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## Supplemental Material

# Evidence Synthesis of Observational Studies in Environmental Health: Lessons Learned from a Systematic Review on Traffic-Related Air Pollution

Hanna Boogaard, Richard W. Atkinson, Jeffrey R. Brook, Howard H. Chang, Gerard Hoek, Barbara Hoffmann, Sharon K. Sagiv, Evangelia Samoli, Audrey Smargiassi, Adam A. Szpiro, Danielle Vienneau, Jennifer Weuve, Frederick W. Lurmann, and Francesco Forastiere

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List of main modifications to the OHAT approach for the traffic review. [adapted from 1]

- In contrast to OHAT guidance[2], all types of cohort studies (not only prospective) and case-control studies based on incident cases were given an initial rating of moderate because three key study design features were often met (exposure precedes the outcome, individual-level data, comparison group). Similar to the OHAT approach[2], the Panel decided to start with an initial rating of low confidence for cross-sectional studies because one cannot typically assert that the exposure precedes the outcome. Ecologic studies were excluded from consideration in the traffic review. Note that in original GRADE guidance[3], all observational studies start at low confidence, but this disregards typical and potentially critical differences in quality across observational study designs.
- The decision to downgrade because of unexplained inconsistency was considered if heterogeneity was high (operationalized as $I^2$>75%, see Woodward[4]) and applied after reviewing the potential sources of heterogeneity, including risk of bias, and considering the direction of the effect estimate rather than its magnitude. Note that thresholds for the interpretation of $I^2$ can be misleading, since its value also depends on the magnitude, direction and precision of the effect estimates from the individual studies.[5] The OHAT methods provides slightly different thresholds, e.g., between 50 and 90 as substantial; and 75 to 100 as considerable heterogeneity.[2] This distinction was considered less useful by the Panel because the thresholds are not mutually exclusive, reflecting the challenges of thresholds for the interpretation of $I^2$. Of note, inconsistency was less of a concern for a group of studies all reporting associations, albeit with inconsistent magnitude, as the purpose of the assessment was to identify the presence of an association rather than to estimate its magnitude. This purpose may differ for other applications in environmental health.
- In its assessment of imprecision, the Panel considered the number of the participants included in the meta-analysis and the width of the 95% confidence intervals if the interval clearly included unity. The decision to downgrade because of imprecision was considered if the criterion for study power was met, but the effect estimate was imprecise with a wide 95% confidence interval and the confidence interval clearly included unity. For ratio measures (like relative risks), a wide (imprecise) confidence interval was defined as a difference on the log scale >0.1 from the upper to the lower 95% confidence limit.[6,7]
- To upgrade for exposure response, at least two large studies should have evaluated the actual form of the relationship (e.g., using splines or quantile analyses) and documented a monotonic exposure–response function. The Panel did not accept a statement of no deviation from linear if the linear association was null.
- The Panel considered upgrading for consistency across populations when there was clear evidence of an association across different populations, specifically in different geographical areas and between different time periods. In addition, the Panel upgraded the confidence when results were based on different study designs supported the same conclusions.
- We did not use two grading factors—indirectness and large magnitude of effect—in the process of downgrading and upgrading of confidence in the body of evidence. Indirectness was not applicable because we included only studies of human exposure to TRAP in direct association with the health outcomes. Large magnitude of effect was unlikely to be meaningful, based on experiences in the systematic reviews informing the World Health Organization Air Quality Guidelines, where large or very large effect sizes (i.e., large RR > 2 or very large RR > 5 as defined in the OHAT approach) never occurred.[8,9] Large RRs were not observed in our review either.

