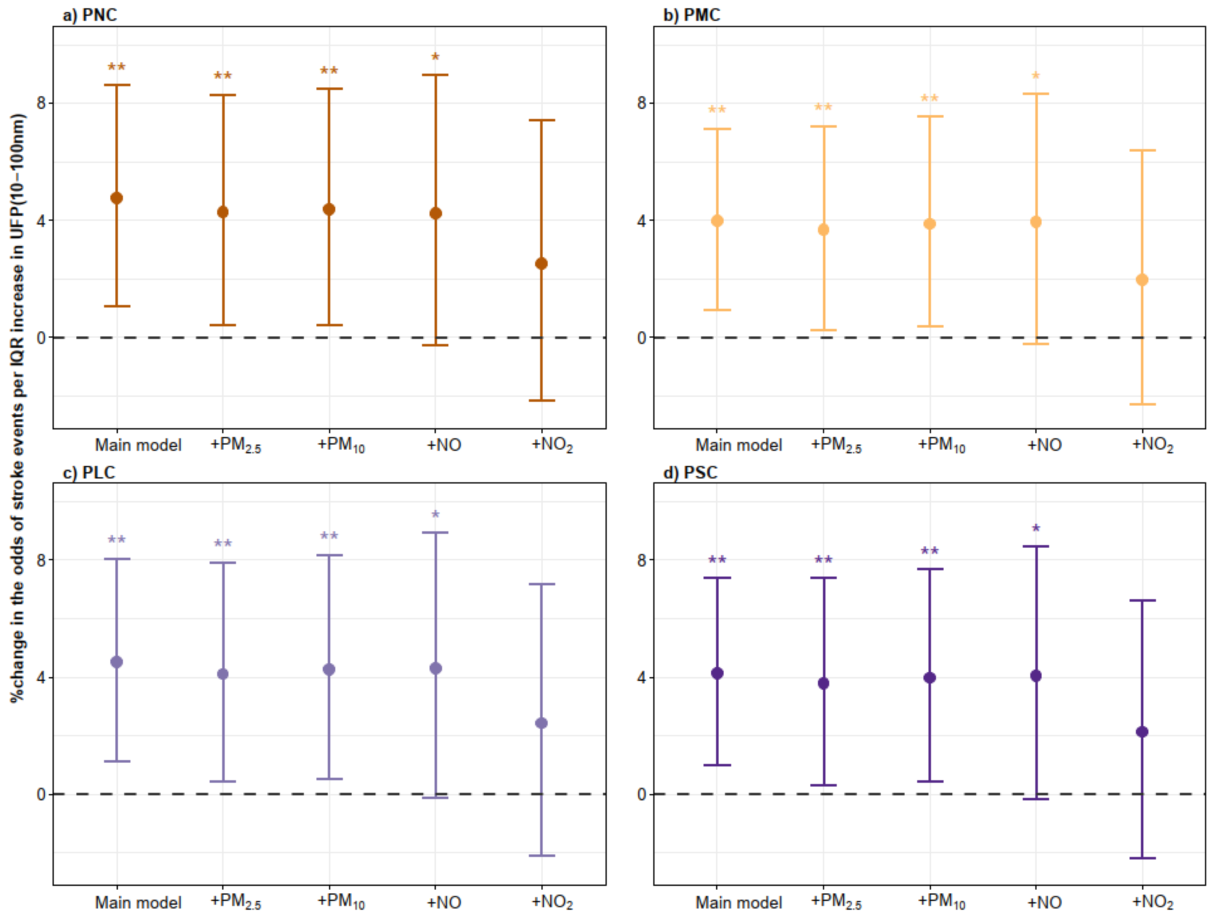
sFig 10. Effect modification by the consecutive a) 2 days, b) 4 days and c) 6 days of 95.0 thresholds of heat waves on the association between lag 3 days of UFP metrics (10-100 nm) and the percent changes in the odds of overall stroke events.



sFig 11. Effect modification by the consecutive a) 2 days, b) 4 days and c) 6 days of P95.0 thresholds of heat waves on the association between lag 0-6 days of UFP metrics (10-100 nm) and the percent changes in the odds of overall stroke ev

