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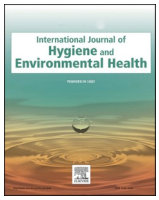

Long-term exposure to traffic-related air pollution and stroke: A systematic review and meta-analysis

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ABSTRACT

Background: Stroke remains the second cause of death worldwide. The mechanisms underlying the adverse association of exposure to traffic-related air pollution (TRAP) with overall cardiovascular disease may also apply to stroke. Our objective was to systematically evaluate the epidemiological evidence regarding the associations of long-term exposure to TRAP with stroke.

Methods: PubMed and LUDOK electronic databases were searched systematically for observational epidemiological studies from 1980 through 2019 on long-term exposure to TRAP and stroke with an update in January 2022. TRAP was defined according to a comprehensive protocol based on pollutant and exposure assessment methods or proximity metrics. Study selection, data extraction, risk of bias (RoB) and confidence assessments were conducted according to standardized protocols. We performed meta-analyses using random effects models; sensitivity analyses were assessed by geographic area, RoB, fatality, traffic specificity and new studies.

Results: Nineteen studies were included. The meta-analytic relative risks (and 95% confidence intervals) were: 1.03 (0.98–1.09) per 1 μg/m^3 EC, 1.09 (0.96–1.23) per 10 μg/m^3 PM_{10}, 1.08 (0.89–1.32) per 5 μg/m^3 $PM_{2.5}$, 0.98 (0.92; 1.05) per 10 μg/m^3 NO_2 and 0.99 (0.94; 1.04) per 20 μg/m^3 NO_x with little to moderate heterogeneity based on 6, 5, 4, 7 and 8 studies, respectively. The confidence assessments regarding the quality of the body of evidence and separately regarding the presence of an association of TRAP with stroke considering all available evidence were rated low and moderate, respectively.

Conclusion: The available literature provides low to moderate evidence for an association of TRAP with stroke.

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1. Introduction

According to the World Stroke Organization Fact Sheet 2022, stroke remains the second leading cause of death and the third leading cause of death and disability combined (Feigin et al., 2022). Stroke is defined by broad and inclusive clinical and tissue criteria and encompasses central nervous system infarction, ischemic stroke, and intracerebral, cerebral and subarachnoid haemorrhage (Sacco et al., 2013).

Important risk factors for stroke morbidity and mortality include health states (e.g., high blood pressure, diabetes), behaviours that contribute to those states (e,g., smoking, features of the diet), and socioeconomic conditions that shape the former, and other factors influencing risk. Among these other factors are environmental pollutants. Air pollution, in particular, is of interest because of its adverse association with several cardiovascular outcomes (Franklin et al., 2015; Kaufman et al., 2020; Newman et al., 2020). Also, it is estimated that 6% of global mortality attributable to air pollution is traffic-related (McDuffie et al., 2021).

Abbreviations

TRAP	Traffic Related Air Pollution
PM	Particulate Matter
EC	Elemental Carbon
NOx	Nitrogen oxides
NO_2	Nitrogen Dioxide
CO_2	Carbon Dioxide
UFP	Ultrafine Particles
GRADE	Grading of Recommendations Assessment, Development and Evaluation
OHAT	Office of Health Assessment and Translation

A major and growing source of air pollution is traffic. Traffic-related air pollution (TRAP) is a complex mixture and refers to ambient air pollution resulting from the use of motor vehicles including heavy-duty and light-duty vehicles, buses, passenger cars, and motorcycles. Motor vehicles are important contributors of pollutants from combustion including nitrogen dioxide (NO_2) and oxides (NO_x), elemental carbon (EC), particulate matter (i.e. PM_{10} and $PM_{2.5}$) and ultrafine particles (UFPs). These pollutants can be directly emitted through the vehicle exhaust (i.e. tailpipe emissions) or through resuspension of road dust, mechanical wear of brakes and tires, and abrasion of road surfaces (i.e. non-tailpipe emissions) (Health Effects Institute, 2018).

TRAP exposure is associated with mechanisms such as cerebrovascular dysfunction that appear to be manifested through several pathways that can increase stroke risk, including inflammation and oxidative stress, endothelial dysfunction, blood pressure, atherosclerosis, procoagulant changes, increased thrombogenicity, loss of vascular flexibility and alterations in autonomic nervous system balance (Landrigan et al., 2018; Miller, 2020).

TRAP continues to be of public health interest; notably, TRAP has been the target of successful interventions, thus also making it a concern to policy makers and motor vehicle manufacturers. Advances in systematic review methods for environmental health (Whaley et al., 2020; Woodruff and Sutton, 2014) provide more specific guidance for the conduct of literature reviews, thereby enhancing consistency and transparency. Using this refined guidance, we aimed to systematically evaluate the epidemiological evidence on long-term exposure to TRAP in relation to stroke in adults. Results were quantitatively combined to evaluate the magnitude of the association. We also assessed the quality of the evidence base and the level of confidence in the presence of an association between TRAP and stroke.

2. Methods

This study is part of an extensive systematic review (conducted by the Health Effects Institute (HEI)) on the effects of TRAP on key health outcomes, involving a Panel of 13 experts in epidemiology, exposure assessment, and statistics (Boogaard et al., 2022; Health Effects Institute, 2022). The methods were based on standards set by the Cochrane Collaboration (Higgins et al., 2019), the NIEHS Office of Health Assessment and Translation handbook (OHAT, 2019), the systematic reviews conducted as part of the World Health Organization Air Quality Guidelines (WHO AQG) (Chen and Hoek, 2020; Huangfu and Atkinson, 2020; WHO, 2021) and the newly published COSTER recommendations for the conduct of systematic reviews in toxicology and environmental health research (Whaley et al., 2020). This review complies with the Preferred Reporting Items for Systematic reviews and Meta-Analyses (PRISMA) (PRISMA, 2021) as well as the Meta-analysis of Observational Studies in Epidemiology (MOOSE) guidelines (Stroup et al., 2000). The review protocol was published in 2019 and registered in Prospero (Health Effects Institute, 2019). Outcomes, including ischemic and haemorrhagic stroke, were selected based on evidence on causality (causal or likely causal) according to the latest determination for general air pollution (Health Canada, 2016; The International Agency for Research on Cancer, 2016; U.S. Environmental Protection Agency, 2019; 2016). Where applicable, included studies were approved by the respective institutional review boards.

2.1. Search strategy

The PubMed and the Swiss Literature Database and Services on Health Effects of Ambient Air Pollution (LUDOK) electronic databases (https://www.swisstph.ch/de/projects/ludok/) were searched comprehensively for studies matching the PECOS question (Higgins et al., 2019) by independent reviewers (M.K.J., R.K., H.B. and A.P.) (Supplementary Table 1). The HEI review covered papers published from January 01, 1980, to July 31, 2019. We repeated the stroke component of the search by including papers published through January 06, 2022. Keywords included TRAP or proximity measures and stroke as described in the main HEI report (Health Effects Institute, 2022). We also considered references in other reviews of health effects of air pollution including the HEI 2010 report (Health Effects Institute, 2018) and in the individual bibliographic databases maintained by members of the Panel. Contact to authors or identification of unpublished studies or data was not attempted.

2.2. Eligibility criteria

Eligible studies met the following criteria: (1) original epidemiological study with individual-level data and adopting a cohort, case-cohort, case-control, cross-sectional, or intervention design; (2) reported on the general population, of all ages, with no geographical restrictions; (3) assessed long-term exposure (months to years) to a specific traffic pollutant or used proximity metrics of TRAP (distance to or density of traffic); (4) defined the outcome as total and/or type-specific stroke from ICD-9-CM 430–434 and 436 and ICD-10 I60–I69; (5) estimated the association between a continuously or categorically modelled/parameterized exposure and fatal and/or non-fatal stroke morbidity and mortality (odds ratio (OR), hazard ratio (HR), incident relative risk (IRR) and relative risk (RR)); and (6) published or accepted for publication in a peer-reviewed journal and written in English. Limitation to English publications was chosen as the state of the art of publication in the area of research.

The exclusion criteria eliminated studies reporting on: (1) exposure in occupational settings or exclusively indoor settings; (2) exposure for combined-source air pollution and not specific to traffic; (3) short-term (minutes to months) or self-reported exposures to TRAP; (4) only ecological or area-level analyses; (5) only unadjusted results and clear

evidence of an analytical error; and (6) methodological papers, or studies focusing on gene-environment-interaction.

2.3. Exposure framework

A novel framework to determine exposure to TRAP was developed to ensure that the included studies were informative about health effects specific to TRAP. The framework combined three aspects of TRAP measurement: (1) exposure metric (including pollutants, distance and density metrics) (Supplementary Table 2); (2) spatial scales of the pollution surface and participant addresses, to exploit/ensure TRAP contrasts (i.e., at local and neighbourhood scale); and (3) exposure assessment methods including appropriate models or monitoring (Supplementary Table 3).

The review included NO_2, EC, CO and other pollutants in which traffic is usually the main source; results pertaining to $PM_{2.5}$ and PM_{10} were also included except if exclusively based on surface monitoring. As none of these pollutants are universally TRAP, a traffic specificity indicator based on stricter criteria for the three elements of the general framework was developed.