Table S1. Comparison of main similarities and differences between the modified OHAT assessment and the "narrative" assessment. [adapted from 1]

| | | **Modified OHAT assessment** | **"Narrative" assessment** |
|---|---|---|---|
| | Main purpose | To assess confidence in the quality of the body of evidence | To assess confidence in the presence of an association |
| | Inclusion of studies | All studies, though can be heavily geared towards the studies entering a meta-analysis | All studies—both the meta-analytic results and results of studies that were not included in meta-analysis |
| | Formal rating scheme | Formal rating scheme of up- and downgrading of certain factors with equal weighting | No formal rating scheme, and factors differ in how they are considered and weighted |
| Factors | Number, location, and sample size | Partial | Yes |
| | Study design | Yes | Yes |
| | Study population (generalizability) | Partial | Yes |
| | Magnitude and direction of the association | Partial[a] | Yes |
| | 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 populations, age groups, time periods, study designs and pollutants) | Partial | Yes |
| | Unexplained inconsistency | Yes | Yes |
| | Imprecision (chance) | Yes | Yes |
| | Publication bias | Yes | No |
| | Exposure-response | Yes | Yes |
| | Residual confounding | Yes | Yes |

[a] The OHAT approach[2] has an upgrading factor for "large magnitude of effect" that applies only if the effect size is large or very large (i.e., large RR > 2 or very large RR > 5) because residual confounding is then less likely. Large magnitude of effect was unlikely to be meaningful, based on experiences in the systematic reviews informing the World Health Organization Air Quality Guidelines, where large or very large effect sizes (i.e., large RR > 2 or very large RR > 5 as defined in OHAT) never occurred.[8,9] Large RRs were not observed in our review either.

Table S2. Summary of number of up- and downgrading factors used in the modified OHAT confidence assessment between TRAP and selected health outcomes.
adapted from 1

| | Modified OHAT rating for TRAP | Meta-analyses | | Factors decreasing confidence | | | | Factors increasing confidence | | |
|---|---|---|---|---|---|---|---|---|---|---|
| **Health outcome** | | **N** | **Pollutants** | **Risk of bias** | **Unexplained inconsistency** | **Imprecision** | **Publication bias** | **Monotonic exposure-response function** | **Consideration of residual confounding** | **Consistency across populations** |
| **Birth outcomes** | | | | | | | | | | |
| Term low birth weight | Moderate | 6 | $NO_2$, $NO_x$, CO, EC, $PM_{10}$, $PM_{2.5}$ | 4 ($NO_x$, CO, EC, $PM_{2.5}$) | 0 | 2 (CO, $PM_{10}$) | 0 | 3 ($NO_2$, $NO_x$, $PM_{2.5}$) | 2 (EC, $PM_{2.5}$) | 0 |
| Term birth weight | Low | 4 | $NO_2$, $NO_x$, EC, $PM_{2.5}$ | 4 | 2 ($NO_2$, $NO_x$) | 0 | 0 | 3 ($NO_2$, NOx, $PM_{2.5}$) | 0 | 0 |
| Small for gestational age | Moderate | 4 | $NO_2$, EC, $PM_{10}$, $PM_{2.5}$ | 2 (EC, $PM_{2.5}$) | 0 | 1 (EC) | 0 | 0 | 0 | 0 |
| Preterm birth | Low | 5 | $NO_2$, $NO_x$, NO, EC, $PM_{2.5}$ | 2 (NO, EC) | 2 ($NO_2$, $NO_x$) | 2 ($NO_x$, $PM_{2.5}$) | 0 | 0 | 0 | 0 |
| **Respiratory outcomes — Children** | | | | | | | | | | |
| Asthma onset[a] | High | 4 | $NO_2$, $NO_x$, EC, $PM_{2.5}$ | 1 ($NO_x$) | 1 ($NO_x$) | 3 ($NO_x$, EC, $PM_{2.5}$) | 0 | 1 ($NO_2$) | 0 | 0 |
| Asthma ever[b] | Moderate | 6 | $NO_2$, $NO_x$, CO, EC, $PM_{10}$, $PM_{2.5}$ | 0 | 0 | 3 (EC, $PM_{10}$, $PM_{2.5}$) | 0 | 0 | 0 | 1 ($NO_2$) |
| Active asthma[b] | Moderate | 4 | $NO_2$, $NO_x$, EC, $PM_{10}$ | 0 | 0 | 3 ($NO_x$, EC, $PM_{10}$) | 0 | 0 | 0 | 1 ($NO_2$) |
| ALRI[a] | Moderate | 2 | $NO_2$, EC | 0 | 0 | 1 (EC) | 0 | 0 | 0 | 0 |
| **Respiratory outcomes — Adults** | | | | | | | | | | |
| Asthma onset[a] | Moderate | 1 | $NO_2$ | 0 | 0 | 0 | 0 | 0 | 0 | 0 |
| ALRI[a] | Very low | 1 | $NO_2$ | 0 | 1 | 1 | 0 | 0 | 0 | 0 |
| COPD[a] | Low | 3 | $NO_2$, $NO_x$, $PM_{2.5}$ | 0 | 2 ($NO_2$, $PM_{2.5}$) | 3 | 0 | 0 | 0 | 0 |