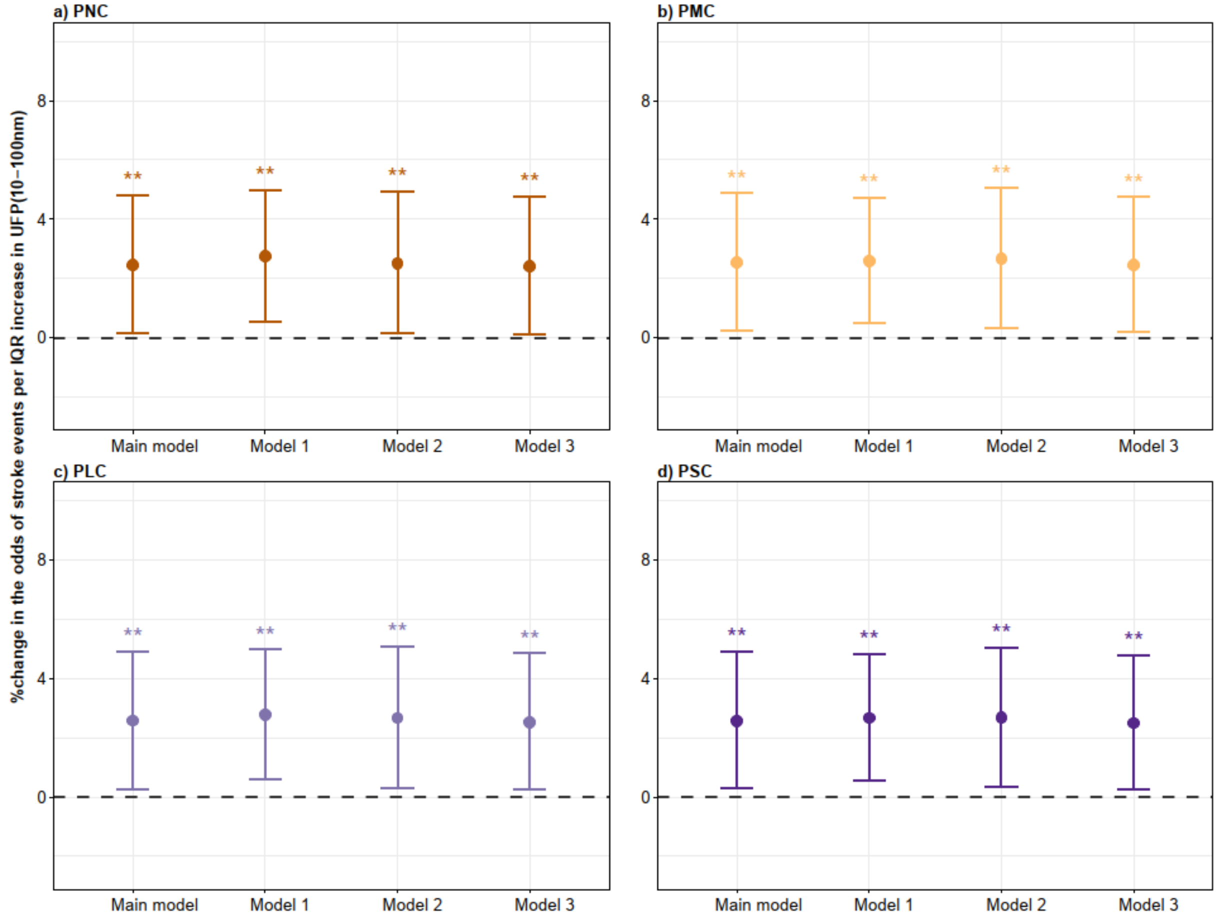


sFig 12. Percent change (95%CI) in the odds of overall stroke events per IQR increase in lag 3 day of four UFP metrics (10-100 nm). Note: the x-axis shows the results of the main model and the two-pollutants model: adjusted for ambient pollutants with a Spearman correlation coefficient less than 0.7. * P<0.10; ** P<0.05.