2.4. Study selection and data extraction

DistillerSR, a web–based, systematic review software program (DistillerSR, 2021), was used for screening of studies to ensure standardization of process. Two reviewers independently screened titles and abstracts of the search results. The studies were classified by health outcomes and full-text articles and supplements were retrieved for those that provisionally met the inclusion criteria. Next, a full-text screening was conducted to confirm that effect estimates were reported for stroke and that the exposure framework criteria described above were met (Health Effects Institute, 2022). Disagreements were resolved through discussion or consultation with the Panel.

Data extraction was performed by MK, RK and PH as well as by a number of students to extract key information for meta-analysis such as study name, details on the study population, study design, method of exposure assessment, pollutants, method of outcome assessment, outcomes, statistical analysis, effect estimates with pollutant increments and 95% confidence intervals. After completion of data extraction, all data from *DistillerSR* were exported to Excel spreadsheets, quality controlled and processed into figures and summary tables.

2.5. Meta-analysis

To quantify the overall association with stroke, meta-analyses were performed in cases where three or more studies reported associations of a given exposure with stroke. The full list of inclusion and exclusion criteria for meta-analysis are found in the Supplement Table 4. Standardized results (Department for Environment, Food and Rural Affairs, 2014) were quantitatively combined using random effects models using restricted maximum likelihood to estimate the between studies' variance (Veroniki et al., 2016). Effect estimates from single pollutant models were selected for the meta-analysis, because we considered the associations of single pollutants to represent the associations of the TRAP mixture. Random effects models were chosen a priori because of the expected differences in populations and pollution mixtures. Statistical heterogeneity was assessed using Cochran's Q I^2, and τ^2 (tau-squared). Tau^2 is also presented in the form of a 95% prediction interval around the mean effect of the random effects meta-analysis (Borenstein et al., 2017). We reported RR in the review as a non-specific term to indicate any of the ratio measures. Thus HR, IRR and OR were included in the same meta-analyses on the assumption that when the RR is close to the null and the stroke prevalence in the population is less than 10%, all these measures approximate the risk ratio (Anderson et al., 2013; Davies et al., 1998; Khreis et al., 2017). Also, we expressed summary RR estimates over the increments of pollutant concentration used by the ESCAPE study, to reflect a realistic range of exposure contrasts in most studies (Beelen et al., 2014, 2015).

In primary meta-analyses, we used estimates for the combined endpoint of non-fatal and fatal stroke, if available; if separate estimates were generated for non-fatal and fatal stroke, we used the former, as non-fatal stroke cases numbers were/are typically higher. Sensitivity analyses were conducted for every pollutant and stratified by at least one of the following: region, risk of bias (RoB) assessment domain, smoking, study design and fatality. Additional estimates for $PM_{2.5}$ and NO_2 from the updated search in January 2022 were included as sensitivity-analyses. We conducted these analyses using R (version 3.6.0), and the libraries "metafor" (v.2.4–0),"meta", (v. 4.16–2), "forestplot" (v.1.10.1),"ggplot" (v. 3.3.3) for the analyses and plots.

2.6. Overall assessment of the evidence

We rated the overall evidence using complementary assessments of (1) its quality and (2) the degree to which it supported the presence of an adverse association between TRAP exposure and stroke.

For the rating of quality, we adapted the GRADE (Grading of Recommendations Assessment, Development and Evaluation) assessment of confidence in the quality of the body of meta-analysed evidence, using the Office of Health Assessment and Translation (OHAT) method as a guide (OHAT, 2019). We grouped studies by key design features, with each given an initial confidence rating. This initial confidence rating could then be downgraded corresponding to factors that decreased confidence in the quality of the body of evidence (high RoB, unexplained inconsistency, imprecision, and publication bias) or upgraded corresponding to factors that increased confidence in the body of evidence (monotonic exposure-response, consistency across populations, and consideration of residual confounding) (Supplementary Fig. 1). For RoB assessment, we used a modified tool developed for the RoB assessment in the WHO AQG review (WHO, 2020). The modified OHAT assessment in the quality of the body of evidence was rated high, moderate, low or very low.

Because the GRADE assessment focused on the quality of the body of evidence rather than on the presence of an association, and because it was heavily geared towards the studies entering a meta-analysis, the Panel conducted a narrative assessment to evaluate the level of confidence in the presence of an association of TRAP with stroke, considering both meta-analysed studies and all other studies not included in the meta-analysis. (Supplementary Table 5). For the comprehensive narrative assessment, we evaluated the number, size, and location of the evidence base; study design, study population and representativeness, the strength and nature of the association, quality of the studies. consistency of the findings. Monotonic exposure-response function, and other considerations. The comprehensive narrative assessment of the confidence in the presence of an association, based on the complete study base, was rated as high, moderate, low or very low.

Subsequently the findings from the modified OHAT assessment and the comprehensive narrative assessment were combined into an overall confidence assessment (Supplementary Table 6).

3. Results

3.1. Study selection

The initial search of the larger HEI review (Boogaard et al., 2022; Health Effects Institute, 2022), that included several key health outcomes, identified 13660 unique articles of which 206 were identified as cardiometabolic studies (i.e.: ischemic heart disease, stroke, diabetes mellitus and coronary events) after title and abstract screening. During full-text screening, 149 studies were excluded for the following reasons: study design (N = 18), exposure assessment (i.e. nationwide study with no or insufficient area-specific adjustments or spatial scale too crude for either the pollution surface or the health data) (N = 85), health outcome

(N = 34) and other (N = 12). Of the 57 remaining studies for the selected cardiometabolic outcomes – out of which 37 included estimates on stroke – 19 were included in the current review (Fig. 1, Table 1). A list of the 18 excluded articles and the reasons behind their exclusion can be found in Supplementary Table 7.

3.2. Study characteristics

Most of the 19 studies had starting dates in the 1990s (Table 1). The majority of the studies were located in Europe (N = 12). The 14 cohort studies (Alexeeff et al., 2018; Andersen et al., 2012; Atkinson et al., 2013; Carey et al., 2016; Dirgawati et al., 2019; Gan et al., 2012; Hoffmann et al., 2015; Katsoulis et al., 2014; Korek et al., 2015; Kulick et al., 2018; Sørensen et al., 2014; Stafoggia et al., 2014; Stockfelt et al., 2017) had sample sizes between 3287 and 819,370 participants and mean follow up times between 3 and 21 years. One study was a multi-cohort analysis of 11 European cohorts that were analysed within the harmonized framework of the ESCAPE study (Stafoggia et al., 2014). Data sources for stroke ascertainment varied, including self-reported events, medical care records, hospital admissions, disease and death registries, insurance claims or health administrative databases (Table 1).

The three case-control studies (Johnson et al., 2013; Oudin et al., 2009, 2011) had sample sizes between 6302 and 556,912 with recruitment times of two to four years. Oudin et al. (2009) included incident ischemic stroke cases (fatal and non-fatal). For the second analysis, Oudin et al. (2011) obtained personal covariates data from questionnaires sent to surviving cases of ischemic stroke (fatal and non-fatal), thus included prevalent cases only. Oudin et al. (2011, 2009) used national and local stroke registries to identify cases; controls who shared the same date of birth as the cases and were residing in Scania, were sampled from the national statistics databases. The third case-control study included incident all-stroke cases (fatal and non-fatal) (Johnson et al., 2013). Johnson et al. (2013) identified first-time stroke cases from hospital emergency administrative data and sampled controls from persons visiting the same emergency administrative data for minor trauma.

The three cross-sectional studies (Lazarevic et al., 2015; Pindus et al., 2016; Qin et al., 2015) included 905 to 26,991 participants. The study populations included survivors of non-fatal all-stroke events only. Stroke ascertainment relied primarily on self-reports.

The majority of studies assigned TRAP exposures based on land-use regression or dispersion models. Most studies estimated exposures at

