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Long-Term Exposure to Traffic-Related Air Pollution and Diabetes: A Systematic Review and Meta-Analysis

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Objectives: We report results of a systematic review on the health effects of long-term traffic-related air pollution (TRAP) and diabetes in the adult population.

Methods: An expert Panel appointed by the Health Effects Institute conducted this systematic review. We searched the PubMed and LUDOK databases for epidemiological studies from 1980 to July 2019. TRAP was defined based on a comprehensive protocol. Random-effects meta-analyses were performed. Confidence assessments were based on a modified Office for Health Assessment and Translation (OHAT) approach, complemented with a broader narrative synthesis. We extended our interpretation to include evidence published up to May 2022.

Results: We considered 21 studies on diabetes. All meta-analytic estimates indicated higher diabetes risks with higher exposure. Exposure to NO_2 was associated with higher diabetes prevalence (RR 1.09; 95% CI: 1.02; 1.17 per 10 μg/m^3), but less pronounced for diabetes incidence (RR 1.04; 95% CI: 0.96; 1.13 per 10 μg/m^3). The overall confidence in the evidence was rated moderate, strengthened by the addition of 5 recently published studies.

Conclusion: There was moderate evidence for an association of long-term TRAP exposure with diabetes.

Keywords: diabetes, particulate matter, traffic-related air pollution, NO_2, confidence assessment

INTRODUCTION

Diabetes is a major metabolic disease characterized by persistent hyperglycemia if untreated [1]. According to the International Diabetes Federation (IDF), 537 million adults are living with diabetes worldwide with an estimated 45% who are undiagnosed. By 2045, 783 million adults are projected to have diabetes. The most common form of diabetes, type 2, accounts for approximately 90% of cases. Type 2 diabetes is characterized by insulin resistance, a diminished response to insulin of cells in the muscles, liver and fat [2]. Apart from genetic factors that contribute to diabetes risk, the most familiar risk factors include behaviors such as lack of physical activity and diet. Environmental exposures, such as air pollution are also expected to play a role [3].

In 2019, 19.9% of diabetes-related deaths and 19.6% of the diabetes-related disability-adjusted life-years (DALY) were attributed to particulate air pollution [4]. Several systematic reviews have concluded that ambient air pollution is associated with diabetes mellitus [5, 6], diabetes type 1 [7] or gestational diabetes mellitus [8]. Understanding how diabetes risk is affected by air pollution from specific sources informs useful air quality policies and other interventions. Automotive vehicular traffic is a prevalent source of air pollution, especially in cities. In animal studies, traffic-related air pollution (TRAP) was shown to elicit oxidative stress and subclinical inflammation, resulting in impaired insulin signaling and insulin resistance [9]. The sole systematic review to date evaluating the association of TRAP exposure with diabetes concluded there was a positive association between the two [10]. TRAP is a complex mixture and includes tailpipe and non-tailpipe emissions. Tailpipe emissions, from combustion of fossil fuels, contain particulate matter (PM), particularly as elemental carbon (EC) or soot, and nitrogen oxides. Non-tailpipe emissions originate from brake, tire, and road surface abrasion, and re-suspension of dust [11] and include PM trace metals such as copper (Cu), iron (Fe) and zinc (Zn). In high-income countries, non-tailpipe emissions comprise over half of the PM from traffic [12].

The Health Effects Institute (HEI) appointed an expert Panel to systematically evaluate the epidemiological evidence on the associations between TRAP and selected health outcomes including mortality, respiratory diseases, birth outcomes, and cardiometabolic health effects including diabetes. The resulting HEI Special Report was published in 2022 [13], along with a short communication paper of the main findings [14].

Here, we elaborate in depth on the findings and confidence assessment on TRAP in relation to effects on diabetes in adults, and in supplemental analyses we extend our interpretation to include evidence published after completion of the original literature search.

METHODS

The 2022 review was led by an expert Panel of 13 experts in environmental sciences, epidemiology, exposure assessment and statistics, supported by an external team and HEI staff. We used a systematic approach to search and select the literature for inclusion in the review, assess study quality, summarize results, and assess the confidence in the association between TRAP and diabetes. The methods were based on standards set by Cochrane Collaboration [15], the World Health Organization [16], and the National Institute of Environmental Health Sciences Office of Health Assessment and Translation (NIEHS OHAT) [17] and are described in more detail in the special report [13]. The protocol was published [18] and registered in PROSPERO 2019 CRD42019150642 available from: https://www.crd.york.ac.uk/prospero/display_record.php?ID=CRD42019150642.

Exposure Framework for TRAP

Pollutants emitted by motorized traffic are also emitted by other (combustion) sources. A novel framework to formalize the process of determining whether the air pollution exposure contrast in a study was dominated by traffic, we developed a novel framework [18]. In brief, the framework combined three aspects of TRAP assessment and results from a study had to entail all three aspects to be included: 1) Included studies used measures of defined traffic-related pollutants and/or indirect traffic measures, such as distance to major roads or traffic density. Eligible pollutants were NO_2, NO_x, NO, carbon monoxide (CO), EC (including related metrics such as black carbon, black smoke, and PM absorbance), ultrafine particles (UFP), non-tailpipe PM trace metals [e.g., copper (Cu), iron (Fe) and Zinc (Zn)], polycyclic aromatic hydrocarbons (PAHs), benzene, PM_{10}, $PM_{2.5}$ and PM_{coarse} (**Supplementary Table S1**). 2) Both the pollution surface and participants' addresses in the included studies had to meet the framework's thresholds for spatial resolution (e.g., 5 km grid). 3) Eligible exposure assessment methods included appropriate models or surface monitoring at sufficient spatial resolutions (**Supplementary Table S2**).

Following this framework, we excluded studies on short-term (minutes to months) effects or self-reported exposures to TRAP. We included studies that assigned individual-level exposure based on models exploiting within-city (i.e., neighborhood) contrasts, that were considered to stem primarily from traffic. Studies that exclusively used between-city contrasts were excluded. In general, the larger the study area, the less likely a measured or modelled contrast in pollution stems primarily from traffic emissions. Therefore, epidemiological studies in larger regions (e.g., state- or country-wide studies) were only included when they adjusted for area in their analysis. PM is generally not specific to traffic. We included results pertaining to PM measures (aerodynamic diameter ≤10 µm [PM_{10}] or ≤2.5 µm [$PM_{2.5}$]) in certain settings, e.g., urban areas, so long as they met more stringent requirements for inclusion. For example, PM studies based exclusively on surface monitoring were excluded, but studies using chemical transport models, dispersion models or land-use regression models with a resolution finer or equal to 5 km were included.

To specify how well the studies met the multiple criteria of the exposure framework, we defined an indicator for high traffic specificity based on even stricter criteria. We used this indicator for sensitivity analyses. High traffic specificity was mainly assigned to models with finer resolution (<1 km) or PM models considering only traffic-specific sources/emissions also with a resolution <1 km.