| | Modified OHAT rating for TRAP | Meta-analyses | | Factors decreasing confidence | | | | Factors increasing confidence | | |
|---|---|---|---|---|---|---|---|---|---|---|
| **Health outcome** | | **N** | **Pollutants** | **Risk of bias** | **Unexplained inconsistency** | **Imprecision** | **Publication bias** | **Monotonic exposure-response function** | **Consideration of residual confounding** | **Consistency across populations** |
| **Cardiometabolic outcomes** | | | | | | | | | | |
| Ischemic heart disease events[a] | Moderate | 5 | $NO_2$, $NO_x$, EC, $PM_{10}$, $PM_{2.5}$ | 0 | 0 | 2 ($NO_2$, $PM_{2.5}$) | 0 | 2 ($PM_{10}$, $PM_{2.5}$) | 0 | 0 |
| Coronary events[a] | Low | 1 | $NO_2$ | 0 | 0 | 1 | 0 | 1 | 0 | 0 |
| Stroke events[a] | Low | 5 | $NO_2$, $NO_x$, EC, $PM_{10}$, $PM_{2.5}$ | 0 | 0 | 4 ($NO_2$, EC, $PM_{10}$, $PM_{2.5}$) | 0 | 2 ($PM_{10}$, $PM_{2.5}$) | 0 | 0 |
| Diabetes[a, b] | Moderate | 7 | $NO_2$ (2x), $NO_x$, EC, $PM_{10}$, $PM_{2.5}$ (2x) | 0 | 1 ($NO_2$) | 6 ($NO_2$, $NO_x$, EC, $PM_{10}$, $PM_{2.5}$ (2x)) | 0 | 1 ($NO_2$) | 1 ($NO_2$) | 0 |
| **Mortality** | | | | | | | | | | |
| All-cause | High | 7 | $NO_2$, $NO_x$, EC, $PM_{10}$, $PM_{2.5}$, Cu, Fe | 1 (Cu) | 0 | 3 ($NO_x$, $PM_{10}$, Fe) | 0 | 5 ($NO_2$, $NO_x$, EC, $PM_{10}$, $PM_{2.5}$) | 0 | 1 ($NO_2$) |
| Circulatory | High | 5 | $NO_2$, $NO_x$, EC, $PM_{10}$, $PM_{2.5}$ | 0 | 1 ($NO_x$) | 2 ($NO_x$, $PM_{10}$) | 0 | 3 ($NO_2$, EC, $PM_{2.5}$) | 0 | 1 ($PM_{2.5}$) |
| Respiratory | Moderate | 5 | $NO_2$, $NO_x$, EC, $PM_{10}$, $PM_{2.5}$ | 0 | 1 ($NO_x$) | 3 ($NO_x$, $PM_{10}$, $PM_{2.5}$) | 0 | 1 ($NO_2$) | 0 | 0 |
| Lung cancer | High | 4 | $NO_2$, EC, $PM_{10}$, $PM_{2.5}$ | 1 ($PM_{10}$) | 0 | 2 (EC, $PM_{10}$) | 0 | 2 ($NO_2$, $PM_{2.5}$) | 0 | 0 |
| Ischemic heart disease | High | 4 | $NO_2$, $NO_x$, EC, $PM_{2.5}$ | 0 | 0 | 1 ($NO_x$) | 0 | 1 ($NO_2$) | 0 | 0 |
| Stroke | Moderate | 3 | $NO_2$, $NO_x$, $PM_{2.5}$ | 0 | 0 | 1 ($NO_x$) | 0 | 0 | 0 | 0 |
| COPD | Low | 1 | $NO_2$ | 1 | 0 | 0 | 0 | 0 | 0 | 0 |
| **TOTAL** | | **87** | | **16 (18%)** | **11 (13%)** | **44 (51%)** | **0 (0%)** | **25 (29%)** | **3 (3%)** | **4 (5%)** |