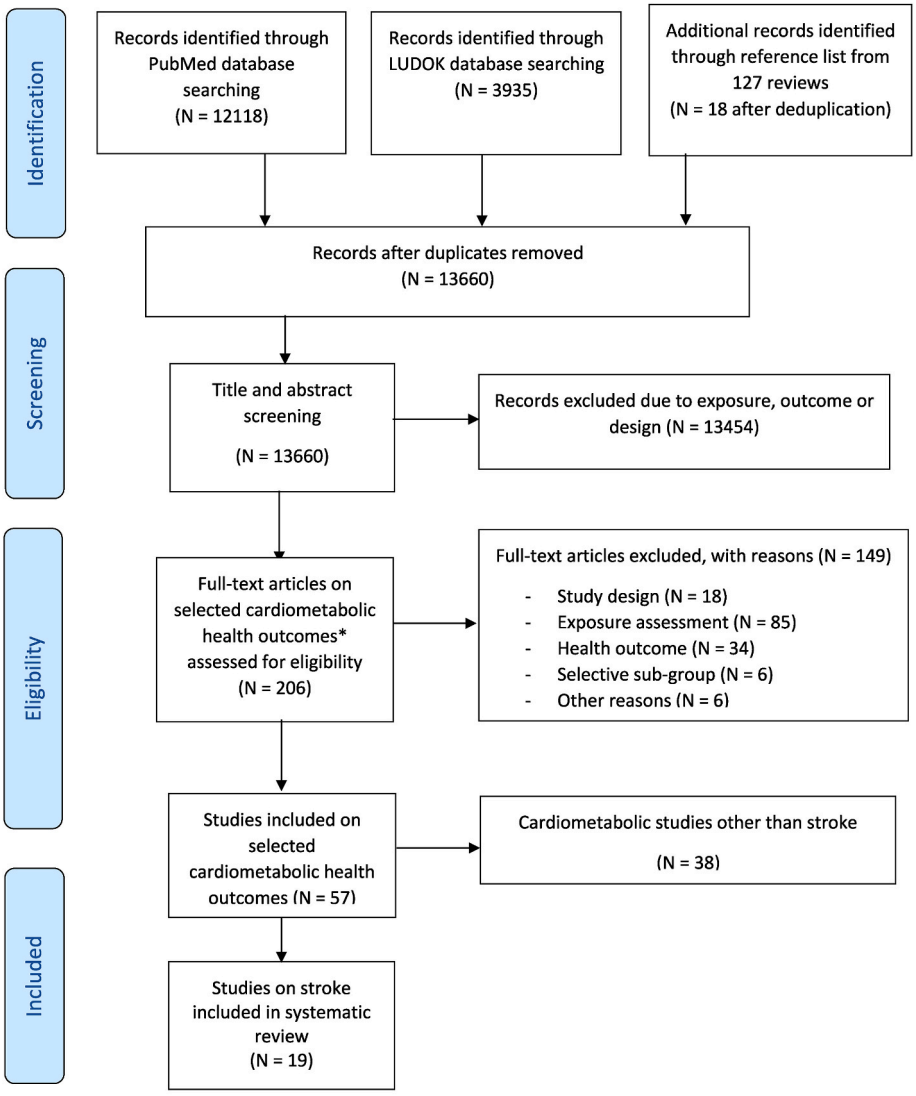

Fig. 1. Study Selection Flow Chart
*Selected outcomes: ischemic heart disease, stroke, diabetes mellitus and coronary events.

Table 1
Key study characteristics of articles included in the systematic review for stroke-pollutants.

Reference	Study Name	Location	Study period	Study design and Sample size	Exposure Assessment	Age at baseline	Sex	Stroke outcome ascertain-ment	Confounder adjustment	Results (estimate[a], 95% CI, increment)
Alexeeff et al., 2018	KPNC Oakland	Oakland, California, United States	2010–2015	Cohort	Surface monitoring	Age Range: 18–65+	Males and Females	Medical record and death certificates	Age, sex, race, BMI, smoking, co-morbidities[b], use of medication, neighbourhood socioeconomic status (nSES)	**Fatal and non-fatal all stroke (HR)** BC[c] 0.96 (0.85, 1.08) per 0.17 μg/m^3 NO 0.98 (0.87, 1.11) per 3.8 ppb NO_2[c] 0.97 (0.85, 1.11) per 3.8 ppb
				41869						**Fatal all stroke (HR)** BC 0.92 (0.58, 1.45) per 0.17 μg/m^3 NO 1.13 (0.86, 1.49) per 3.8 ppb NO_2 1.38 (0.93, 2.06) per 3.8 ppb
Andersen et al., 2012	DDCH	Copenhagen and Aarhus, Denmark	1993–2006	Cohort	Dispersion/ Chemical Transport Model (CTM)	Age Range: 50-65	Males and Females	Hospital admission and death certificates	Age, sex, smoking, environmental tobacco smoke (ETS), BMI, education, sports, alcohol, fruit/veg intake, fat intake, co-morbidities[b]	**Non-fatal all stroke (HR)** NO_2 1.05 (0.99, 1.11) per 6.2 μg/m^3 Density 1.02 (0.99, 1.04) per 1700 vehicle-km/ day Distance 1.09 (0.94, 1.26) <50 vs. >50 m
				52215	And density measures					**Fatal all stroke (HR)** NO_2 1.22 (0.99, 1.49) per 7.5 μg/m^3 Density 0.99 (0.91, 1.09) per 1700 vehicle-km/ day Distance 1.17 (0.70, 1.98) <50 vs. >50 m
Atkinson et al., 2013	CPRD London	England	2003–2007	Cohort	Dispersion	Age Range: 40-89	Males and Females	Primary care records, hospital admissions and death certificates	Age, sex, smoking, BMI, co-morbidities[b], index of multiple deprivation (IMD)	**Fatal and non-fatal all stroke (HR)** PM_{10}[c] 1.00 (0.93, 1.06) per 3.0 μg/m^3
				819370	and CTM					
Carey et al., 2016	CPRD London	London, United Kingdom	2005–2011	Cohort	Dispersion /CTM And density and distance measures	Age Range: 40-79	Males and Females	Primary care records, hospital admissions and death certificates	Age, sex, smoking, BMI, IMD, night-time noise[d]	**Fatal and non-fatal all stroke (HR)** NO_2[c] 0.88 (0.82, 0.95) per 10 μg/m^3 NO_x[c] 0.90 (0.85, 0.96) per 20 μg/m^3 $PM_{2.5\ traffic}$ 0.88 (0.81,

(*continued on next page*)

Table 1 (*continued*)

Reference	Study Name	Location	Study period	Study design and Sample size	Exposure Assessment	Age at baseline	Sex	Stroke outcome ascertain-ment	Confounder adjustment	Results (estimate[a], 95% CI, increment)
				207047						0.97) per 1 μg/m^3 Density 1.00 (0.88, 1.15) >100000 heavy vehicle-km/year vs. none Density 1.02 (0.96, 1.11) <100000 heavy vehicle-km/year vs. none Distance 0.98 (0.86, 1.12) <100 vs. >250 m Distance 1.02 (0.95, 1.10) 100–250 vs. >250 m
Dirgawati et al., 2019	HIMS	Perth, Australia	1996–2012	Cohort	Land-Use Regression Model (LUR)	Age: ≥65	Males only	Hospital records and death register	Age, smoking, education, BMI, co-morbidities[b], physical inactivity, high-fat diet, alcohol	**Fatal and non-fatal all stroke (HR)** $PM_{2.5\ abs}$[c] 0.86 (0.71, 1.03) per 1 1e-5/m NO_2[c] 0.96 (0.85, 1.08) per 10 μg/m^3 NO_x[c] 1.00 (0.95, 1.04) per 10 μg/m^3 $PM_{2.5\ mass}$[c] 1.01 (0.84, 1.21) per 5 μg/m^3
				10126						**Fatal all stroke (HR)** $PM_{2.5\ abs}$ 0.70 (0.47, 1.03) per 1 1e-5/m NO_2 0.93 (0.72, 1.19) per 10 μg/m^3 NO_x 0.97 (0.88, 1.07) per 10 μg/m^3 $PM_{2.5\ mass}$ 0.71 (0.49, 1.02) per 5 μg/m^3
Gan et al., 2012	Vancouver Administrative	Vancouver, British Columbia, Canada	1999–2002	Cohort	LUR	Age Range: 45-85	Males and Females	Death registration database	Age, sex, co-morbidities[b], nSES, noise[d]	**Fatal all stroke (RR)** $PM_{2.5\ abs}$[c] 1.04 (1.00, 1.09) per 0.97 1e-5/m
				445868						
Hoffmann et al., 2015	HNR	Ruhr Areas, Germany	2000–2012	Cohort	LUR and density measures	Age Range: 45-74	Males and Females	Patient records and death certificates	Marital status, education, employment, smoking, co-morbidities[b], BMI, physical activity, alcohol, noise[d]	**Fatal and non-fatal all stroke (HR)** $PM_{2.5\ abs}$ 1.57 (0.86, 2.86) per 0.98 1e-5/m $PM_{10\ mass}$ 2.38 (1.06, 5.35) per 6.32 μg/m^3
				4222						$PM_{2.5\ mass}$ 2.90 (1.18,

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Table 1 (*continued*)