We converted effect estimates for pollutants expressed as ppb or ppm to μg/m³, or mg/m³ using standard WHO scaling factors (standardization of units). For example, 1 ppb NO_2 = 1.88 μg/m³, assuming an ambient pressure of 1 atm and a temperature of 25°C [19]. Effect estimates for black carbon (BC), black smoke (BS) and $PM_{2.5}$ absorption (soot) were converted into EC-equivalent estimates [20, 21].

Search Strategy

We performed a systematic literature search in PubMed and the specialized LUDOK (Literature database and services on Health Effects of Ambient Air Pollution https://www.swisstph.ch/en/projects/ludok/datenbanksuche/) database matching the PECOS (Population, Exposure, Comparator, Outcome and Study) question [15] for epidemiologic studies:

"In the adult population (P), what is the increase in risk of prevalence and incidence of diabetes (O) per unit increase (C) of long-term exposure to traffic-related air pollution (E), observed in studies relevant for the health outcome and exposure duration of interest (S)."

We searched the databases from 1 January 1980 through 31 July 2019. This end date was chosen *a priori* for the comprehensive HEI special report comprising dozens of exposures and health outcomes. The search strategy was based on a review protocol developed by the NIEHS OHAT (OHAT) and further refined using a combination of medical subheadings (MeSH) and keywords (**Supplementary Table S3**). The search strategy was supplemented with hand-searches of references in recent reviews. These were identified by the original search, an additional search in the LUDOK database or individual bibliographic databases curated by HEI and Panel members.

Eligibility Criteria

We applied the following inclusion and exclusion criteria according to the predefined PECOS statement. Studies needed to be published in English in a peer-reviewed journal.

Population

We included studies reporting on the general human adult population, aged 18 and older, from all geographical areas were included. We excluded studies reporting on occupational exposure or exclusively indoor settings as they would be difficult to compare with general population outdoor exposures.

Exposure

Studies that assessed long-term exposure (months to years) to TRAP as defined in the exposure framework were included.

Comparator

Studies analyzing health effects of TRAP either on a continuous scale or in exposure categories and reporting a quantitative measure of association plus a measure of precision were included.

Outcome

Eligible studies evaluated the incidence or prevalence of diabetes, and defined diabetes as fasting blood glucose levels above a threshold, self-reported physician-diagnosed diabetes, clinical diagnosis (ICD-9: 250, ICD-10: E10–E14) in medical records or claims, or the use of blood glucose-lowering medication.

Study Design

We included original epidemiologic studies with individual level data adopting a cohort, case–cohort, case–control, cross-sectional, or intervention design.

We excluded studies that: analyzed only area-level data, evaluated effects of short-term exposure (e.g., time-series or case cross-over studies), reported only unadjusted results, showed clear evidence of an analytical error, were strictly methodological of focused on gene-environment interactions.

Study Selection

We used DistillerSR, a web–based, systematic review software program version 2.29.8 [22], for screening, data extraction and risk of bias assessment. Initial screening based on title and abstract was done by two independent reviewers. Secondary screenings of study eligibility, especially regarding the exposure criterion, were conducted by two independent reviewers based on the full-text, supplements and related exposure assessment papers. At this full-text review stage, the reviewers documented reasons for excluding any given study (**Supplementary Table S4**). Any disagreement on inclusion was resolved by discussion.

Risk of Bias

We assessed risk of bias (RoB) in the estimation of all exposure–outcome associations that were included in the meta-analyses. We used a modified version of the tool developed for the risk of bias assessment in systematic reviews for the WHO Air Quality Guidelines [16, 23]. In brief, the risk of bias tool guides the assessment of each study's potential for bias from six domains and related subdomains of systematic error sources: 1) confounding; 2) selection bias; 3) exposure assessment; 4) outcome measurement; 5) missing data; and 6) selective reporting. Most domains have subdomains. The risk of bias for each subdomain and for each domain overall was given a rating of low, moderate or high. No summary classification was derived across the domains.

Meta-Analysis

We conducted meta-analysis for each exposure-outcome pair where three or more studies reported results; we separately analysed findings from incidence and prevalence studies. Effect estimates from single-pollutant models were selected for the meta-analysis. For presenting results on each pollutant, we applied a uniform pollutant contrast to all contributing estimates and the resulting meta-analytic summary estimate (e.g., RR per 10 μg/m³ increment in NO_2), which necessitated converting some contributing estimates (see **Supplementary Eq. S1**). We chose the contrast of a given pollutant to reflect a realistic range of exposures in most studies, by using the pollutant concentration increments from a large European ESCAPE study [24]. Meta-analysis was not conducted for the exposure metrics related to distance and density of traffic, because the varying definitions across the studies precluded such analyses. We computed summary effect estimates with random effects models, using restricted maximum likelihood to estimate the between study variance [25]. Random effects models were chosen *a priori* because of the expected differences in effect estimates related to differences in populations and pollution mixtures. Statistical heterogeneity was assessed using primarily I^2, where I^2 values of <50% were interpreted as low; between 50% and 75% as moderate; and >75% as high degree of heterogeneity [26]. The risk estimates hazard ratio (HR), relative risk (RR), incidence rate ratio (IRR) and odds ratio (OR) were considered to approximate the risk ratio [27] and were therefore analysed together as done previously [28]. We use the general term RR to indicate any of the ratio measures.

If a sufficient number of studies were available, we performed additional meta-analyses to assess consistency of the association by: geographic regions; level of risk of bias (selection bias, missing data, confounding, exposure assessment, outcome assessment); smoking adjustment; traffic specificity; and adjustment for the co-exposure noise. All analyses and plots were done with the statistical program R (version 3.6.0), using the libraries "metafor" (v.2.4-0), "meta," (v. 4.16-2), "forestplot" (v.1.10.1), "ggplot" (v. 3.3.3).

Assessment of the Evidence

We assessed: 1) the quality of the body of evidence using a modified OHAT protocol [17], which itself is based on the GRADE (Grading of Recommendations Assessment, Development and Evaluation) approach; and 2) the confidence in an association between TRAP and diabetes in a "narrative" assessment. These complementary methods are described fully in the HEI Special Report, Additional Materials 5.3 [13]. We also reflect on the confidence assessment in a separate paper (under review).

For studies included in meta-analyses, we conducted the quality assessments separately for each pollutant and study design. Starting with a confidence rating depending on study design (moderate for cohort studies and low for cross-sectional studies), the rating was then downgraded for factors that decrease confidence (high RoB, unexplained inconsistency, imprecision, and publication bias) and upgraded for factors that increase confidence in the body of evidence (monotonic exposure-response, consistency across populations, and consideration of residual confounding). We did not consider the downgrading factor "indirectness" because we included only studies of human exposure to TRAP in direct association with diabetes. Furthermore, we did not use the upgrading factor "large magnitude of effect," because this factor was unlikely to be meaningful. This *a priori* decision was based on experiences in the WHO systematic reviews of air pollution, where large or very large effect sizes (i.e., large RR > 2 or very large RR > 5 as defined in OHAT) never occurred [30, 31]. Large RRs were also not observed in our review (**Supplementary Figure S1**). Next, evaluations per pollutant were combined across study designs, and then across pollutants which was informed by the pollutant with the highest rating.