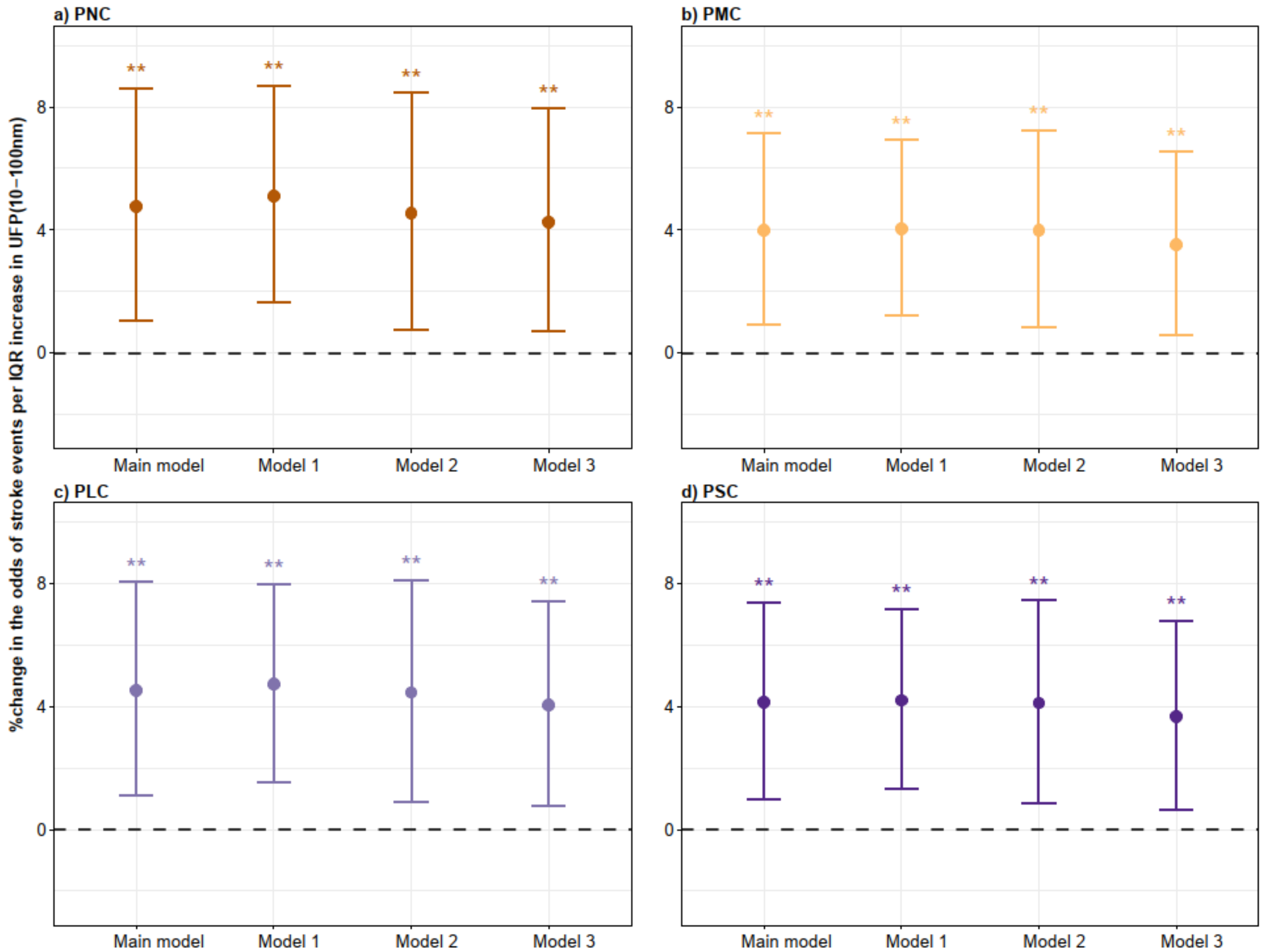


sFig 13. Percent change (95%CI) in the odds of overall stroke events per IQR increase in lag 0-6 days of four UFP metrics (10-100 nm). Note: the x-axis shows the results of the main model and the two-pollutants model: adjusted for ambient pollutants with a Spearman correlation coefficient less than 0.7. * P<0.10; ** P<0.05