ALRI = acute lower respiratory infection; COPD = chronic obstructive pulmonary disease; [a]Incidence. [b]Prevalence.

Table S3. Summary of "narrative" assessment between TRAP and selected health outcomes. [adapted from 1]

| Health outcome | "Narrative" assessment rating for TRAP | Summary "narrative" assessment |
|---|---|---|
| **Birth outcomes** | | |
| Term low birth weight | Moderate | Sizable number of well-designed large birth cohorts, mostly in North America and Europe with high traffic specificity. Associations found for $NO_X$ and $PM_{2.5}$; indirect traffic measures showed mostly null associations. |
| Term birth weight | Low | Modest number of large birth cohort and case-control studies, mostly in North America and Europe and with high traffic specificity. Many studies had high risk of bias (mainly birth registries). Strongest associations with $PM_{2.5}$; other pollutants, while trending in the expected direction, were much closer to the null; mostly null results for the indirect traffic measures. |
| Small for gestational age | Moderate | Modest number of well-designed large birth cohort and case-control studies, mostly in North America and Europe. Consistent associations across $PM_{2.5}$ and $PM_{10}$, supported by distance to roadways studies. |
| Preterm birth | Low | Sizable number of large birth cohort and case-control studies, mostly in North America and Europe with high traffic specificity. Many studies had high risk of bias (mainly birth registries). Associations largely null for the main pollutants, though the few traffic-PM and distance to roadway studies support an association. Clear associations with $NO_2$ exposure in the third trimester. |
| **Respiratory outcomes — Children** | | |
| Asthma onset[a] | Moderate | $NO_2$ estimate consistent with an association and positive but imprecise summary estimate for the other pollutants. Sizable number of well-designed large cohort studies in a variety of locations, with associations found for some pollutants and indirect traffic measures. |
| Asthma ever[b] | Moderate | Positive summary estimate for $NO_2$; $NO_x$ estimate consistent with an association; largely positive but imprecise summary estimate for most other pollutants. Sizable number of well-designed large cross-sectional studies and some cohort studies in a variety of locations, with associations found for some pollutants and indirect traffic measures. |
| Active asthma[b] | Moderate | Positive summary estimate for $NO_2$ and positive but imprecise summary estimate for the other pollutants. Sizable number of well-designed cross-sectional studies and some cohort studies in a variety of locations, with associations found for some pollutants and indirect traffic measures. |
| ALRI[a] | High | Positive summary estimate for $NO_2$ and positive but imprecise summary estimate for EC. Sizable number of well-designed large cohort and case control studies along with a smaller number of cross-sectional studies in a variety of locations, supporting associations for multiple pollutants and indirect traffic measures. |
| **Respiratory outcomes — Adults** | | |
| Asthma onset[a] | High | Positive summary estimate for $NO_2$. Sizable number of well-designed large cohort studies in a variety of locations, supporting associations for multiple pollutants. |