Since the OHAT assessment is geared toward studies entering a meta-analysis and focusses on the quality of the body of evidence rather than the presence of an association, the Panel also conducted a more inclusive "narrative" assessment. This additionally considered, e.g., pollutants with less than three studies reporting results or those studying indirect traffic measures. While many of the same aspects relevant to evidence synthesis were included in both assessments, there were some subtle differences, most notably regarding the magnitude and direction of the association, and the consistency across pollutants and indirect traffic measures.

In both assessments we rated the level of confidence as high, moderate, low or very low. The two approaches were considered complementary and combined into an overall confidence assessment.

Updated Search and Supplemental Analyses

To interpret results of our original review (indicated in tables and figures as "Global 2022") in light of evidence published after the ending date of this review's literature search, we repeated the search for eligible studies, starting from June 2019 up to May 2022. Studies identified in this new search were not incorporated into the risk of bias and confidence assessment. However, we incorporated their findings into supplemental meta-analyses to investigate the robustness of our original meta-analytic results to the inclusion of recently published evidence (indicated in tables and figures as "Global 2023").

RESULTS

Study Selection

The search strategy for all health outcomes considered for the comprehensive review yielded 13,660 unique articles. After initial screening, exclusion of studies not meeting the inclusion criteria, and restricting to articles on diabetes outcomes, we identified 45 studies, 21 of which entered this review after full-text assessment (**Table 1**, **Supplementary Figure S2**: PRISMA flow chart). Most studies were excluded, because the spatial scale of the pollution surface or participants' address did not meet the criteria (**Supplementary Table S4**).

Study Description

All studies were published after 2010. Nine studies estimated the association of TRAP with incidence of diabetes, 10 with diabetes prevalence, and two with both incidence and prevalence (the Rome Longitudinal [32] and the SAPALDIA study [33, 34]). The majority of the studies were conducted in Europe (10) or North America (8), followed by China (2) and Australia (1). Three studies were exclusively of women (BWHS [35, 36], SALIA [37], ALSWH [38]). NO_2 or NO_x were the most commonly studied pollutants (17), 11 studies investigated at least one particle metric, and seven included proximity metrics. Exposure levels ranged from very low (e.g., Australia, Canada) to high (e.g., Rome, Italy, China), with ranges in annual means

TABLE 1 | Characteristics of the studies reporting on the association of traffic-related air pollution and diabetes incidence or prevalence (Global 2022).

References	Study name	Location	Study period	Study design in analysis	Sample size N (% women)	Age at baseline	Ascertainment of diabetes	Confounder adjusted for	Results (estimate[a], 95% CI, increment)
[45]	DDCH	Copenhagen and Aarhus, Denmark	1993–2006	Cohort	51,818 (53%)	56	Disease register	Age, sex, iSES, smoking, behavior[b], BMI	Incidence NO_2 1.04 (1.00, 1.08) per 4.9 μg/m[3c] NO_x 1.02 (1.00, 1.04) per 11.4 μg/m[3c] Distance 1.07 (0.95, 1.21) <50 vs. >50 m Density 1.02 (1.00, 1.04) per 1,200 vehicle-km/day
[40]	ONPHEC	Toronto, Canada	1996–2012	Cohort	1,056,012 (53%)	51	Administrative data from hospital and insurance registries	Age, sex, nSES, comorbidities[d]	Incidence NO_2 1.06 (1.05, 1.07) per 4.0 ppb[c] PNC 1.06 (1.05, 1.08) per 9948.4 particles/cm^3
[41]	British Columbia Diabetes Cohort	Vancouver, British Columbia, Canada	1994–2002	Cohort	380,738 (54%)	58	Administrative data from insurance registry	Age, sex, nSES	Incidence NO_2 1.00 (0.98, 1.02) per 8.4 μg/m[3c] NO 1.04 (1.01, 1.05) per 13.13 μg/m^3 $PM_{2.5abs}$ 1.03 (1.01, 1.04) per 0.9 1e-5/m[c] $PM_{2.5}$ 1.03 (1.01, 1.05) per 1.6 μg/m[3c]
[35]	BWHS	Los Angeles, California, United States	1995–2005	Cohort	39,922 (100%)	39	Doctor-diagnosed	Age, iSES, nSES, smoking, behavior, BMI, familial diabetes	Incidence NO_x 1.25 (1.07, 1.46) per 12.4 ppb[c]
[36]	BWHS	United States	1995–2013	Cohort	430,032 (100%)	39	Doctor-diagnosed	Age, iSES, nSES, smoking, behavior, BMI, area, questionnaire cycle	Incidence NO_2 0.90 (0.82, 1.00) per 9.7 ppb[c]
[63]	Hoorn Diabetes Screening	West Friesland, Netherlands	1998–2000	Cross sectional	8018 (51%)	Range: 50–75	Multimodal[e]	Age, sex, nSES, (BMI)[f]	Prevalence NO_2 1.03 (0.82, 1.31) 14.2–15.2 vs. 8.8–14.2 μg/m^3 NO_2 1.25 (0.99, 1.56) 15.2–16.5 vs. 8.8–14.2 μg/m^3 NO_2 0.80 (0.63, 1.02) 16.5–26 vs. 8.8–14.2 μg/m^3 Distance 0.88 (0.70, 1.13) 2–74 vs. 220–1,610 m Distance: 1.17 (0.93, 1.48) 74–140 vs. 220–1,610 m Distance: 1.12 (0.88, 1.42) 140–220 vs. 220–1,610 m Density: 1.09 (0.85, 1.38) 882–2007 vs. 63–516 thousand vehicles/day Density: 1.13 (0.89, 1.44) 680–882 vs. 63–516 thousand vehicles/day Density: 1.25 (0.99, 1.59) 516–680 vs. 63–516 thousand vehicles/day
[44]	Plovdiv Diabetes Survey	Plovdiv, Bulgaria	2014–2014	Cross sectional	513 (61%)	36	Doctor-diagnosed	Age, sex, iSES, smoking, behavior, BMI, familial diabetes, noise	Prevalence $PM_{2.5}$ 1.32 (0.28, 6.24) >25 vs. <25 μg/m^3 PAH (BaP) 1.76 (0.52, 5.98) >6 vs. <6 ng/m^3

(Continued on following page)

TABLE 1 | (*Continued*) Characteristics of the studies reporting on the association of traffic-related air pollution and diabetes incidence or prevalence (Global 2022).

