Supplementary Table 1 Inclusion and Exclusion Criteria for each PECOS Domain in Relation to the Selected Health Effects of Long–Term Exposure to TRAP

|  |  |  |
| --- | --- | --- |
| **PECOS** | **Inclusion** | **Exclusion** |
| Population | General human population, of all ages, developed and developing areas, both urban and rural  No geographical restrictions | Populations exposed in occupational settings or exclusively indoors. |
| Exposure | Long–term exposure (months to years) to TRAP.  Indirect measures of TRAP, such as distance to or traffic density at nearest road.  Include studies regardless of whether they adjust for co–pollutant exposures. | Short–term exposure studies (minutes to months). |
| Comparator | Exposure to lower levels of TRAP in the same or in a referent population. |  |
| Outcome | Stroke events (I60-I69) |  |
| Study | Human studies include cohort studies, case-cohort, case-control, cross-sectional studies, and intervention studies.  Only human studies that are published (or accepted for publication i.e., in press) between January 1980 and June 2019, in peer–reviewed journal articles and written in English.  Studies that report a quantitative measure of association and a measure of precision. | Qualitative studies, studies reporting only unadjusted results, and clear evidence of an analytical error  Studies without individual level data (i.e., fully ecological outcome, exposure, and covariates data)  Studies where no original data were analysed, reviews, or methodological papers  Genome-wide association study (GWAS) and all other -omics studies Nonhuman studies (in vivo, in vitro, other) and controlled exposure (chamber) studies  Grey literature, conference abstracts, conference papers, notes, editorials, letters, and unpublished data |

Supplementary Table 2 Traffic‐Related Pollutants and Exposure Indicators Included in Review

|  |  |
| --- | --- |
| **Exposure Metric** | **Consideration** |
| NO2, NOx, NO | Frequently used in epidemiological studies; NAAQS or limit values |
| CO | Frequently used particularly in earlier traffic studies; NAAQS or limit values |
| EC, BC, BS, PM absorption (‘soot’)\* | Frequently used in epidemiologic studies |
| PM10, PMcoarse, and PM2.5 | Frequently used in epidemiological studies; in specific settings PM contrast may have a clearly resolvable relative traffic contribution |
| Non‐tailpipe PM trace metals from wearing of brakes and tires or from the resuspension of road dust (e.g., Cu, Fe and Zn) | Increased interest because of reduction of tailpipe emissions |
| UFPs, particle number concentration, quasi‐ultrafine, different particle modes (nucleation, Aitken, accumulation), particle size distribution | Fraction of fine particles produced through combustion and with potentially distinct health effects |
| PAH | Added for completeness  Some increased by traffic, though not a very specific marker and most human exposure is via diet |
| Benzene | Added for completeness  Some VOCs are increased by traffic, though VOCs are generally not specific for traffic.  Benzene chosen as a marker for mobile source air toxics |
| Indirect traffic measures (metrics based on distance or traffic density) | Very specific for local traffic but concerns about validity  Indicators represent more than air pollution (e.g., noise) and no quantitative concentration estimates available |

\* Elemental carbon (EC), black carbon (BC), Black Smoke (BS), and PM absorption (PMabs) are referred to as EC throughout this report. These carbonaceous pollutants are defined by operational measurement techniques rather than by fundamental chemical properties alone.