| | | |
|---|---|---|
| ALRI[a] | Low | Two of the three studies found positive associations with $NO_2$, but there were large differences in the effect estimates. In all three studies the confidence intervals included unity. There was only limited evidence for an association with $PM_{2.5}$ and indirect measures of traffic exposure. |
| COPD[a] | Low | Positive but imprecise summary estimate for $NO_2$ and $NO_x$. Small number of well-designed large cohort studies, inconsistent associations across pollutants and indirect traffic measures. |
| **Cardiometabolic outcomes** | | |
| Ischemic heart disease events[a] | Moderate | Positive summary estimate with marginal overlap of the null for $PM_{10}$ and evidence suggesting a monotonic exposure–response function. Evidence available for other meta-analyzed pollutants was suggestive for EC and $PM_{2.5}$, but overall less consistent. No evidence for an association with $NO_2/NO_x$. |
| Coronary events[a] | Low | Positive but imprecise summary estimate for $NO_2$ and some evidence suggesting a monotonic exposure– response function for $NO_2$. Limited evidence for other pollutants from a small number of studies. Absence of consistent confounding by noise. Limited evidence from indirect traffic measures. |
| Stroke events[a] | Moderate | Positive but imprecise summary estimates for EC, $PM_{10}$, and $PM_{2.5,}$ and evidence suggesting a monotonic exposure–response function for those pollutants. Additional evidence from studies not meta-analyzed but highly specific to traffic, and indirect traffic measures. Absence of consistent confounding by noise. No evidence for an association with $NO_2/NO_x$. |
| Diabetes[a, b] | Moderate | Positive summary estimate for $NO_2$ and diabetes prevalence, supported by consistent positive but imprecise meta-analytic estimates for the other meta-analyzed pollutant–outcome pairs. Higher effect estimates in studies with more valid outcome assessment and more comprehensive confounder control. Indirect traffic measures positive in most studies. |
| **Mortality** | | |
| All-cause | High | Sizable number of well-designed large cohort studies in a variety of locations, supporting associations for multiple pollutants and indirect traffic measures. |
| Circulatory | High | Sizable number of well-designed large cohort studies in a variety of locations, supporting associations for multiple pollutants and indirect traffic measures. |
| Respiratory | Moderate | Sizable number of well-designed large cohort studies in a variety of locations, with associations found only for some pollutants and indirect traffic measures. |
| Lung cancer | Moderate | Modest number of well-designed large cohort studies mostly in Europe, associations for some pollutants and indirect traffic measures. |
| Ischemic heart disease | High | Modest number of well-designed large cohort studies) mostly in Europe, supporting associations for multiple pollutants and indirect traffic measures. |
| Stroke | Low | Small number of well-designed large cohort studies, inconsistent associations across pollutants and indirect traffic measures. |
| COPD | Low | Small number of well-designed large cohort studies, inconsistent associations across pollutants and indirect traffic measures. |

ALRI = acute lower respiratory infection; COPD = chronic obstructive pulmonary disease; [a]Incidence. [b]Prevalence.