Reference	Study Name	Location	Study period	Study design and Sample size	Exposure Assessment	Age at baseline	Sex	Stroke outcome ascertain-ment	Confounder adjustment	Results (estimate[a], 95% CI, increment)
										7.12) per 3.51 μg/m^3 $PM_{coarse\ mass}$ 1.79 (0.72, 4.46) per 5.26 μg/m^3 Density 1.06 (0.69, 1.64) 4302 vehicle-km/day
Johnson et al., 2013	Edmonton Stroke	Edmonton, Alberta, Canada	2007–2009	Case-control 42419	LUR	Mean Age cases: 69.7 controls: 39.8	Males and Females	Cases: Emergency administrative data Controls: hospitalization data	Age, sex, contextual SES, smoking, BMI	**Fatal and non-fatal all stroke (OR)** NO_2[c] 1.01 (0.94, 1.08) per 5 ppb
Katsoulis et al., 2014	EPIC Athens	Athens, Greece	1994–2011	Cohort 2752	LUR	Age Range: 21-82	Males and Females	Self-reported data and death certificates	Sex, age, smoking, BMI, education, physical activity, total energy intake, co-morbidities[b], alcohol	**Fatal and non-fatal all stroke (HR)** NO_2[c] 0.98 (0.71, 1.34) per 10 μg/m^3 $PM_{10\ mass}$[c] 1.17 (0.60, 2.26) per 10 μg/m^3
Korek et al., 2015	SDPP, SIXTY, SALT, SNAC-K	Stockholm, Sweden	1992–2011	Cohort 20070	Dispersion and CTM	Age Range: 35-56	Males and Females	Hospital registry and death registry	Gender, education, smoking, socio-economic index	**Fatal and non-fatal all stroke (HR)** NO_x[c] 1.20 (0.64, 2.29) per 20 μg/m^3 $PM_{10\ traffic}$ 1.20 (0.89, 1.63) per 10 μg/m^3
Kulick et al., 2018	NOMAS	Manhattan, United States	1993–2016	Cohort 3287	Distance measures	Median Age: 69	Males and Females	Self-reported, medical records, death certificates	Age, sex, race, education, insurance status, year of enrolment, nSES, smoking, alcohol, physical activity, BMI, co-morbidities[b]	**Fatal and non-fatal ischemic stroke (HR)** Distance 1.42 (1.01, 2.02) <100 vs. >400 m Distance 1.14 (0.81, 1.60) 100–200 vs. >400 m Distance 1.08 (0.80, 1.45) 200–400 vs. >400 m
Lazarevic et al., 2015	ALSWH	Australia	2006–2011	Cross sectional 26991	LUR and distance measures	3 age cohort (younger, middle aged, older)	Females only	Self-reported	Age, BMI, smoking, alcohol, physical activity, fruit/veg, degree of residential urbanisation, mean temperature, marital status, education, self-assessed financial resources	**Non-fatal (prevalence) all stroke (RR)** NO_2 0.83 (0.58, 1.19) per 3.3 ppb Distance 1.01 (0.90, 1.14) 1 km
Oudin et al., 2009	Scania Stroke	Scania, Sweden	2001–2005	Case-control	Dispersion and CTM	Birth year: 1923–1965	Males and Females	Cases: hospital admissions from national stroke register	Sex, marital status, country of birth, smoking, co-morbidities[b]	**Fatal and non-fatal (prevalence) ischemic stroke (OR)**

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Table 1 (*continued*)

Reference	Study Name	Location	Study period	Study design and Sample size	Exposure Assessment	Age at baseline	Sex	Stroke outcome ascertain-ment	Confounder adjustment	Results (estimate[a], 95% CI, increment)
				556912						NO_x 0.87 (0.73, 1.03) 30–60 vs. <10 μg/m^3 NO_x 0.97 (0.90, 1.05) 10–20 vs. <10 μg/m^3 NO_x 0.95 (0.86, 1.06) 20–30 vs. <10 μg/m^3
Oudin et al., 2011	Scania Stroke	Scania, Sweden	2001–2006	Case-control 6302	Dispersion and CTM	Birth year: 1923–1965	Males and Females	Cases: hospital admissions from national stroke register	Sex, marital status, country of birth, smoking, co-morbidities[b], physical inactivity	**Non-fatal (prevalence) ischemic stroke (OR)** NO_x[c] 0.93 (0.82, 1.95) 10 μg/m^3
Pindus et al., 2016	RHINE Tartu	Tartu, Estonia	2011–2012	Cross sectional 905	Dispersion and CTM	Mean age: 50	Males and Females	Self-reported	Gender, age, BMI, education, smoking, ETS	**Non-fatal (prevalence) all stroke (OR)** $PM_{10\ traffic}$ 1.21 (0.53, 2.77) per 2.2 μg/m^3
Qin et al., 2015	33 CCHS	Shenyang and Anshan and Jinzhou, China	2009–2009	Cross sectional 14646: normal weight, 1435: obese, 8764: overweight	Surface monitoring	Age Range: 18-74	Males and Females	Self-reported	Age, sex, race, education, income, smoking, drinking, exercise, diet, sugar, family co-morbidities[b], study district	**Non-fatal (per weight category; prevalence) all stroke (OR)** NO_2 1.01 (0.84, 1.22) per 9 μg/m^3 NO_2 1.15 (0.64, 2.07) per 9 μg/m^3 NO_2 1.22 (0.98, 1.51) per 9 μg/m^3
Sørensen et al., 2014	DDCH	Copenhagen and Aarhus, Denmark	1993–2009	Cohort 51569	Dispersion and CTM	Age Range: 50-64	Males and Females	National registries, medical records	Sex, length of school attendance, nSES, smoking, fruit/veg, alcohol, coffee, physical activity, BMI, calendar year, noise[d]	**Fatal and non-fatal all stroke (IRR)** NO_2[c] 1.08 (1.01, 1.16) per 10 μg/m^3 NO_x[c] 1.02 (0.98, 1.07) per 20 μg/m^3 **Fatal all stroke (IRR)** NO_2 1.47 (1.21, 1.80) per 10 μg/m^3 NO_x 1.17 (1.05, 1.31) per 20 μg/m^3
Stafoggia et al., 2014	ESCAPE	Multiple cities, Multiple countries	1992–2010	Cohort 99446	LUR and density measures	Mean Age range: 44–74	Males and Females	Self-reported, medical record, death certificates	Sex, calendar year, marital status, education, occupation, smoking, area level SES, noise[d]	**Fatal and non-fatal all stroke (HR)** $PM_{2.5\ abs}$[c] 1.08 (0.83, 1.41) per 1 1e-5/m NO_2[c] 0.99 (0.89, 1.11) per 10 μg/m^3 NO_x[c] 0.98 (0.89, 1.07) per 20 μg/m^3 $PM_{10\ mass}$[c] 1.11 (0.90,

(*continued on next page*)

Table 1 (*continued*)

Reference	Study Name	Location	Study period	Study design and Sample size	Exposure Assessment	Age at baseline	Sex	Stroke outcome ascertain-ment	Confounder adjustment	Results (estimate[a], 95% CI, increment)
										1.36) per 10 μg/m^3 $PM_{2.5\ mass}$[c] 1.19 (0.88, 1.62) per 5 μg/m^3 PM_{coarse} 1.02 (0.90, 1.16) per 5 μg/m^3 Density 1.02 (0.95, 1.10) 4000 vehicle-km/day
Stockfelt et al., 2017	GOT-MONICA	Gothenburg, Sweden	1990–2011	Cohort 4500	Dispersion and CTM	Age Range: 25-64	Males and Females	Death register, self-reported, hospital discharge register	Age, smoking, marital status, physical activity, calendar year, mean income of area, sex, enrolment year	**Fatal and non-fatal all stroke (HR)** BC[c] 1.25 (0.89, 1.76) per 1 μg/m^3 NO_x[c] 1.04 (0.90, 1.20) per 20 μg/m^3 $PM_{10\ nontailpipe}$ 1.10 (0.97, 1.24) per 1.48 μg/m^3 $PM_{10\ exhaust}$ 1.07 (0.92, 1.23) per 0.29 μg/m^3 $PM_{10\ traffic}$ 1.09 (0.97, 1.23) per 1.77 μg/m^3 $PM_{10\ mass}$[c] 1.48 (0.88, 2.49) per 10 μg/m^3 $PM_{2.5\ mass}$[c] 1.50 (0.90, 2.51) per 5 μg/m^3
Stockfelt et al., 2017	PPS	Gothenburg, Sweden	1990–2011	Cohort 5850	Dispersion and CTM	Age Range: 64-75	Males only	Death register, self-reported, hospital discharge register discharge register	Age, smoking, marital status, physical activity, calendar year, mean income of area, occupational class	**Fatal and non-fatal all stroke (HR)** BC[c] 1.09 (0.90, 1.31) per 1 μg/m^3 NO_x[c] 1.04 (0.97, 1.12) per 20 μg/m^3 $PM_{10\ nontailpipe}$ 1.03 (0.96, 1.10) per 1.41 μg/m^3 $PM_{10\ exhaust}$ 1.04 (0.97, 1.28) per 0.29 μg/m^3 $PM_{10\ traffic}$ 1.03 (0.97, 1.10) per 1.77 μg/m^3 $PM_{10\ mass}$[c] 1.08 (0.80, 1.45) per 10 μg/m^3 $PM_{2.5\ mass}$[c] 1.06 (0.78, 1.44) per 5 μg/m^3

[a] Effect estimates can be ORs, RRs, HRs or IRRs, depending on the analysis; Estimates of incidence of stroke are reported unless otherwise mentioned.
[b] Co-morbidities include at least one of the following: diabetes, hypertension, COPD, hyperlipidemia, medications for the latter.

[c] Included in the meta-analysis; see Supplementary Table 4 for inclusion and exclusion criteria.
[d] Also adjusted for noise in sensitivity analyses but estimates are not shown in Table 1.

participants' residential locations, while others (Andersen et al., 2012; Atkinson et al., 2013; Carey et al., 2016) estimated exposures at participants' high-resolution postal codes. NO_x was the most frequently investigated pollutant (N = 9), followed by NO_2, EC, PM_{10} and $PM_{2.5}$. Annual mean exposures varied considerably across the studies: from 8 to 39 μg/m^3 for NO_2 and 5–31 μg/m^3 for $PM_{2.5}$. Six studies analysed proximity metrics such as distance to or density of traffic. Four studies evaluated the influence of concurrent noise exposure as a source of confounding or effect modification on the association between TRAP and stroke (Gan et al., 2012; Hoffmann et al., 2015; Sørensen et al., 2014; Stafoggia et al., 2014).