References	Study name	Location	Study period	Study design in analysis	Sample size N (% women)	Age at baseline	Ascertainment of diabetes	Confounder adjusted for	Results (estimate[a], 95% CI, increment)
[34]	SAPALDIA	Multiple cities, Switzerland	2002–2002	Cross sectional	6,392 (52%)	52	Multimodal	Age, sex, iSES, nSES, smoking, behavior, BMI, area	Prevalence NO_2 1.21 (1.05, 1.39) per 10 μg/m^{3c} PM_{10} 1.44 (1.21, 1.71) per 10 μg/m^{3c}
[33]	SAPALDIA	Multiple cities, Switzerland	2002–2011	Cohort	2,631 (52%)	53	multimodal	Age, sex, iSES, nSES, smoking, behavior, BMI, area	Incidence NO_2 0.92 (0.67, 1.26) per 15 μg/m^{3c}
[42]	CANHEART	Ontario, Canada	2008–2008	Cross sectional	2,496,458 (52%)	53	Disease register	Age, sex, iSES, nSES, area	Prevalence NO_2 1.16 (1.14, 1.17) per 10 ppb[c]
[37]	SALIA	North Rhine-Westphalia, Germany	1985–2006	Cohort	17,752 (100%)	54	Multimodal	Age, sex, smoking, BMI	Incidence NO_2 1.42 (1.16, 1.73) per 15 μg/m^{3c} $PM_{2.5abs}$ 1.27 (1.09, 1.48) per 0.39 1e-5/m[c] Distance 2.54 (1.31, 4.91) (low education) < 100 vs. >100 m Distance 0.92 (0.58, 1.47) (high education) < 100 vs. >100 m
[38]	ALSWH	Australia	2006–2011	Cross sectional	269,912 (100%)	Range: 31–90	Doctor-diagnosed	Age, smoking, behavior, BMI, area	Prevalence NO_2 1.04 (0.91, 1.20) per 3.7 ppb[c] Distance: 0.99 (0.95, 1.04) 3 per 1 km
[64]	CAFEH	Boston, Massachusetts, United States	2009–2012	Cross sectional	653 (58%)	60	Doctor-diagnosed	Age, iSES	Prevalence PNC 0.71 (0.46, 1.10) per 1 particles/cm^3; log-transformed
[65]	CHAMPIONS	Leicestershire, United Kingdom	2004–2011	Cross sectional	10,443 (47%)	59	Clinical examination	Age, sex, iSES, nSES, smoking, behavior, BMI, area	Prevalence NO_2 1.10 (0.92, 1.32) per 10 μg/m^{3c} PM_{10} 1.3 (0.5, 2.9) per 10 μg/m^{3c} $PM_{2.5}$ 1.6 (0.4, 4.6) per 10 μg/m^{3c}
[66]	MESA	Multiple cities, United States	2000–2012	Cohort	5,135 (53%)	62–64 (with diabetes)	Clinical examination	Age, sex. iSES, nSES, smoking, behavior, BMI, familial diabetes, area	Incidence NO_x 1.04 (0.77, 1.40) per 47.1 ppb[a] $PM_{2.5}$ 1.05 (0.87, 1.26) per 2.43 μg/m^{3a} Distance 0.96 (0.80, 1.16) <100 vs. >100 m Prevalence NO_x 1.29 (0.94, 1.76) per 47.1 ppb $PM_{2.5}$ 1.16 (0.94, 1.42) per 2.43 μg/m^{3c} Distance 1.10 (0.91, 1.34) <100 vs. >100 m
[67]	Nurses' Health Health Professionals Follow-Up	United States	1989–2002	Cohort	89,460 (83%)	55	Multimodal	Age, sex, iSES, smoking, behavior, BMI, familial diabetes, hypertension, year, area	Incidence Distance 1.11 (1.01, 1.23) 0–49 vs. >200 m Distance 0.96 (0.63, 1.48) 50–99 vs. >200 m Distance 0.96 (0.87, 1.06) 100–199 vs. >200 m

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TABLE 1 | (*Continued*) Characteristics of the studies reporting on the association of traffic-related air pollution and diabetes incidence or prevalence (Global 2022).

References	Study name	Location	Study period	Study design in analysis	Sample size N (% women)	Age at baseline	Ascertainment of diabetes	Confounder adjusted for	Results (estimate[a], 95% CI, increment)
[32]	Rome Longitudinal	Rome, Italy	2008–2013	Cohort	1,319,193 (55%)	Range: 35–70	Administrative data from hospital and insurance registries	Age, sex, iSES	Incidence NO_2 1.00 (1.00, 1.01) per 10 μg/m^{3c} NO_x 1.01 (1.00, 1.01) per 20 μg/m^{3c} $PM_{2.5abs}$ 1.00 (0.98, 1.02) per 1 × 10^{-5}/m^c PM_{10} 1.00 (0.99, 1.02) per 10 μg/m^3 $PM_{2.5}$ 1.00 (0.98, 1.02) per 5 μg/m^{3c} PMcoarse 0.99 (0.97, 1.02) per 10 μg/m^3 Prevalence NO_2 1.00 (1.00, 1.01) per 10 μg/m^{3c} NO_x 1.01 (1.00, 1.01) per 20 μg/m^3 $PM_{2.5abs}$ 0.98 (0.96, 0.99) per 1 × 10^{-5}/m PM_{10} 0.99 (0.98, 1.00) per 10 μg/m^{3c} $PM_{2.5}$ 0.98 (0.96, 1.00) per 5 μg/m^{3c} PM_{coarse} 0.96 (0.94, 0.98) per 10 μg/m^3
[68]	ELISABET	Lille and Dunkirk, France	2011–2013	Cross sectional	2,797 (53%)	53	Clinical examination	Age, sex, iSES, smoking, behavior, BMI, area	Prevalence NO_2 1.06 (0.90, 1.25) per 5 μg/m^{3c} PM_{10} 1.04 (0.86, 1.25) per 2 μg/m^{3c}
[39]	HNR	Ruhr Areas, Germany	2000–2008	Cohort	3,607 (52%)	59	Clinical examination	Age, sex, iSES, nSES, smoking, behavior, BMI, area	Incidence PM_{10} 1.05 (1.00, 1.10) per 1 μg/m^3 $PM_{2.5}$ 1.03 (0.95, 1.12) per 1 μg/m^{3c} traffic $PM_{2.5}$ 1.36 (0.97, 1.89) per 1 μg/m^3 Distance 1.37 (1.04, 1.81) <100 vs. 100–200 m
[69]	33 CCHS	Multiple cities, China	2009–2009	Cross sectional	15,477 (47%)	45	Clinical examination	Age, sex, iSES, smoking, behavior, BMI, familial diabetes, area	Prevalence NO_2 1.22 (1.12, 1.33) per 9 μg/m^3
[43]	33 CCHS	Multiple cities, China	2009–2009	Cross sectional	15,477 (47%)	45, both	Clinical examination	Age, sex, iSES, nSES, smoking, behavior, (BMI)[e], familial CVD, co-pollutants	Prevalence NO_2 1.20 (1.08, 1.32) per 10 μg/m^{3c}

Abbreviations: CI, confidence interval; iSES, measures of individual socioeconomic status such as education; income; nSES, measures of neighborhood socioeconomic status such as neighborhood household income; BMI, body mass index; area, area level adjustments such as city DDCH.