Supplementary Table 3 Exposure Assessment Methods Combining Selected Criteria

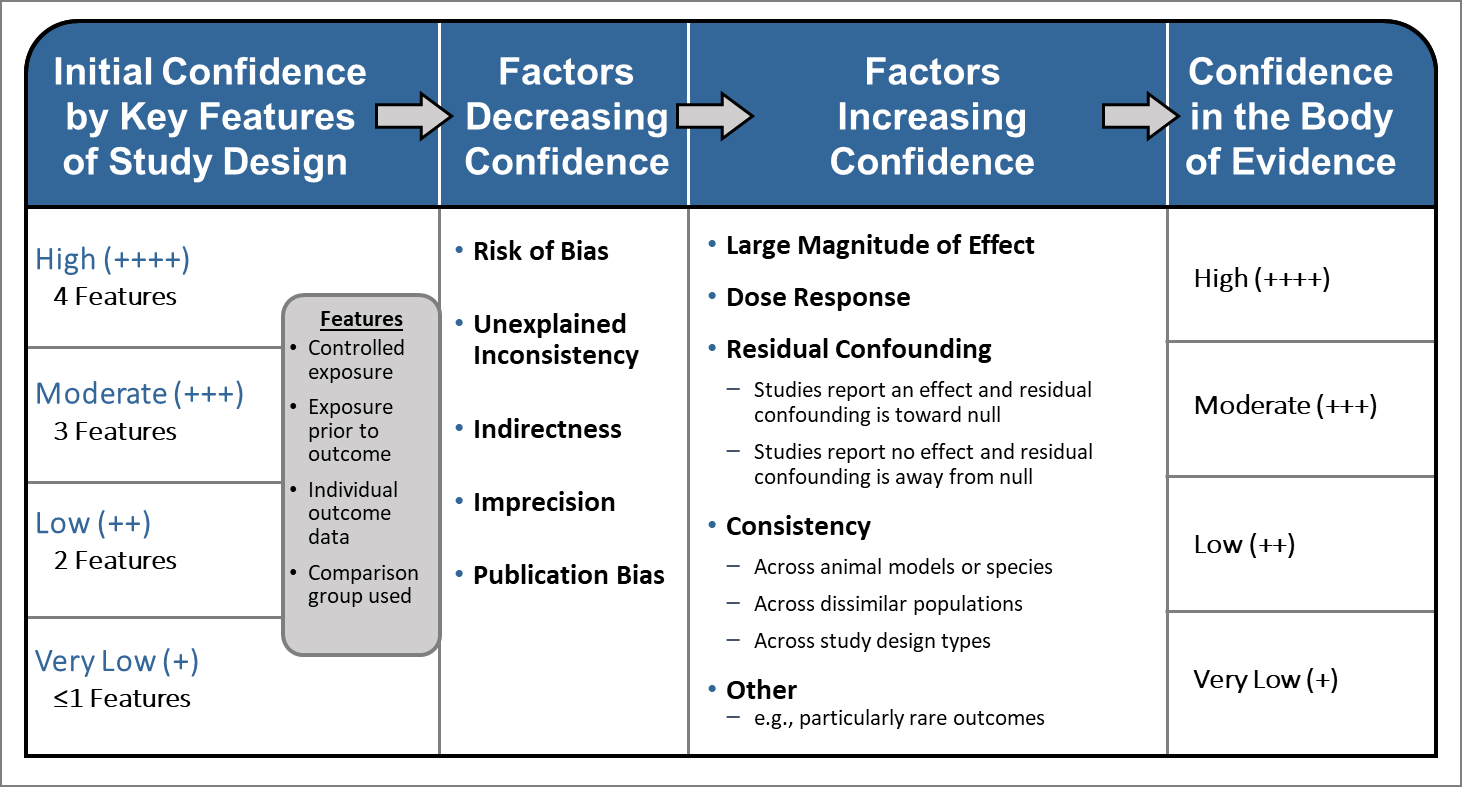
|  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- |
| **Exposure metric** | **Exposure assessment methods** | **Spatial resolution “pollution surface”** | **Spatial resolution address** | **Spatial resolution address for study identification** | **Traffic contribution to exposure and other considerations\*** |
| All pollutants from Supplementary Table 2 | Dispersion / CTM models of traffic emissions or traffic-specific source-tracking/apportionment | ≤5 km | ≤5 km | Residential address as exact address, neighborhood, census tract, zip code acceptable (city or county not) | Assumed by method |
| All pollutants from Supplementary Table 2 | Dispersion / CTM models of all sources | ≤5 km | ≤5 km | Residential address as exact address, neighborhood, census tract, zip code acceptable (city or county not) | Judgement needed (e.g., required area adjustment in epidemiological analysis if spatial extent of the study area was >10,000 km2, determination of whether exposures met long-term criteria) |
| All pollutants from Supplementary Table 2 | LUR. Models that contain at least one traffic predictor (e.g., traffic intensity or road density) or broader surrogates of traffic (e.g., address density, household density, population density, impervious surface) | ≤5 km | ≤5 km | Residential address as exact address, neighborhood, census tract, zip code acceptable (city or county not) | Judgement needed (e.g., required area adjustment if spatial extent of the study area was >10,000 km2, determining whether exposures met long-term criteria) |
| All pollutants from Supplementary Table 2 except PM10, PMcoarse and PM2.5 | Surface, satellite and personal monitoring | ≤5 km; operationalized as up to 5 km between the residence and the monitor, or up to 10 km between monitors, or at least one site per 50 km2 | ≤5 km | Residential address as exact address, neighborhood, census tract or block, or postal code (but not city or county) | Judgement needed (e.g., unclear monitor density, determination of whether exposures met long-term criteria) |
| PM10, PMcoarse, PM2.5 | Surface, satellite and personal monitoring | Excluded | Excluded | Excluded | Excluded |
| Indirect traffic measures (Metrics based on distance or traffic density) | Objective | ≤1000 m from a highway or a major road | ≤100 m | Residential address as exact address or detailed zip code (street segment) | Assumed by method |