3.3. Meta-analyses and sensitivity analyses

A sufficient number of studies (≥3) were available to perform meta-analyses on NO_2, NO_x, EC, PM_{10}, and $PM_{2.5}$ in association with stroke (Fig. 2). The summary effect estimates indicated positive associations for EC, PM_{10}, and $PM_{2.5}$ with confidence intervals overlapping unity, and null associations for NO_2 or NO_x.

3.4. NO_2

For NO_2 the summary effect estimate was 0.98 (95% CI: 0.92; 1.05) per 10-μg/m^3 increment (N = 7) (Fig. 3A). The individual associations were moderately heterogeneous (I^2 = 64%) and varied in direction. Three studies estimated associations of NO_2 with fatal stroke separately, and with fatal and non-fatal stroke combined. In two of those studies, the Danish DDCH (Hoffmann et al., 2015) and the KPNC Oakland (Alexeeff et al., 2018), the estimated effects on fatal stroke were large and positive (RR = 1.47 and 1.57 respectively), in contrast to the smaller estimated effects on the combined stroke (RR = 1.08 and 0.96 respectively) (Supplementary Fig. 2). The two studies investigating a positive and negative exposure-response function were the DDCH (Andersen et al., 2012; Sørensen et al., 2014) and HIMS (Dirgawati et al., 2019), a highly selected population of older men, respectively.

3.5. NO_x

The meta-analysis of NO_x and stroke (Fig. 3B) yielded a summary estimate of 0.99 (95% CI: 0.94; 1.04) per 20-μg/m^3 increment (N = 8). The heterogeneity of the associations was moderate (I^2 = 50%): the most heavily weighted association was inverse, from the CPRD London study (Carey et al., 2016), while the others were closer to null and/or estimated with less precision. One study was a case-control study analysing prevalent cases (Oudin et al., 2011). Regarding sensitivity analyses, no clear picture emerged from a comparison of associations with fatal stroke and associations with fatal and non-fatal stroke combined. However, similar to the findings for NO_2, the positive association of NO_x with fatal events in the DDCH study (Sørensen et al., 2014) was stronger than any of the individual associations with combined stroke (Supplementary Fig. 2). There was mixed evidence regarding the exposure-response function (e.g., negative slope in Dirgawati et al., 2019, and positive for categories of NO_x in Oudin et al., 2011).

3.6. EC

For EC the summary RR was 1.03 (95% CI: 0.98; 1.09) per 1-μg/m^3 increment. (N = 6) (Fig. 4A). Heterogeneity was low; four studies

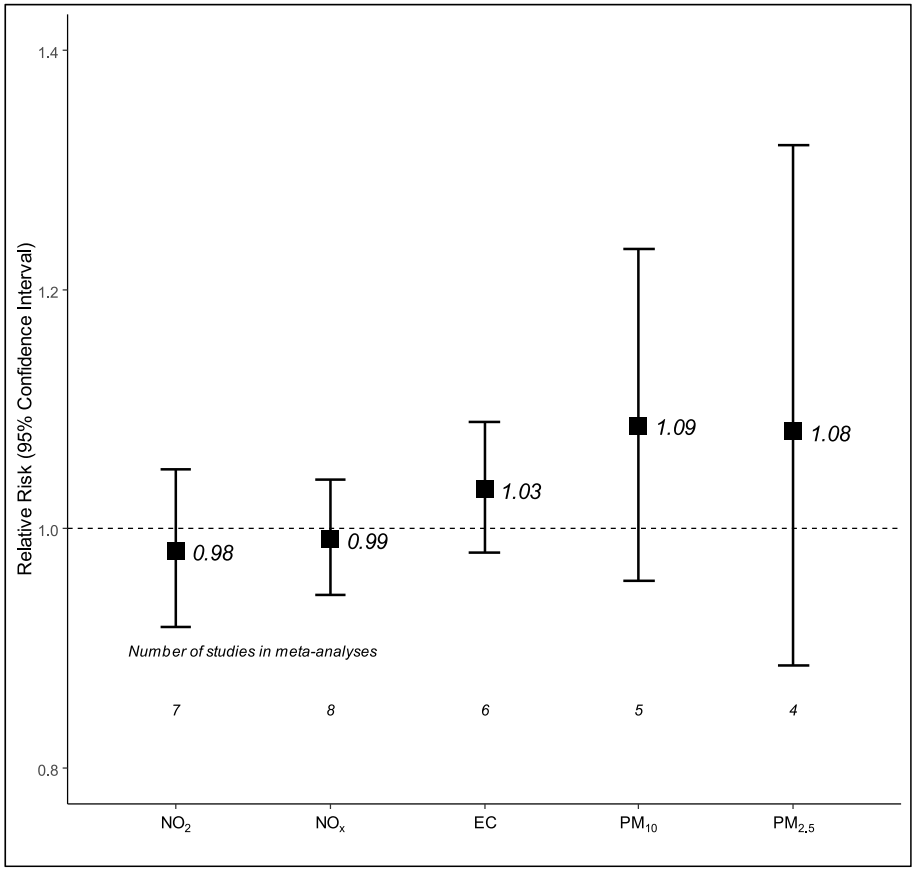

Fig. 2. Meta-analysis of associations between TRAP and incidence of stroke.

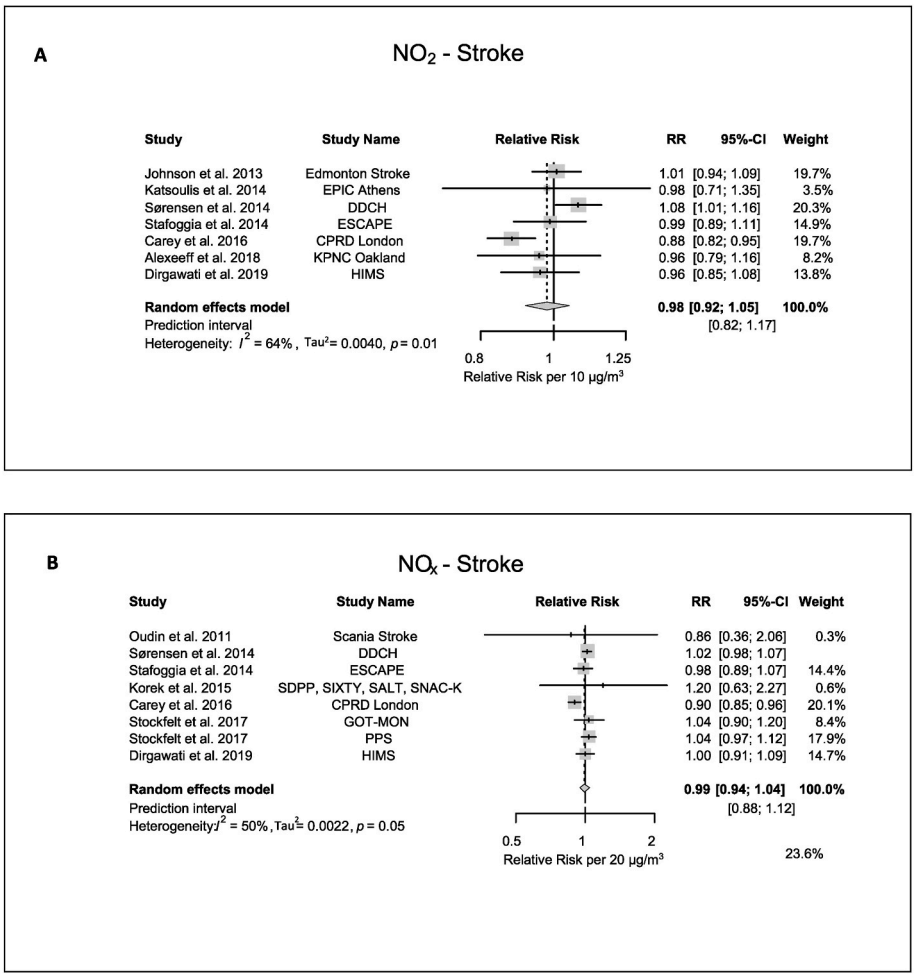

Fig. 3. Associations between gaseous traffic-related pollutants (NO_2 (A) and NO_x (B)) and incidence of stroke: Meta-analysis.

reported positive, though mostly imprecise, associations. The meta-analysis was dominated by the positive estimate from the Vancouver Administrative cohort study (Gan et al., 2012) with 84% of the overall weight. The Vancouver study had limited individual-level information on potential important sources of confounding, such as smoking, and adjusted for health conditions (i.e., diabetes mellitus, chronic obstructive pulmonary disease, and hypertensive heart disease) as proxies of behavior-related stroke risk factors. When we excluded the estimate from this study from meta-analysis, the summary estimated effect was virtually the same (RR = 1.02) although substantially less precise (95% CI: 0.86; 1.20) (Supplementary Fig. 2). Similar to NO_2 and NO_x, Dirgawati et al. (2019) reported a negative slope for incidence of non-fatal strokes over the study's relatively low concentration range of 0.1–1.5 10^5 m^{-1} for PM absorbance. On the other hand, Stafoggia et al. (2014) reported that a linear exposure-response function was a good approximation of the EC-stroke association in most of the 11 European cohorts in the ESCAPE study.