[a]Effect estimates can be ORs, RRs, HRs, or IRRs, depending on the analysis.

[b]Adjusted for other behavioral factors other than smoking such as diet, alcohol consumption or physical activity.

[c]Effect estimates included in meta-analysis.

[d]Adjusted for hypertension, COPD, asthma, congestive heart failure, acute myocardial infarction, and cancer.

[e]Multimodal strategies to identify diabetes cases include a combination of self-reported doctor-diagnosed cases, clinical examinations of blood sugar levels or use of medication for glycaemic control.

[f]BMI was not included but considered.

of 5–42 µg NO_2/m^3 and 4–25 µg $PM_{2.5}/m^3$. The 11 cohort studies, all conducted in Europe or North America, included 2,931 to over 1 million participants with a range of follow-up of 4–16 years. The ten cross-sectional studies had 513 up to 2.5 million participants.

Diabetes definitions varied, and included self-report of physician-diagnosed diabetes (five studies), disease registers (two studies), administrative data (e.g., insurance claims) indicating diabetes diagnosis or prescription of hypoglycemic medications (three studies), clinical examinations at study centers, measuring blood glucose (five studies), or using a combination of different data sources (blood glucose measurements, questionnaire, medication, data linkage, six studies). Most smaller cohort studies (n < 10,000 participants) used clinical examinations (SAPALDIA, HNR, MESA, CHAMPIONS) or self-reported physician-diagnosed diabetes, whereas larger administrative cohort or cross-sectional studies typically relied on linkage to administrative databases or registers (e.g., ONPHEC, Rome longitudinal, **Table 1**).

Results of Meta-Analysis

Meta-analyses indicated positive associations of all traffic-related air pollutants with diabetes incidence and prevalence, though estimates were imprecise (**Figure 1**). For example, higher exposure to NO_2, the TRAP for which there were the most studies (seven studies), corresponded to higher diabetes prevalence (RR 1.09; 95% CI: 1.02; 1.17 per 10 µg/m^3); the individual estimates were highly heterogeneous, especially for the NO_2 results (**Figure 2**). The association was less pronounced for diabetes incidence (RR 1.04; 95% CI: 0.96; 1.13 per 10 µg/m^3; **Figure 3**). The summary estimates for EC, $PM_{2.5}$ and PM_{10} were also positive but even less precise and based on fewer individual studies.

Results From Studies Not Entering Meta-Analysis

For pollutants not included in the meta-analyses (such as ultrafine particles PNC or NO, marked in **Table 1** without [c]) elevated risks were observed for measures of NO_x but not the various measures of PM in the prevalence analyses. The incidence analyses showed elevated risks for diabetes with NO and PNC. Notably, the traffic-specific $PM_{2.5}$ in the HNR cohort [39] yielded a substantially larger association compared to the total $PM_{2.5}$ mass estimates (RR 1.36 vs. 1.03 or 1.05 per 1 µg/m^3). All but one study (MESA) showed positive (though imprecise) associations with distance and density of traffic (**Table 1**, **Supplementary Figures S3, S4**).

Risk of Bias and Subgroup and Sensitivity Analysis

The ONPHEC [40], British Columbia Diabetes Cohort [41], CANHEART [42], and Rome Longitudinal study [32] were considered to have high RoB due to incomplete confounder control (missing adjustment for smoking or socioeconomic status). The SAPALDIA cohort [33, 34] was considered to have high potential for selection bias due to long survival in a cohort before inclusion into the analysis and the 33 CCHS study had extensive missing data [43] (**Supplementary Table S5**).

In subgroup analyses excluding these studies, association magnitudes were similar or larger (**Supplementary Tables S6, S7**). For example, restricting to prevalence studies with smoking adjustment eliminated heterogeneity entirely and yielded meta-analytic estimates for NO_2 of 1.09 [95% CI: 1.02; 1.17] (from 1.17 [1.09; 1.25]), and for PM_{10} of 1.19 [0.87; 1.63] (from 1.43 [1.28; 1.59]).

Five studies evaluated confounding by concurrent noise exposure (British Columbia Diabetes Cohort, Plovdiv Diabetes Survey, both SAPALDIA analyses, Rome longitudinal [32–34, 41, 44], **Supplementary Table S8**). Most TRAP effect estimates were attenuated upon noise adjustment, but still showed elevated risks. For example, the NO_2 prevalence results in the SAPALDIA study were reduced from 1.21 [1.05; 1.39] to 1.19 [1.03, 1.38] when adjusting for noise [34].

Confidence Assessments

The modified OHAT assessment was conducted for the 16 studies entering meta-analyses (**Table 2**). Among factors reducing the quality of the evidence, the most common factor was imprecision (wide CI and including unity despite sufficient sample size). For NO_2 and diabetes incidence, the confidence was upgraded due to monotonic exposure-response functions reported in two studies [40, 45]. We upgraded the evidence on NO_2 and prevalence due to potential downward bias. We arrived at a moderate confidence assessment for overall TRAP based on the moderate confidence for NO_2. While the confidence was low for the other pollutants, the associations for these pollutants were suggestive of an association, though imprecise.

A confidence rating of moderate was also reached in the narrative assessment that considered all studies. This rating was based on the meta-analytical evidence of an association of NO_2 with diabetes prevalence and suggestive evidence of an association of NO_2, NO_x, traffic-related PM with incident and prevalent diabetes. The confidence in the evidence was further supported by the monotonic exposure-response relationships reported in two studies, positive albeit imprecise associations involving indirect traffic measures, and numerous positive associations from studies that adjusted for likely confounders. Further, associations generally remained positive after adjustment for noise exposure (**Supplementary Table S8**). Finally, effect estimates were larger among the subgroup of studies with more extensive confounder adjustment, and among studies that used comprehensive outcome ascertainment methods (versus self-report and administrative data) (**Supplementary Tables S6, S7**).