\*In general, the larger the study area, the less likely a measured or modelled contrast in pollution is primarily due to traffic emissions. Therefore, nationwide epidemiological studies were designated as ‘possibly in’ requiring Panel assessment. The spatial resolution of a pollution surface was selected based on its capacity to identify within-city contrasts in ambient air pollution.

Supplementary Table 4 Inclusion and Exclusion Criteria for Meta-Analysis

|  |
| --- |
| **Inclusion criteria** |
| General population studies, and studies in selected ‘representative’ population subgroups (e.g., California Teachers study, Nurses’ Health study).  Adjusted risk estimates from single pollutant model result. If single pollutant model results were not reported, multipollutant results were selected.  Adjusted risk estimates from the full study population. If a study reported two or more estimates for subgroups of the study population separately only (e.g., male and female, age groups), the Panel combined the estimates by a fixed-effect meta-analysis first before entering the random effects model.  Ability to standardize the results.  Studies were included unless the same study population and exposure assessment was used in several publications on the same exposure-outcome pair. When the same study population was used in several publications on the same exposure-outcome, selection was basis of the following order:   * largest population sample size, number of events or number of cases * most appropriate adjustment for confounders * most recent publication date |
| **Exclusion criteria** |
| Exposure metric analyzed as log-transformed terms, categories, such as quartiles of exposures, high versus low.  Indirect traffic measures (distance and traffic density measures) and personal exposure studies.  Insufficient information available to standardize estimates and precision (e.g., not reported, pollutant increment not clear) |

Supplementary Figure 1 Assessing Confidence in the Body of Evidence from OHAT 2019



Supplementary Table 5 Comparison of main similarities and differences between the narrative assessment and the modified OHAT assessment.

|  |  |  |
| --- | --- | --- |
|  | **Narrative assessment** | **Modified OHAT assessment** |
| Main purpose | to assess confidence in the presence of an association | to assess confidence in the quality of the body of evidence |
| Inclusion of studies | All studies - both the metanalytic results and results of studies that were not included in meta-analysis | All studies, though heavily geared towards the studies entering a meta-analysis |
| Number, location, and size of the studies | Yes | Partial |
| Study design | Yes | Yes |
| Study population (generalizability) | Yes | No |
| Strength (magnitude) of the association | Yes | No\* |
| Robustness of the association | Yes | No |
| Statistical methodology | Yes | No |
| Risk of bias | Yes | Yes |
| *Confounding* | Yes | Yes |
| *selection bias* | Yes | Yes |
| *exposure assessment* | Yes | Yes |
| *outcome assessment* | Yes | Yes |
| *missing data* | Yes | Yes |
| *selective reporting* | Yes | Yes |
| Consistency of the findings (e.g., across locations, time periods, study designs, and different pollutants and indirect traffic measures) | Yes | Partial |
| Unexplained inconsistency | Yes | Yes |
| Imprecision (chance) | Yes | Yes |
| Publication bias | No | Yes |
| Exposure-response | Yes | Yes |
| Residual confounding | Yes | Yes |

\*The OHAT has an upgrading factor for *large magnitude of effect* that applies only if the effect size is large or very large (i.e., large relative risk > 2 or very large relative risk > 5) because residual confounding is then less likely. However, the Panel consider a *large* effect to be both ambiguous to define and unlikely to occur. Thus, the Panel has decided not to consider this specific upgrading factor.