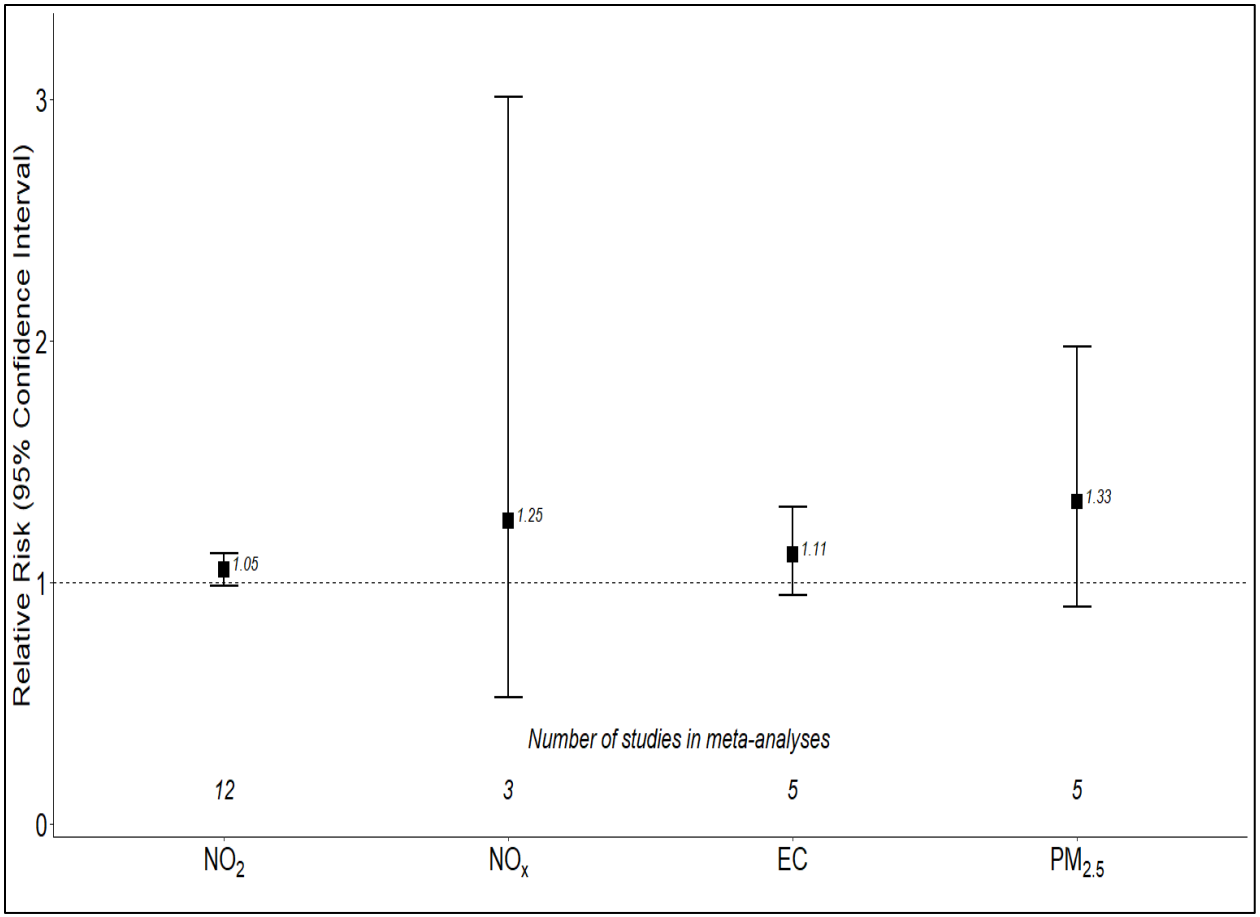


**Figure S1. Meta-analysis of associations between traffic-related air pollutants and asthma onset in children.**[adapted from 1]

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 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.

Table S4. Confidence rating for TRAP and asthma onset in children using the modified OHAT assessment.[adapted from 1]