Study Characteristic and Supplemental Analysis of Studies From the Extended Search

Since our systematic search ending in July 2019, new studies have been published on TRAP and diabetes. We extended our search to May 2022 resulting in 304 hits. Five studies met the inclusion

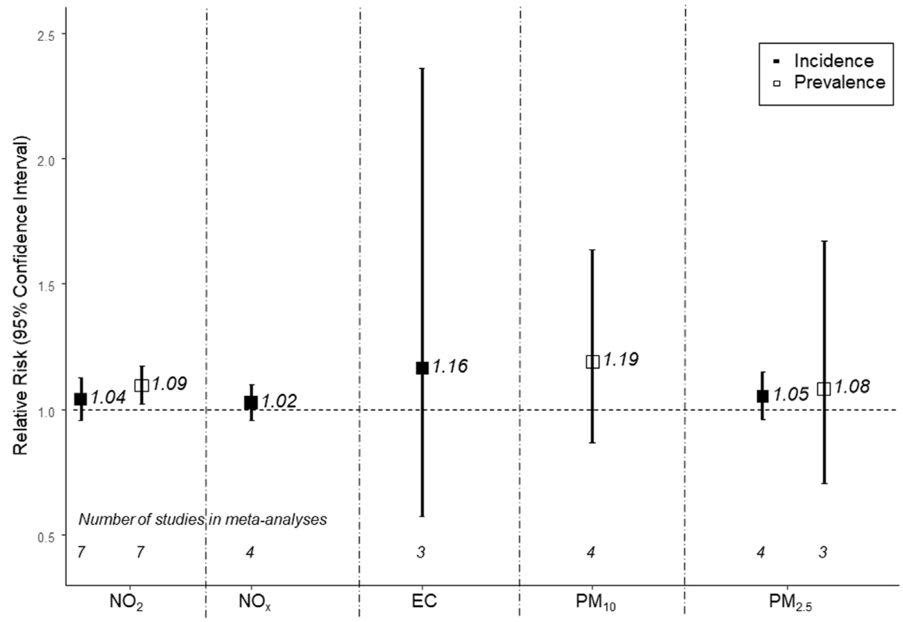

FIGURE 1 | Meta-analysis of associations between traffic-related air pollutants and diabetes prevalence (empty squares) and incidence (filled squares) (Global 2022). The following increments were used: 10 μg/m^3 for NO_2, 20 μg/m^3 for NO_x, 1 μg/m^3 for EC, 10 μg/m^3 for PM_{10}, and 5 μg/m^3 for $PM_{2.5}$. 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.

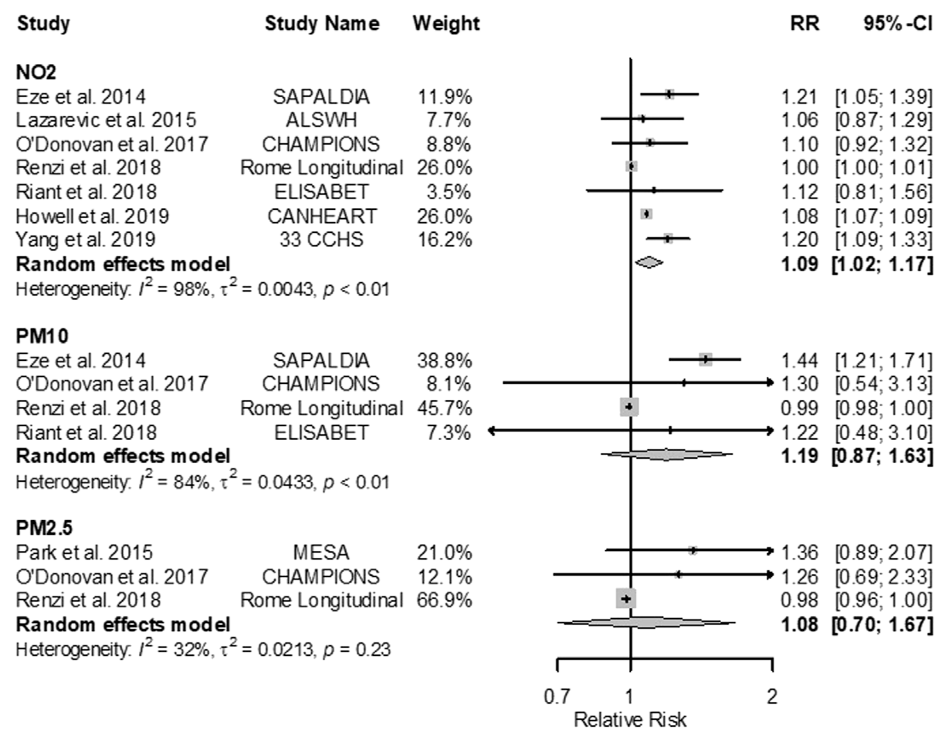

FIGURE 2 | Forest plots of adjusted RRs (95% CIs) for diabetes prevalence with NO_2, PM_{10}, and $PM_{2.5}$ (Global 2022). The size of the grey squares represents the weight of the study in the meta-analysis. The following increments were used: 10 μg/m^3 for NO_2, 20 μg/m^3 for NO_x, 1 μg/m^3 for EC, 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.

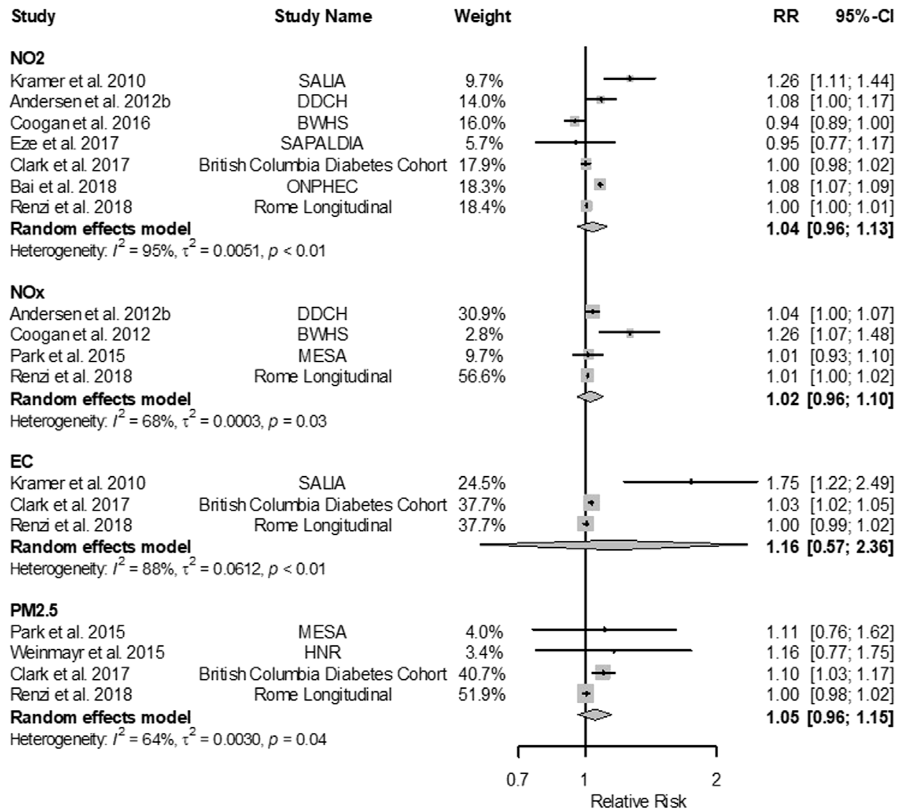

FIGURE 3 | Forest plots of adjusted RRs (95% CIs) for diabetes incidence with NO_2, NO_x, EC and $PM_{2.5}$ (Global 2022). The size of the grey squares represents the weight of the study in the meta-analysis. The following increments were used: 10 μg/m^3 for NO_2, 20 μg/m^3 for NO_x, 1 μg/m^3 for EC, 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.