3.7. PM_{10}

The meta-analysis of PM_{10} exposure (Fig. 4B) and combined fatal and non-fatal stroke incidence (N = 5) yielded a summary RR of 1.09 (95% CI: 0.96–1.23) with no heterogeneity; the RRs from all but one study exceeded unity (Atkinson et al., 2013). A linear and monotonically increasing exposure-response function over the 5–26 µg/m^3 range was reported in the GOT-MONICA cohort (Stockfelt et al., 2017), and Stafoggia et al. (2014) reported a roughly linear shape of the exposure-response function for most of the 11 cohorts in ESCAPE.

3.8. $PM_{2.5}$

The effect estimates included in the meta-analysis of $PM_{2.5}$ (Fig. 4C) and stroke all exceeded unity, with no heterogeneity, and the summary RR was 1.08 (95% CI: 0.89–1.32) per 5-µg/m^3 increment (N = 4). Upon exclusion of the Australian study (Dirgawati et al., 2019) in analyses by geographic region, the estimate for the remaining Western European studies was substantially higher (1.17, 95% CI: 0.82; 1.67) (Supplementary Fig. 2). Both the ESCAPE study (Stafoggia et al., 2014) and the GOT-MONICA cohort (Stockfelt et al., 2017) reported a linear and monotonically increasing exposure-response function.

3.9. Results of studies not entering meta-analyses

There were too few cross-sectional studies on stroke prevalence to conduct meta-analysis. Briefly, a positive association was observed in the very small Estonian study of traffic specific PM_{10} and stroke (Pindus et al., 2016). The large 33CCHS study in China observed positive associations between NO_2 and stroke, specifically in overweight and obese subjects (Qin et al., 2015). The cross-sectional medium-sized study on Australian women showed an inverse, though imprecise association between NO_2 and stroke (Pindus et al., 2016).

A small number of studies examined other pollutants (PM_{coarse}, $PM_{traffic\text{-}specific}$), with the findings generally supportive of an association of TRAP with stroke (Table 1). Specifically, the ESCAPE study reported risks for PM_{coarse} of 1.02 (95% CI: 0.90, 1.16) per 5 µg/m^3 increment (Stafoggia et al., 2014) and the Heinz Nixdorf Recall (HNR) also reported an elevated estimate for PM_{coarse} (Hoffmann et al., 2015).

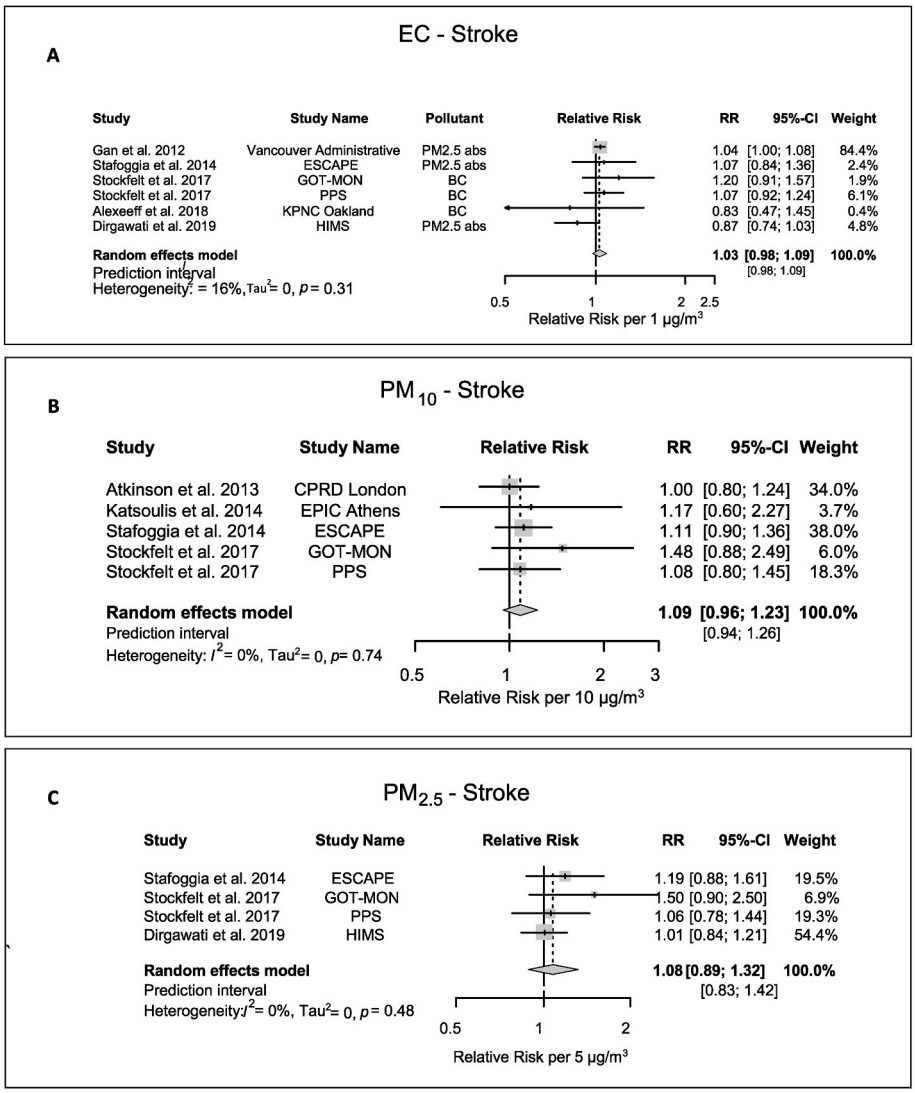

Fig. 4. Associations between particulate pollutants (EC (A), PM_{10} (B) and $PM_{2.5}$ (C)) and incidence of stroke: Meta-analysis.

Overall, four studies investigated indicators of $PM_{traffic\text{-}specific}$, all of which found positive associations with stroke (Korek et al., 2015; Pindus et al., 2016; Stockfelt et al., 2017) except one in the inverse direction (Atkinson et al., 2013).

Altogether six studies investigated associations with proximity to roads and/or traffic density, one of which was the ESCAPE multi-cohort (Stafoggia et al., 2014). Two studies reported positive associations (Andersen et al., 2012; Kulick et al., 2018), one of them with a monotonic exposure-response relationship. (Table 1). The four studies examining the effect of noise adjustment for one or more traffic-related pollutants showed stable or even larger effect estimates (Andersen et al., 2012; Gan et al., 2012; Hoffmann et al., 2015; Sørensen et al., 2014).

3.10. Overall assessment

The modified OHAT formal confidence assessment was conducted for the studies and exposure-stroke pairs for which a meta-analysis was conducted (N = 12). As the studies included in the meta-analysis were cohort or case-control, the initial rating for confidence was moderate for all exposure-stroke pairs (Table 2).

Among the factors that may reduce confidence, RoB was ranked low or moderate in most exposure-stroke pairs and domains (Supplementary Table 8). Two studies ranked as high RoB, due to lack of confounder control for smoking and BMI and/or selection bias (Gan et al., 2012; Johnson et al., 2013). No downgrade was applied because results were robust in sensitivity analyses excluding high RoB studies. We downgraded the level of confidence for all pollutants except NO_x for imprecision because although all meta-analyses met the sample size criterion and had sufficient power, the confidence intervals were wide, clearly including unity. Given the small number of studies in each exposure-stroke pair, an analysis of publication bias was infeasible; this did not lead to a downgrade.

We upgraded the evidence for associations of PM_{10} and $PM_{2.5}$ with stroke following the demonstration of a monotonic exposure-response function in the GOT-MONICA cohort (Stockfelt et al., 2017) and the results of a subset analyses in the 11 studies of the ESCAPE analysis. In this study, evaluations of individual cohort exposure-response functions with spline models (Stafoggia et al., 2014) showed that the estimates did not clearly deviate from linearity. Several mechanisms of potential bias towards the null were identified in the analysis including potential for over-adjustment or inclusion of potential intermediates (Alexeeff et al., 2018; Andersen et al., 2012; Atkinson et al., 2013; Carey et al., 2016). However, an upgrade was not considered appropriate, based on the small number of studies with potential underestimation of the association. Similarly, too few studies were available to evaluate consistency across geographic regions, populations or study period and therefore no upgrade was performed.

The final rating of the quality of the evidence base of the individual

Table 2
Confidence rating for TRAP and stroke incidence.