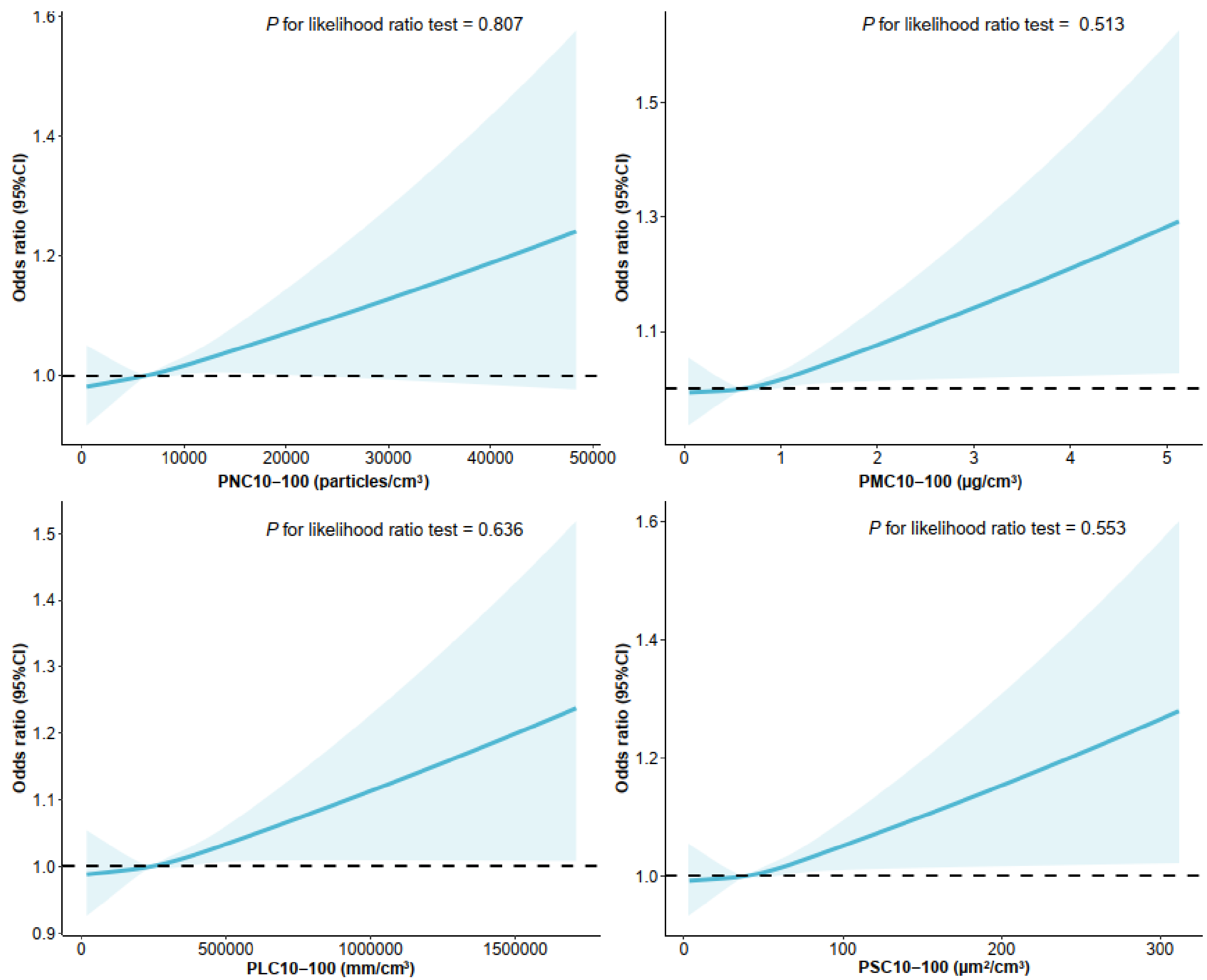
36



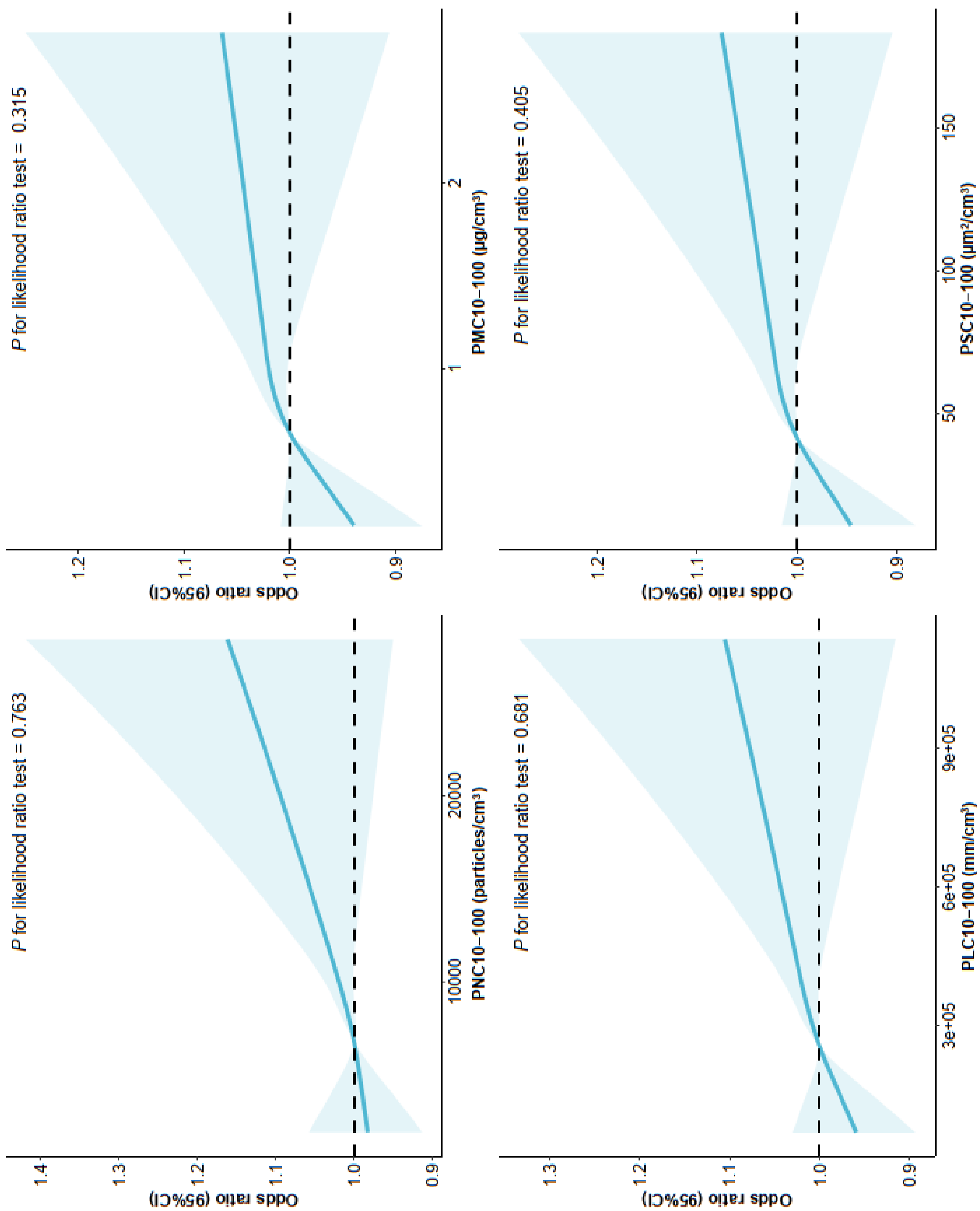
sFig 14. Percent change (95%CI) in the odds of overall stroke events per IQR increase in lag 3 day of four UFP metrics (10-100 nm) in three models. Note: the x-axis shows the results of the main model and different sensitivity analyses: Model 1 represents results estimated using 1-neighbouring week values imputed data; Model 2 represents results specifically excluded patients after the beginning of the COVID-19 pandemic; Model 3 represents results specially adjusted for the warm and cold temperatures calculated based on the annual levels of ambient air temperature. * P<0.10; ** P<0.05.