criteria (**Table 3**) adding estimates to all meta-analyses on diabetes incidence and the $PM_{2.5}$ prevalence analyses (**Supplementary Figures S5–S7**). While the pooled estimates did not change dramatically, risk estimates were still elevated and confidence intervals became narrower; especially for the $PM_{2.5}$-incidence analyses that was borderline significant (**Supplementary Figure S5**). Additionally, the Danish study [46] with traffic-specific pollutant estimates and the HNR analysis from 2020 [47] with longer follow-up and refined source-specific exposure assessment as compared to the 2015 analysis [39] showed significantly elevated risks related to traffic-specific NO_2, EC, and $PM_{2.5}$. Both also add to the evidence on ultrafine particles. However, measures were not comparable and thus meta-analysis was not possible for the different metrics of UFP. Overall, the results of the HEI 2022 review were strengthened by supplemental analyses of the studies identified in the updated search.

DISCUSSION

In this comprehensive systematic review of epidemiologic evidence on the association of TRAP with adult diabetes, we identified 21 pertinent studies. Our summary estimates generally suggested an adverse association of TRAP with diabetes risk, although some of the effect estimates were imprecise and based on small numbers of studies per pollutant-outcome pair. A statistically significant association was reported between NO_2 and diabetes prevalence with a summary estimate of 1.09 (95% CI: 1.02; 1.17) per 10 μg/m^3, supported by consistently positive but imprecise estimates for the other traffic-related air pollutants. Results were strengthened by the reporting of a monotonic exposure-response function in two studies [40, 45], positive associations in studies examining indirect traffic measures, and robust results correcting for traffic noise. The confidence assessment yielded a moderate confidence in the evidence for an association between long-term exposure to TRAP and diabetes. We noted more consistent associations of TRAP with diabetes prevalence than incidence.

The newly identified five studies, with mostly rigorous outcome assessments strengthened the results. Confidence intervals of meta-analytic estimates in the supplemental analyses were less wide, though estimates were still not significantly elevated.

Findings in Relation to Other Reviews

Recent reviews of ambient air pollution—as opposed to our focus on traffic-related air pollution—in association with

TABLE 2 | Confidence rating for the quality in the body of evidence for traffic-related air pollution and diabetes (Global 2022).

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	Rating across study designs
	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	+++ (N = 7)	0	-	-	0	+	0	0	++ (Low)	+++ (Moderate) The combined rating is based on the higher confidence rating. Both study designs show evidence of a positive association, therefore no reason for a downgrade
	Rationale	Cohort design initially rated as moderate	Four studies with high RoB but results not sensitive to exclusions of those studies	High heterogeneity (I^2 = 95%), due to both magnitude and direction	Sample size met, but confidence interval wide and includes unity	No formal evaluation possible	Two influential studies show monotonic ERF (Andersen, 2012b; Bai, 2018)	Confounding in both directions possible	Too few studies to evaluate		
	Cross-sectional	++ (N = 7)	0	0	0	0	0	+	0	+++ (Moderate)	
	Rationale	Cross-sectional design initially rated as low	Three studies with high RoB, increased or stable effect estimates after excluding high RoB studies	High heterogeneity (I^2 = 98%) due to magnitude not direction	Sample size met, and confidence interval does not include unity	No formal evaluation possible	No evidence of plausible shape of ERF.	Larger estimates in studies with better confounder control suggests residual confounding toward the null	Across different populations robust effect, but too few studies		
NO_X	Cohort	+++ (N = 4)	0	0	-	0	0	0	0	++ (Low)	NA
	Rationale	Cohort design initially rated as moderate	One study high RoB, but increased estimate after exclusion	Moderate heterogeneity (I^2 = 68%) mostly due to magnitude not direction	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 to assess robustness across populations		
EC	Cohort	+++ (N = 3)	0	0	-	0	0	0	0	++ (Low)	NA
	Rationale	Cohort design initially rated as moderate	Elevated estimate based on one study with moderate RoB. Two studies with high RoB show effect closer to the null	High heterogeneity (I^2 = 88%) due to magnitude not direction	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	Insufficient evidence for robustness across populations		

(Continued on following page)

TABLE 2 | (*Continued*) Confidence rating for the quality in the body of evidence for traffic-related air pollution and diabetes (Global 2022).

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	Rating across study designs
	Study design	**Initial confidence rating (# studies)**	**Risk of bias**	**Unexplained inconsistency**	**Imprecision**	**Publication bias**	**Monotonic exposure-response**	**Consideration of residual confounding**	**Consistency across populations**		
PM_{10}	Cross-sectional	++ (N = 4)	0	0	-	0	0	0	0	+ (Very low)	NA
	Rationale	Cross-sectional design initially rated as low	One of 4 studies high RoB but increased estimate upon exclusion of the high RoB study	High heterogeneity (I^2 = 84%) due to magnitude not direction	Sample size met, but confidence interval wide and includes unity	No formal evaluation possible	No evidence of plausible shape of ERF.	Larger estimates in studies with better confounder control, but number of studies considered too small for upgrade	All studies European, no consistency check possible		
$PM_{2.5}$	Cohort	+++ (N = 4)	0	0	-	0	0	0	0	++ (Low)	++ (Low)
	Rationale	Cohort design initially rated as moderate	Two studies high RoB, but increased estimate upon exclusion of high RoB studies	Moderate heterogeneity (I^2 = 64%) due to magnitude not direction	Sample size met, but confidence interval wide and includes unity	No formal evaluation possible	No evidence of plausible shape of ERF.	Larger estimates in studies with better confounder control, but number of studies considered too small for upgrade	Insufficient evidence for robustness across populations		Both study designs show estimates in the same direction
	Cross-sectional	++ (N = 3)	0	0	-	0	0	0	0	+ (Very low)	
	Rationale	Cross-sectional design initially rated as low	One study high RoB, no sensitivity analysis due to low numbers	Low heterogeneity (I^2 = 32%)	Sample size met, but confidence interval wide and includes unity	No formal evaluation possible	No evidence of plausible shape of ERF	Larger estimates in studies with better confounder control, but number of studies too small	Insufficient evidence for robustness across populations		

The downgrading factor indirectness and the upgrading factor large magnitude of effect were not considered further.

TABLE 3 | Characteristics of the studies from extended search up to May 2022 reporting on the association of traffic-related air pollution and diabetes incidence or prevalence (Global 2023).