Pollutant	High ++++ Moderate +++ Low ++ Very low +		Factors decreasing confidence "0" if no concern; if serious concern to downgrade confidence				Factors increasing confidence "0" if not present; "+" if sufficient to upgrade confidence			**Final confidence rating**
	Study design	**Initial confidence rating** (# studies)	Risk of Bias	Unexplained inconsistency	Imprecision	Publication bias	Monotonic exposure-response	Consideration of residual confounding	Consistency across populations	
NO_2	Cohort, CC	+++ (N = 7)	0	0	–	0	0	0	0	++ (Low)
	Rationale	Cohort and case-control initially rated as moderate.	Not sensitive to exclusion of two studies with high RoB.	Moderate heterogeneity (I^2 = 64%).	Sample size met but confidence interval wide and includes unity.	No formal evaluation possible.	No evidence of plausible shape of ERF.	Confounding in both directions possible.	Too few studies across different populations.	
NO_X	Cohort, CC	+++ (N = 8)	0	0	0	0	0	0	0	+++ (Moderate)
	Rationale	Cohort and case-control initially rated as moderate.	No studies rated high RoB.	Moderate heterogeneity (I^2 = 50%), at least partly explained by one influential study with concerns.	Sample size met and confidence interval includes unity, but precise.	No formal evaluation possible.	No evidence of plausible shape of ERF.	Confounding in both directions possible.	Too few studies across different populations.	
EC	Cohort	+++ (N = 6)	0	0	–	0	0	0	0	++ (Low)
	Rationale	Cohort design initially rated as moderate.	Not sensitive to exclusion of one study with high RoB.	Low heterogeneity (I^2 = 16%).	Sample size met but confidence interval wide and includes unity.	No formal evaluation possible.	One multi-cohort study with monotonic ERF (Stafoggia et al., 2014).	Confounding in both directions possible.	Too few studies across different populations.	
PM_{10}	Cohort	+++ (N = 5)	0	0	–	0	+	0	0	+++ (Moderate)
	Rationale	Cohort design initially rated as moderate.	No studies rated high RoB.	Low heterogeneity (I^2 = 0).	Sample size met but confidence interval wide and includes unity.	No formal evaluation possible.	Two studies with either monotonic ERF or stable estimates in subset analysis (Stafoggia et al., 2014; Stockfelt et al., 2017).	Confounding in both directions possible.	Too few studies across different populations.	
$PM_{2.5}$	Cohort	+++ (N = 4)	0	0	–	0	+	0	0	+++ (Moderate)
	Rationale	Cohort design initially rated as moderate.	No studies rated high RoB.	Low heterogeneity (I^2 = 0).	Sample size met but confidence interval wide and includes unity.	No formal evaluation possible	Two studies with either monotonic ERF or stable estimates in subset analysis (Stafoggia et al., 2014; Stockfelt et al., 2017).	Confounding in both directions possible.	Too few studies across different populations.	

pollutant-stroke pairs was low for NO_2 and EC, and moderate for NO_x, $PM_{2.5}$ and PM_{10}, with EC, $PM_{2.5}$ and PM_{10} showing a positive meta-analytic estimate and NO_2 and NO_x indicating no effect in the meta-analysis (Table 2, Fig. 2). Combined confidence rating for the quality of the evidence base for measures of TRAP across all meta-analysed pollutants started with moderate confidence. We downgraded to low, because all $PM_{2.5}$ and PM_{10} studies were rated only as moderately traffic-specific studies whereas the highly traffic-specific NO_2 and NO_x meta-analytic estimates were null.

In our comprehensive narrative assessment, we concluded a moderate level of evidence in an association of exposure to TRAP with stroke. Overall, the study base and the meta-analyses provided evidence of an association of PM_{10} and suggestive evidence of an association of EC and $PM_{2.5}$ with stroke from a moderately large number of studies. Several high-quality studies from different regions across Europe and in North America yielded positive estimates for EC, PM_{10} and $PM_{2.5}$ in different populations, albeit the precision of the estimates was low, and the CIs of the meta-analytic estimates included unity. The determination was supported by some evidence from individual pollutant or proximity metric studies not included in meta-analyses, and relative stability in

noise-adjusted models. What made the evidence less compelling was the absence of evidence for NO_2 and NO_x, the pollutants considered highly traffic specific, yielding null findings in the meta-analyses.

Based on both assessments, the overall evaluation of an association between TRAP exposure and stroke was rated low to moderate.

3.11. Study characteristics and sensitivity-analyses following the new search

On January 06, 2022, we identified 64 newly published studies on stroke, 6 of which met the original inclusion criteria (Amini et al., 2020; Andersson et al., 2020; Magnoni et al., 2021; Rodins et al., 2020; Vivanco-Hidalgo et al., 2019) (Table 3). Estimates reported a positive association between different pollutants and stroke except the very large study in Milan (Magnoni et al., 2021) showing no association. The DNC, ELAPSE and HNR studies reported an RR for $PM_{2.5}$, NO_2 and PM_{10} of 1.12 (95%CI: 1.05; 1.25), 1.08 (95%CI: 1.04, 1.12) and 1.08 (95%CI: 1.01, 1.16) respectively. All 6 studies adjusted for traffic noise, reporting stable estimates. After including the new studies in sensitivity meta-analyses for $PM_{2.5}$ and NO_2 (Supplementary Fig. 2), we found slightly more robust adverse estimates for $PM_{2.5}$ (1.22; 95% CI: 1.03–1.21) and a null association for NO2 (1.01; 95% CI: 0.96–1.06).

4. Discussion

Based on 19 publications, we found low to moderate evidence for an association of long-term exposure to TRAP with stroke. This was based on a formal confidence rating according to the modified OHAT framework and on a comprehensive narrative assessment of the body of evidence. The meta-analytic estimates of EC, PM_{10} and $PM_{2.5}$ indicated positive associations for stroke, but for all pollutants the confidence intervals included unity. The evidence was strengthened by several high-quality studies with a positive exposure-response function or subset analysis indicating stable effects across levels of exposure. In addition, several individual studies investigating pollutants highly likely indicative of traffic, such traffic-specific PM fractions provided support for an association. Several studies also observed associations of proximity metrics such as residential distance to high traffic roadways or traffic density with stroke. Because cardiometabolic disease is likely influenced by traffic noise, some studies investigated possible confounding or effect modification by noise with mostly very stable results. However, the evidence for TRAP and stroke was generally weakened by null associations for the gaseous pollutants NO_2 and NO_x in the meta-analyses.

Following the systematic search in July 2019, six new studies have been published on stroke in association with TRAP. Overall, the recently published studies support the overall results from this review, showing no association for NO_2 and a significant adverse association for $PM_{2.5}$ in sensitivity analyses.

In a review and meta-analysis of general air pollution and stroke, Scheers et al. (2015) found statistically significant, but slightly lower associations with $PM_{2.5}$ and PM_{10} in a set of 20 studies. In contrast to our study, they targeted all studies exposed to $PM_{2.5}$ and PM_{10} from all source and not only TRAP related exposure studies, thus the higher number of studies included in their meta-analyses. They also reported unexplained geographical variability in these associations due to null results for PM_{10} exposures in Asia, while studies of PM_{10} exposures in North America and Europe were positive.

Contrary to our findings, in a recent review by Rugel and Brauer (2020), who analysed the effects of TRAP, noise, natural spaces and neighbourhood walkability in urban populations, the authors concluded that “when TRAP and noise were considered jointly, evidence was sufficient for increased cardiovascular morbidity with higher noise exposures; sufficient for no effect of TRAP on cardiovascular disease morbidity”. This review was limited to studies of at least two environmental exposures and outcomes were grouped more broadly, preventing a direct comparison of results with our study. Nevertheless, the conclusion of a vanishing TRAP effect upon adjustment for noise is contrary to ours, where studies generally showed little influence on the TRAP effect upon adjustment for noise in the few studies that did so.

Major strengths of this review include the systematic approach to study selection and evaluation using an a priori specified framework for exposure assessment and for a systematic evaluation of the epidemiological evidence. The use of several indicators of TRAP allowed the evaluation of consistency across pollutants and enabled us to base conclusions on a larger number of studies with diverse exposure metrics, rather than focusing only on a few meta-analysed pollutants. The outcomes of the overall review were grouped into relatively specific subgroups of cardiovascular disease to allow a more detailed evaluation. The identified studies were located in diverse areas of the world with different populations and different study designs. Several studies with in-depth characterization of the study population were available. The more recent studies also were more likely to include an evaluation of traffic noise.

One of the limitations of this review was the low number of studies per exposure-stroke pair for most pollutants. This prevented us from conducting more in-depth, stratified analyses by region, traffic-specificity or study design, the evaluation of publication bias, and inconclusive stratified and sensitivity analyses in many cases. A second specific limitation of this body of evidence was the potential underassessment and misclassification of stroke, depending on study design, age of the study population and data source. Third, the studies provided only limited opportunity to study the influence of potentially important co-exposures such as traffic noise, area-level SES or green space in a detailed manner, although each have been shown to be related to cardiovascular disease (World Health Organization, 2018; Yuan et al., 2021).

We followed the earlier 2010 HEI Report in recognizing that a major challenge for epidemiological research on TRAP and for the objective of selecting and evaluating studies remains – i.e., that no commonly measured or modelled pollutant is fully specific to traffic sources. Other sources, such as heating and energy production also contribute to commonly used indicators of TRAP (for example NO_2 and UFPs). Therefore, the use of accepted indicators of TRAP would ideally be evaluated in the context of the major drivers of exposure contrast in the geographic region and the specific design of each epidemiological study. However, given that detailed evaluation of the sources and data underlying exposure assessment in individual studies is not feasible, we consider it a strength that a novel exposure framework was developed to guide transparent selection and evaluation of the included studies.

One further challenge is identifying the most important time period for the elicitation of adverse effects on stroke. This question of relevant time of exposure also includes the role of short-term traffic exposures, which was not covered in this review. While in the triggering of acute events due to short term exposure has been demonstrated in many studies (Mills et al., 2015), it remains unclear how repeated high short-term exposures contribute to disease development. Also a better understanding of the molecular and cellular actions of nitrogen oxides on the cardiometabolic system is necessary to provide mechanistic evidence for a plausible adverse health effect. So far, only limited evidence is available from toxicological studies at relevant ambient concentrations (Burbure et al., 2007; Channell et al., 2012; Huang et al., 2012; Li et al., 2011; Riedl et al., 2012).