sFig 15. Percent change (95%CI) in the odds of overall stroke events per IQR increase in lag 0-6 day of four UFP metrics (10-100 nm) in three models. Note: the x-axis shows the results of the main model and different sensitivity analyses: Model 1 represents results estimated using 1-neighbouring week values imputed data; Model 2 represents results specifically excluded patients after the begin of COVID-19 pandemic; Model 3 represents results specially adjusted for the warm and cold temperatures calculated based on the annual levels of ambient air temperature. * P<0.10; ** P<0.05.



sFig 16. The exposure-response relationship between lag 3 days of four UFP metrics (10-100 nm) and the odds ratios (95%CI) of overall stroke events using the restricted curved spline. Note: the likelihood test was used, with a *P* value < 0.05 indicating potential non-linearity.



sFig 17. The exposure-response relationship between lag 0-6 days of four UFP metrics (10-100 nm) and the odds ratios (95%CI) of overall stroke events using the restricted curved spline. Note: the likelihood test was used, with a *P* value < 0.05 indicating potential non-linearity.

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May your life set sail, heading towards great ideals — 愿人生扬帆起航，平波致远

List of all scientific publications to date

Publication included in this cumulative dissertation:

1. **Liao M**, Zhang S, Wolf K, Bolte G, Laxy M, Schwettmann L, Peters A, Schneider A, Kraus U. Long-term associations between ambient air pollution and self-perceived health status: Results from the population-based KORA-Fit study. *Int J Hyg Environ Health*. 2025 Mar:264:114513. doi: 10.1016/j.ijheh.2024.114513.
2. **Liao M**, Zhang S, He C, Breitner S, Cyrys J, Naumann M, Brandt L, Traidl-Hoffmann C, Hammel G, Peters A, Ertl M, Schneider A. Air pollution and stroke: short-term exposure's varying effects on stroke subtypes. *Ecotoxicology and Environmental Safety*. 2025 June:298:118296. doi: 10.1016/j.ecoenv.2025.118296.

Submitted manuscript included in this cumulative dissertation:

1. **Liao M**, Zhang S, Schwarz M, He C, Breitner S, Cyrys J, Naumann M, Braadt L, Traidl-Hoffmann C, Hammel G, Peters A, Ertl M, Schneider A. Short-term effects of ultrafine particles on stroke events: An assessment using four different exposure metrics. (under revision)

Conference presentations:

1. **Liao M**, Zhang S, He C, Breitner S, Cyrys J, Naumann M, Brandt L, Traidl-Hoffmann C, Hammel G, Peters A, Ertl M, Schneider A. Short-term effects of ultrafine particles on stroke events: An assessment using four different exposure metrics. Oral presentation in the *International Society for Environmental Epidemiology (ISEE) Conference*; 2025 August 17-20; Atlanta, United States.
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3. **Liao M**, Zhang S, Wolf K, Bolte G, Laxy M, Schwettmann L, Peters A, Schneider A, Kraus U. Long-term associations between ambient air pollution and self-perceived health status: Results from the population-based KORA-Fit study. Oral presentation in the *International Society for Environmental Epidemiology Young (ISEE-Young) Conference*; 2024 June 5-7; Rennes, France.

Other publications:

1. **Liao M**, Mu Y, Su X, Zheng L, Zhang S, Chen H, Xu S, Ma J, Ouyang R, Li W, Cheng C, Cai J, Chen Y, Wang C, Zeng F. Association between Branched-Chain Amino Acid Intake and Physical Function among Chinese Community-Dwelling Elderly Residents. ***Nutrients***. 2022 Oct 18;14(20):4367. doi: 10.3390/nu14204367.

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