Supplementary Table 6 Overall assessment ‐ Descriptors of the Level of the Evidence for an Association\*

|  |  |
| --- | --- |
| High | Evidence is sufficient to conclude that the strength of the evidence for an association is high, that is, the exposure has been shown to be associated with health effects in studies in which chance, confounding, and other biases could be ruled out with reasonable confidence. The determination is based on multiple high‐quality studies conducted in different populations and geographical areas with consistent results for multiple exposure indicators.  High confidence in the association between exposure and the outcome |
| Moderate | Evidence is sufficient to conclude that an association is likely to exist, that is, the exposure has been shown to be associated with health effects in studies where results are not explained by chance, confounding, and other biases, but uncertainties remain in the evidence overall. The determination is based on some high‐quality studies in different populations and geographical areas but the results are not entirely consistent across areas and for multiple exposure indicators.  Moderate confidence in the association between exposure and the outcome |
| Low | Evidence is suggestive but limited, and chance, confounding, and other biases cannot be ruled out. Generally, the body of evidence is relatively small, with few high‐ quality studies available and at least one high‐quality epidemiologic study shows an association with a given health outcome and/or when the body of evidence is relatively large but the evidence from studies of varying quality and across multiple exposure indicators is generally supportive but not entirely consistent.  Low confidence in the association between exposure and the outcome |
| Very Low | Evidence is inadequate to determine if an association exists with the relevant exposures. The available studies are of insufficient quantity, quality, consistency, or statistical power to permit a conclusion regarding the presence or absence of an association.  Very low confidence in the association between exposure and the outcome. |

\*The overall assessment of the association of each health outcome with long‐term exposure to TRAP is a combination of the narrative assessment and the modified OHAT assessment. The descriptors are modified from OHAT (2019) and U.S. EPA (2015).