| | **High ++++<br>Moderate +++<br>Low ++<br>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** | | | |
|---|---|---|---|---|---|---|---|---|---|---|
| **Pollutant** | **Study design** | **Initial confidence rating** (# studies) | Risk of Bias | Unexplained inconsistency | Imprecision | Publication bias | Monotonic exposure-response | Consideration of residual confounding | Consistency across populations | **Final confidence rating** |
| $NO_2$ | Cohort | +++ (*N* = 12) | 0 | 0 | 0 | 0 | +1 | 0 | 0 | ++++ (High) |
| | Rationale | Cohort design initially rated as moderate | One study at high RoB and exclusion did not alter substantially the summary estimate. | Moderate heterogeneity ($I^2$ = 73%). Plausible reasons to explain inconsistency. | Sample size met and estimate consistent with an association. | No evidence found. | Clear evidence of plausible shape of ERF (Lavigne 2018; Tetreault 2016). | Confounding in both directions possible. | Variability too large to assess consistency. | |
| $NO_X$ | Cohort | +++ (*N* = 3) | −1 | −1 | −1 | 0 | 0 | 0 | 0 | + (Very low) |
| | Rationale | Cohort design initially rated as moderate | 2/3 studies high RoB. | High heterogeneity ($I^2$ = 90%) due to magnitude and direction. | Sample size met but confidence interval wide and clearly includes unity. | No formal evaluation possible. | No evidence of plausible shape of ERF. | Confounding in both directions possible. | Too few studies to assess consistency. | |
| EC | Cohort | +++ (*N* = 5) | 0 | 0 | −1 | 0 | 0 | 0 | 0 | ++ (Low) |
| | Rationale | Cohort design initially rated as moderate | One study at high RoB but exclusion increased the summary estimate. | Low heterogeneity ($I^2$ = 47%). Plausible reasons to explain inconsistency. | Sample size met but confidence interval wide and clearly includes unity. | No formal evaluation possible. | No evidence of plausible shape of ERF. | Confounding in both directions possible. | Too few studies to assess consistency. | |
| $PM_{2.5}$ | Cohort | +++ (*N* = 5) | 0 | 0 | −1 | 0 | 0 | 0 | 0 | ++ (Low) |
| | Rationale | Cohort design initially rated as moderate | Few studies at high RoB and exclusion did not alter substantially the summary estimate. | Moderate heterogeneity ($I^2$ = 67%). Plausible reasons to explain inconsistency. | Sample size met but confidence interval wide and clearly includes unity. | No formal evaluation possible. | No evidence of plausible shape of ERF. | Confounding in both directions possible. | Too few studies to assess consistency. | |

**"Narrative" assesment for TRAP and asthma onset in children.**[adapted from 1]

The evidence base included mostly cohort studies from Europe and North America (23 out of a total of 25 studies, mostly birth cohorts); 19 were traditional cohorts with detailed individual information (sample size ranging from 184 to 14,085 children for the ESCAPE pooled cohorts), while six were large cohorts based on administrative data (including up to 761,172 children) with limited information on lifestyle factors. Traditional cohorts usually assessed asthma onset with questionnaires. Most studies used air pollutants estimated with land use regression and dispersion models.

The evidence base provides moderate evidence of an association between TRAP and asthma onset in children. The summary estimates for the association between TRAP and asthma onset in children were positive, both in administrative cohorts and in traditional cohorts with extensive confounding adjustment. However, estimates from administrative cohorts were lower and more precise. Confidence intervals of $NO_2$ estimates marginally overlapped the null, and imprecise summary estimates for the other pollutants were found. All summary estimates were heterogeneous. Factors like type of cohort (traditional or administrative) and age at which asthma onset was assessed, which differed widely between studies, might have contributed to this heterogeneity. Nonetheless, the consistent associations in substantially different populations lent further support to the confidence in the presence of the observed associations with asthma onset in children. Moreover, the fact that the majority of studies with pollutants not meta-analyzed (e.g., $PM_{10}$, $PM_{coarse}$, UFPs, and $PM_{2.5}$ from traffic emissions) also reported positive associations, provided additional support. The presence of a positive association was further supported by positive monotonic exposure–response relationships from two Canadian administrative cohorts.[10,11] Furthermore, all the assessed studies were carefully screened for traffic specificity, increasing the likelihood that the associations found pertain to traffic emissions. On the other hand, indirect traffic measures provided limited evidence of an association.

The Panel's assessment of the level of confidence in the presence of an association was moderate. Effect estimates for most traffic-related air pollutants were highly heterogeneous, and all confidence intervals of the summary estimates included unity, which suggests that some uncertainties remain regarding the association between TRAP and asthma onset in children.

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