5. Conclusions

The available literature provides low-to moderate evidence for an association of TRAP with stroke. As traffic in cities remains the most important source of contrasts in air pollution, future studies should specifically focus on small-scale exposure assessment, ideally also including other factors associated with traffic, such as traffic noise, area-level SES and green space, to improve the evidence base. The role these

Table 3
Key study characteristics of the newly identified studies (up to January 2022).

Reference	Study Name Location	Study period	Study design and sample size	Exposure Assessment	Age at baseline, sex	Stroke outcome ascertainment	Monotonic ER-function	Confounder adjustment	Results (estimate, 95% CI, increment)	Results (estimate, 95% CI, increment) Adjusted for road traffic noise
Magnoni et al. (2021)	Data collected by the Agency for Health Protection (ATS) Milan, Italy	2011–2018	Cohort 1,087,110	LUR model	Mean Age: 54, both	Medical record	No	Age, sex, citizenship, Italian Deprivation Index	**Fatal and non-fatal ischemic (HR)** NO_2 0.99 (0.96, 1.03) per 10 μg/m^3 **Fatal and non-fatal heamorrahgic (HR)** NO_2 0.99 (0.92, 1.06) per 10 μg/m^3	**Fatal and non-fatal ischemic (HR)** NO_2 0.98 (0.94, 1.02) per 10 μg/m^3 **Fatal and non-fatal heamorrahgic (HR)** NO_2 0.96 (0.90, 1.04) per 10 μg/m^3
Amini et al. (2020)	Danish Nurse Study Denmark, nationwide	1993–2014	Cohort 23, 423	Danish air pollution modeling system, called DEHM/UBM/AirGIS	Mean Age: 52.6, female	National patient registry	Yes	Age, year of entry, calendar year, income, degree of urnabanicity, physical activity, alcohol, smoking, marital status, fruit consumption	**Fatal and non-fatal (all stroke) (HR)** $PM_{2.5}$ 1.12 (1.05, 1.25) per 3.9 μg/m^3 PM_{10} 1.05 (0.97, 1.13) per 3.3 μg/m^3 NO_2 1.05 (0.97, 1.13) per 8.0 μg/m^3 NO_x 1.02 (0.99, 1.06) per 11.0 μg/m^3	**Fatal and non-fatal (all stroke) HR** $PM_{2.5}$ 1.13 (1.01, 1.25) per 3.9 μg/m^3 PM_{10} 1.05 (0.97, 1.13) per 3.3 μg/m^3 NO_2 1.05 (0.97, 1.15) per 8.0 μg/m^3 NO_x 1.03 (0.99, 1.06) per 11.0 μg/m^3
Andersson et al. (2020)	PPS Gothenburg, Sweden	1970–2011	Cohort 6304	High resolution dispersion model	Age range: 47–55; men	Hospital discharge register, Swedish national death register	No	Calendar year, marriage/cohabitation, SES, smoking, BMI, cholesterol, stress, heredity, diabetes, physical activity, age	**Fatal and non-fatal (all stroke) (HR)** NO_x 1.02 (0.97, 1.07) per 10 μg/m^3 **Fatal and non-fatal (all stroke) (HR) categorized** NO_x 1.14 (0.93, 1.40) 36.1–44.1 versus <36.7 μg/m^3 NO_x 1.05 (0.85, 1.3) 44.1–53.3 versus <36.7 μg/m^3 NO_x 1.05 (0.85, 1.30) 53.3–64.8 versus <36.7 μg/m^3 NO_x 1.25 (1.02, 1.54) >64.8 versus <36.7 μg/m^3	**Results only for categories of exposure** NO_x 1.14 (0.93, 1.41) 36.1–44.1 versus <36.7 μg/m^3 NO_x 1.06 (0.85, 1.31) 44.1–53.3 versus <36.7 μg/m^3 NO_x 1.04 (0.83, 1.32) 53.3–64.8 versus <36.7 μg/m^3 NO_x 1.20 (0.93, 1.56) >64.8 versus <36.7 μg/m^3
Vivanco-Hidalgo et al. (2019)	Barcelona, Spain	2005–2014	Cross-sectional 2786	LUR model	Mean age: 75; both	BASICMAR database	no	Age, sex, smoking status, nSES, comorbidities[a]	**Severe Ishemic stroke (OR)** $PM_{2.5}$ Q2 1.01 (0.80, 1.26) $PM_{2.5}$ Q3 0. 93 (0.74, 1.17) $PM_{2.5}$ Q4 1.04 (0.83, 1.31)	**Severe Ishemic stroke (OR)** $PM_{2.5}$ Q2 0.97 (0.77, 1.21) $PM_{2.5}$ Q3 0.88 (0.70, 1.11) $PM_{2.5}$ Q4 0.95 (0.75, 1.20) **Adjusted for noise and green space**

(*continued on next page*)

Table 3 (*continued*)

Reference	Study Name Location	Study period	Study design and sample size	Exposure Assessment	Age at baseline, sex	Stroke outcome ascertainment	Monotonic ER-function	Confounder adjustment	Results (estimate, 95% CI, increment)	Results (estimate, 95% CI, increment) Adjusted for road traffic noise
(Wolf et al., 2021)	ELAPSE Multiple cities	1992–2015	Cohort 137,148	LUR model	Mean Age: 54, both	Hospital discharge and death registries	yes	Subcohort strata, age, sex, year of baseline visit, marital status, BMI, smoking, employment status, education, 2001 income mean on a nSES	**Fatal and non-fatal stroke (HR)** $PM_{2.5}$ 1.10 (1.01, 1.21) per 5 μg/m^3 NO_2 1.08 (1.04, 1.12) per 10 μg/m^3 BC 1.06 (1.02, 1.10) per 0.5[a]10^{-5}/m	**Fatal and non-fatal stroke (cohort with available data on noise) (HR)** $PM_{2.5}$ 1.09 (0.99, 1.21) per 5 μg/m^3 NO_2 1.08 (1.03, 1.12) per 10 μg/m^3 BC 1.05 (1.01, 1.10) per 0.5[a]10^{-5}/m
Rodins et al. (2020)	HNR Western Germany	2000-14 years follow-up	Cohort 4105	EURAD-CTM	Mean Age: 59.1, both	Self-report, physician interviews and medical records	not specified	Age, sex, iSES, nSES, BMI, smoking, alcohol, physical activity, nutrition, night-time traffic noise	**Fatal and non-fatal stroke (HR)** PM_{10} 1.08 (1.01, 1.16) per 1 μg/m^3 $PM_{10\ traffic}$ 2.55 (1.11, 5.86) per 1 μg/m^3 $PM_{2.5}$ 1.16 (1.02, 1.34) per 1 μg/m^3 $PM_{2.5\ traffic}$ 2.53 (1.07, 5.97) per 1 μg/m^3 PN_{AM} 1.06 (1.01, 1.10) per 100n/cm^3 $PN_{AM\ traffic}$ 1.27 (1.05, 1.55) per 100n/cm^3 AOC 1.07 (1.01, 1.13) per 0.1 μg/m^3 $AOC_{traffic}$ 1.33 (1.00, 1.76) per 0.1 μg/m^3 EC 1.07 (1.01, 1.14) per 0.1 μg/m^3 $EC_{traffic}$ 1.78 (1.02, 3.12) per 0.1 μg/m^3 **All results adjusted for traffic noise**	

[a] Comorbidities: hypertensions, diabetes mellitus, dyslipidemia, prior history of coronary heart disease/stroke/transient ischemic attack.

urban co-exposures needs more attention, given that there is clear evidence that noise and area-level SES, and to a lesser degree lack of green space, have adverse health effects on cardiometabolic health and quality of life (Diez Roux et al., 2016; Schultz et al., 2018; World Health Organization, 2018; Yuan et al., 2021). The interplay of these exposures in terms of confounding and potential synergism needs to be better understood for effective prevention and urban planning. With cities starting to rethink urban planning and the interactions of personal motor vehicles, active transport and increased green space (for example Paris, Barcelona, Copenhagen, etc.), the effects of these changes on cardiometabolic health should be evaluated.

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Declaration of competing interest

No author declares a conflict of interest.

The following increments were used: 10 μg/m^3 for NO_2, 20 μg/m^3 for NO_x, 1 μg/m^3 for EC, 10 μg/m^3 for PM_{10}, and 5 μg/m^3 for $PM_{2.5}$. Effect estimates cannot be directly compared across the different traffic-related pollutants because the selected increments do not necessarily represent the same contrast in exposure.

A. Forest plot of the association between NO_2 and stroke, **B**. Forest plot of the association between NO_x and stroke.

Note: Oudin et al., (2011) are estimates for non-fatal stroke; others combined fatal and non-fatal stroke.

A. Forest plot of the association between EC and stroke; **B.** Forest plot of the association between PM_{10} and stroke; **C.** Forest plot of the association between $PM_{2.5}$ and stroke.

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Appendix A. Supplementary data

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