Supplementary Table 7 List of Excluded Citations with Justification

|  |  |  |
| --- | --- | --- |
| **Title** | **Authors, Year** | **Reason behind exclusion** |
| Road traffic noise is associated with increased cardiovascular morbidity and mortality and all-cause mortality in London | Halonen et al, 2015 | No quantitative measure of association |
| Road traffic noise, air pollution and incident cardiovascular disease: A joint analysis of the HUNT, EPIC-Oxford and UK Biobank cohorts | Cai et al, 2018 | Exposure assessment (main reason: nationwide study with no or insufficient area-specific adjustments) |
| Long-Term Exposure to Ultrafine Particles and Incidence of Cardiovascular and Cerebrovascular Disease in a Prospective Study of a Dutch Cohort | Downward et al, 2018 | Exposure assessment (main reason: nationwide study with no or insufficient area-specific adjustments) |
| Long term effect of air pollution on incident hospital admissions: Results from the Italian Longitudinal Study within LIFE MED HISS project | Gandini et al, 2018 | Exposure assessment (main reasons: spatial scale too crude (pollution surface + health data), correction for area specific but very rough way (rural, urban, metropolitan area)) |
| Effect of seasonal and monthly variation in weather and air pollution factors on stroke incidence in Seoul, Korea | Han et al, 2015 | Exposure assessment (main reason: insufficient information in either paper or the accompanying papers) |
| Effect Modification of Long-Term Air Pollution Exposures and the Risk of Incident Cardiovascular Disease in US Women | Hart et al, 2015 | Exposure assessment (main reason: nationwide study with no or insufficient area-specific adjustments) |
| Ambient Air Pollution Is Associated With the Severity of Coronary Atherosclerosis and Incident Myocardial Infarction in Patients Undergoing Elective Cardiac Evaluation | Hartiala et al, 2015 | Exposure assessment (main reasons: spatial scale too crude (pollution surface), nationwide study with no or insufficient area-specific adjustments) |
| Individual and Neighborhood Stressors, Air Pollution and Cardiovascular Disease | Hazlehurst et al, 2018 | Exposure assessment (main reasons: spatial scale too crude (pollution surface), nationwide study with no or insufficient area-specific adjustments) |
| Acute and chronic effects of particles on hospital admissions in New-England | Kloog et al, 2012 | Exposure assessment (main reason: spatial scale too crude (health data)) |
| Long-term exposure to air pollution and cardiorespiratory disease in the California teachers study cohort | Lipsett et al, 2011 | Exposure assessment (main reason: nationwide study with no or insufficient area-specific adjustments) |
| Particulate matter exposures, mortality, and cardiovascular disease in the health professionals follow-up study | Puett et al, 2011 | Exposure assessment (main reason: nationwide study with no or insufficient area-specific adjustments) |
| Fine particulate matter exposure and incidence of stroke: A cohort study in Hong Kong | Qiu et al, 2017 | Exposure assessment (main reason: PM satellite data) |
| Association between long-term exposure of ambient air pollutants and cardiometabolic diseases: A 2012 Korean Community Health Survey | Shin et al, 2019 | Exposure assessment (main reason: nationwide study with no or insufficient area-specific adjustments) |
| Cardiovascular Effects of Long-Term Exposure to Air Pollution: A Population-Based Study With 900 845 Person-Years of Follow-up | Kim et al, 2017 | Other – Analytical error |
| Associations between exhaust and non-exhaust particulate matter and stroke incidence by stroke subtype in South London | Crichton et al, 2016 | Study design |
| Association between long-term exposure to air pollutants and prevalence of cardiovascular disease in 108 South Korean communities in 2008-2010: A cross-sectional study | Lee et al, 2016 | Study design |
| Outdoor NOx and stroke mortality: adjusting for small area level smoking prevalence using a Bayesian approach | Maheswaran et al, 2006 | Study design |
| Do air pollution and neighborhood greenness exposures improve the predicted cardiovascular risk? | Yitshak-Sade et al, 2017 | Very selective subgroup |

Supplementary Figure 2 Sensitivity and Subgroup Analyses for Stroke Incidence by Fatality (A and B), Risk of Bias (C), Region (D) and New Studies (E and F)

**Study**

**Fatal and non-fatal**

**Fatal**

**Random effects model**

**Random effects model**

Heterogeneity:

*I*

2

= 64%

,



2

= 0.0040

,

*p*

= 0.01

Heterogeneity:

*I*

2

= 77%

,



2

= 0.0628

,

*p*

= 0.01

Johnson et al. 2013

Katsoulis et al. 2014

Sørensen et al. 2014

Stafoggia et al. 2014

Carey et al. 2016

Alexeeff et al. 2018

Dirgawati et al. 2019

Sørensen et al. 2014

Alexeeff et al. 2018

Dirgawati et al. 2019

**Study Name**

Edmonton Stroke

EPIC Athens

DDCH

ESCAPE

CPRD London

KPNC Oakland

HIMS

DDCH

KPNC Oakland

HIMS

0.5

1

2

**Relative Risk**

Relative Risk per 10 µg/m

3

**RR**

**0.98**

**1.25**

1.01

0.98

1.08

0.99

0.88

0.96

0.96

1.47

1.57

0.93

**95%-CI**

**[0.92; 1.05]**

**[0.61; 2.55]**

[0.94; 1.09]

[0.71; 1.35]

[1.01; 1.16]

[0.89; 1.11]

[0.82; 0.95]

[0.79; 1.16]

[0.85; 1.08]

[1.21; 1.79]

[0.90; 2.74]

[0.72; 1.20]

**A: Fatality (Pollutant: NO2)**

**B: Fatality (Pollutant: NOx)**

**Study**

**Fatal and non-fatal**

**Fatal**

**Non-fatal**

**Random effects model**

**Random effects model**

**Random effects model**

Heterogeneity:

*I*

2

= 57%

,



2

= 0.0022

,

*p*

= 0.03

Heterogeneity:

*I*

2

= 72%

,



2

= 0.0172

,

*p*

= 0.06

*Heterogeneity: not applicable*

Sørensen et al. 2014

Stafoggia et al. 2014

Korek et al. 2015

Carey et al. 2016

Stockfelt et al. 2017

Stockfelt et al. 2017

Dirgawati et al. 2019

Sørensen et al. 2014

Dirgawati et al. 2019

Oudin et al. 2011

**Study Name**

DDCH

ESCAPE

SDPP, SIXTY, SALT, SNAC-K

CPRD London

GOT-MON

PPS

HIMS

DDCH

HIMS

Scania Stroke

0.5

1

2

**Relative Risk**

Relative Risk per 20 µg/m

3

**RR**

**0.99**

**1.07**

**0.86**

1.02

0.98

1.20

0.90

1.04

1.04

1.00

1.17

0.94

0.86

**95%-CI**

**[0.94; 1.05]**

**[0.27; 4.20]**

**[0.36; 2.06]**

[0.98; 1.07]

[0.89; 1.07]

[0.63; 2.27]

[0.85; 0.96]

[0.90; 1.20]

[0.97; 1.12]

[0.91; 1.09]

[1.05; 1.31]

[0.77; 1.14]

[0.36; 2.06]

**Study**

**Low/Moderate**

**High**

**Random effects model**

**Random effects model**

Heterogeneity:

*I*

2

= 30%

,



2

= 0.0068

,

*p*

= 0.22

*Heterogeneity: not applicable*

Stafoggia et al. 2014

Stockfelt et al. 2017

Stockfelt et al. 2017

Alexeeff et al. 2018

Dirgawati et al. 2019

Gan et al. 2012

**Study Name**

ESCAPE

GOT-MON

PPS

KPNC Oakland

HIMS

Vancouver Administrative

0.5

1

2

**Relative Risk**

Relative Risk per 1 µg/m

3

**RR**

**1.02**

**1.04**

1.07

1.20

1.07

0.83

0.87

1.04

**95%-CI**

**[0.86; 1.20]**

**[1.00; 1.08]**

[0.84; 1.36]

[0.91; 1.57]

[0.92; 1.24]

[0.47; 1.45]

[0.74; 1.03]

[1.00; 1.08]

**C: Risk of Bias (Pollutant: EC)**

**Study**

**Western Europe**

**Australia/New Zealand**

**Random effects model**

**Random effects model**

Heterogeneity:

*I*

2

= 0%

,



2

= 0

,

*p*

= 0.52

*Heterogeneity: not applicable*

Stafoggia et al. 2014

Stockfelt et al. 2017

Stockfelt et al. 2017

Dirgawati et al. 2019

**Study Name**

ESCAPE

GOT-MON

PPS

HIMS

0.5

1

2

**Relative Risk**

Relative Risk per 5 µg/m

3

**RR**

**1.17**

**1.01**

1.19

1.50

1.06

1.01

**95%-CI**

**[0.82; 1.67]**

**[0.84; 1.21]**

[0.88; 1.61]

[0.90; 2.50]

[0.78; 1.44]

[0.84; 1.21]

**D: Region (Pollutant: PM2.5)**

**E**

**Study**

**Random effects model**

Prediction interval

Heterogeneity:

*I*

2

= 72%

,

Tau2

= 0.0034

,

*p*

< 0.01

Johnson et al. 2013

Katsoulis et al. 2014

Sørensen et al. 2014

Stafoggia et al. 2014

Carey et al. 2016

Alexeeff et al. 2018

Dirgawati et al. 2019

Amini et al. 2020

Magnoni et al. 2021

Wolf et al. 2021

**Study Name**

Edmonton Stroke

EPIC Athens

DDCH

ESCAPE

CPRD London

KPNC Oakland

HIMS

DNC

ATS

ELAPSE

0.8

1

1.25

**Relative Risk**

Relative Risk per 10 µg/m

3

**RR**

**1.01**

1.01

0.98

1.08

0.99

0.88

0.96

0.96

1.06

0.99

1.08

**95%-CI**

**[0.96; 1.06]**

[0.87; 1.16]

[0.94; 1.09]

[0.71; 1.35]

[1.01; 1.16]

[0.89; 1.11]

[0.82; 0.95]

[0.79; 1.16]

[0.85; 1.08]

[0.97; 1.17]

[0.96; 1.03]

[1.04; 1.12]

**Weight**

**100.0%**

11.9%

1.9%

12.3%

8.7%

11.9%

4.6%

8.0%

9.9%

15.4%

15.2%

NO

2

- Stroke (New Studies)

**F**

**Study**

**Random effects model**

Prediction interval

Heterogeneity:

*I*

2

= 7%

,



2

< 0.0001

,

*p*

= 0.37

Stafoggia et al. 2014

Stockfelt et al. 2017

Stockfelt et al. 2017

Dirgawati et al. 2019

Amini et al. 2020

Rodins et al. 2020

Wolf et al. 2021

**Study Name**

ESCAPE

GOT-MON

PPS

HIMS

DNC

HNR

ELAPSE

0.5

1

2

**Relative Risk**

Relative Risk per 5 µg/m

3

**RR**

**1.12**

1.19

1.50

1.06

1.01

1.16

2.10

1.10

**95%-CI**

**[1.03; 1.21]**

[1.03; 1.22]

[0.88; 1.61]

[0.90; 2.50]

[0.78; 1.44]

[0.84; 1.21]

[1.03; 1.29]

[1.06; 4.15]

[1.00; 1.20]

**Weight**

**100.0%**

4.1%

1.5%

4.1%

11.6%

30.8%

0.8%

47.1%

PM

2.5

- Stroke (New Studies)

**A**. Forest plot of the association between NO2 and stroke by fatality, **B**. Forest plot of the association between NOx and stroke by fatality, **C.** Forest plot of the association between EC and stroke by risk of bias assessment on confounding, **D.** Forest plot of the association between PM2.5 and stroke by region, **E.** Forest plot of the association between PM2.5 and stroke by the inclusion of the new studies from the updated search, **F.** Forest plot of the association between NO2 and stroke by the inclusion of the new studies from the updated search

Supplementary Table 8 Summary Table of Risk of Bias Rating for Studies on Stroke Incidence

|  |  |  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- | --- | --- |
|  |  | **Per study** | | | **Per pollutant-study pair** | | |
| Domain | Subdomain | Low-risk | Moderate-risk | High-risk | Low-risk | Moderate-risk | High-risk |
| 1.Confounding | Were all important potential confounders adjusted for in the design or analysis? | 9 | 1 | 2 | 23 | 5 | 2 |
| Validity of measuring of confounding factors | 9 | 3 | 0 | 25 | 5 | 0 |
| Control in analysis | 11 | 1 | 0 | 22 | 8 | 0 |
| **Overall** | 5 | 5 | 2 | 10 | 18 | 2 |
| 2.Selection Bias | Selection of participants into the study | 11 | 0 | 1 | 29 | 0 | 1 |
| 3.Exposure assessment | Methods used for exposure assessment | 12 | 0 | 0 | 30 | 0 | 0 |
| Exposure measurement methods comparable across the range of exposure | 12 | 0 | 0 | 30 | 0 | 0 |
| Change in exposure status | 10 | 2 | 0 | 21 | 9 | 0 |
| **Overall** | 10 | 2 | 0 | 21 | 9 | 0 |
| 4.Outcome measurements | Blinding of outcome measurements | 11 | 1 | 0 | 28 | 2 | 0 |
| Validity of outcome measurements | 11 | 1 | 0 | 28 | 2 | 0 |
| Outcome measurements | 11 | 1 | 0 | 28 | 2 | 0 |
| **Overall** | 10 | 2 | 0 | 26 | 4 | 0 |
| 5.Missing data | Missing data on outcome measures | 12 | 0 | 0 | 30 | 0 | 0 |
| Missing data on exposures | 12 | 0 | 0 | 30 | 0 | 0 |
| **Overall** | 12 | 0 | 0 | 30 | 0 | 0 |
| 6.Selective reporting | Authors reported a priori primary and secondary study aims | 12 | 0 | 0 | 30 | 0 | 0 |