Reference	Study name	Location	Study period	Study design in analysis	Sample size N (% women)	Age at baseline	Ascertainment of diabetes	Confounder adjusted for	Results (estimate[a], 95% CI, increment)
[47]	HNR	Ruhr Areas, Germany	2006–2015	Cohort	2,451 (52%)	58	Self-reported or medication or clinical examination	Age, sex, smoking, behavior, noise (extended models unchanged results iSES, nSES)	Incidence NO_2: 1.02 (0.99, 1.05) per 1 μg/m[3b] traffic NO_2: 1.06 (1.01, 1.12) per 1 μg/m^3 PM_{10}: 1.06 (1.01, 1.12) per 1 μg/m^3 traffic PM_{10}: 2.00 (1.19, 3.34) per 1 μg/m^3 $PM_{2.5}$: 1.06 (0.98, 1.16) per 1 μg/m[3b] traffic $PM_{2.5}$: 2.13 (1.26, 3.61) per 1 μg/m^3 PNC<1: 1.29 (1.10, 1.53) per 500 particles/mL traffic PNC < 1: 2.11 (1.04, 4.28) per 500 particles/mL
[46]	National Danish Register	Denmark	2005–2017	Prospective cohort	2,631,488 (51.4%)	52	Administrative data from hospital and prescription registers	Age, sex, iSES, nSES	Incidence NO_2: 1.056 (1.046, 1.065) per 7.15 μg/m[3b] traffic NO_2: 1.039 (1.031, 1.047) per 5.17 μg/m^3 EC: 1.022 (1.016, 1.027) per 0.28 μg/m[3b] traffic EC: 1.037 (1.030, 1.043) per 0.17 μg/m^3 $PM_{2.5}$: 1.043 (1.031, 1.056) per 1.85 μg/m[3b] traffic $PM_{2.5}$: 1.026 (1.020, 1.031) per 0.37 μg/m^3 PNC: 1.052 (1.042, 1.063) per 4,248 particles/mL traffic PNC: 1.049 (1.040, 1.058) per 1,698 particles/mL
[70]	487 Municipalities	Multiple cities, Indonesia	2013	Cross sectional	647,947 (52%)	42	Self-reported	Age, sex, iSES, smoking, behavior, BMI, area, intermediate	Prevalence $PM_{2.5}$: 1.09 (1.05, 1.14) per 10 μg/m^3
[71]	JHS	Jackson, Mississippi, United States	2000–2008	Cohort	5,128 (63%)	55	Clinical examination or medication	Age, sex, nSES, smoking, behavior, familial diabetes, BMI, others, area	Incidence $PM_{2.5}$: 1.09 (0.90, 1.32) per 0.81 μg/m[3b] Prevalence $PM_{2.5}$: 1.08 (1.00, 1.17) per 0.81 μg/m^3 Distance: 0.91 (0.61, 1.36) <150 vs. 1,000 m Distance: 0.94 (0.74, 1.20) 150–299 vs. 1,000 m Distance: 1.01 (0.91, 1.12) 300–999 vs. 1,000 m
[72]	SALSA	Sacramento, California, United States	1998–2007	Cohort	1,075 (59%)	71	Self-reported, medication or clinical examination	Age, sex, iSES, nSES, smoking, co-pollutant	Incidence NO_2: 1.02 (0.98, 1.05) per 6.1 ppb[b] NO_x: 1.13 (0.96, 1.33) per 2.3 ppb[b] $PM_{2.5}$: 1.20 (1.03, 1.40) per 1.9 μg/m[3b]

Abbreviations: CI, confidence interval; iSES, measures of individual socioeconomic status such as education; income; nSES, measures of neighborhood socioeconomic status such as neighborhood household income, BMI, body mass index; area, area level adjustments such as city DDCH.

[a]*Effect estimates can be ORs, RRs, HRs, or IRRs, depending on the analysis.*

[b]*Effect estimates included in meta-analysis*

diabetes found similar results (**Supplementary Table S9**). With a larger study base, Lui et al. [6] and Yang et al. [5] not only reported significantly elevated risks for diabetes prevalence with NO_2, but also with PM_{10}, and $PM_{2.5}$ (for example, including 11 studies vs. 3 studies in the $PM_{2.5}$ prevalence analyses). Diabetes incidence risk was significantly elevated with $PM_{2.5}$ in both reviews, and additionally with PM_{10} in the analysis by [5] considering two more studies. As in our analysis, the reviews did not find a significantly elevated risk with NO_2 and diabetes incidence. Effect estimates seemed slightly larger in our prevalence analysis, though more imprecise (for example, 1.09 [1.02; 1.17] vs. 1.05 [1.03; 1.08] and 1.07 [1.04; 1.11]) in the NO_2 prevalence analysis. Another review reported elevated diabetes risks in association with living close to major roads [48].

Biological Mechanisms

Plausible pathways regarding how TRAP could lead to diabetes are discussed in the literature. Important mechanisms include oxidative stress induced inflammation leading to endothelial and mitochondrial dysfunction, resulting in impaired insulin signalling and insulin resistance [10]. Animal studies provide evidence that exposure to high concentrations of traffic particles may be a risk factor in the development of diabetes [49–51]. Studies evaluating mechanistic pathways underlying such metabolic perturbations induced by urban PM and near roadway air pollution have identified possible contributory roles played by inflammation and altered fatty acid metabolism. Indeed, Lucht et al. [47] observed that diabetes incidence in an adult population was mediated by markers of inflammation (adiponectin and C-reactive protein). While our results build on evidence found especially for the association with NO_2, mechanistic studies on NO_2 are scarce [52] and NO_2 could be an indicator for other highly correlated pollutants from the same source. However, a recent study on Witstar rats was able to demonstrate reactive oxygen species formation and mitochondrial and endothelial dysfunction after 3 weeks of repeated high NO_2 exposure [53]. Epidemiologic studies also found TRAP-associated higher risks for glucose homeostasis dysregulation measured as insulin concentration in cord blood, fasting blood glucose, insulin sensitivity, HOMA-IR, HbA1c in newborns [54], children [55, 56], adolescents [57], and adults [58] indicating a role of early-life exposure.

Strengths

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 are major strengths of this review. Even though none of the pollutants are uniquely traffic-specific, the use of several indicators of TRAP allowed the evaluation of consistency across pollutants and enabled the Panel to base its conclusions on a larger number of studies with diverse exposure metrics. Additionally, the application of two complementary methods (the modified OHAT assessment for studies entering meta-analyses and the narrative assessment considering all studies for the evaluation of the epidemiological evidence maximizes what can be learned from the epidemiologic studies, including evidence from less studied pollutants like UFP and traffic-specific PM fractions.

Limitations

The overall number of studies per pollutant was small, limiting our ability to conduct meta-analysis or subgroup analysis for some exposure-outcome pairs, and to investigate publication bias.

It has been proposed that effects of air pollutants on the metabolic system commence at an early age [54, 55]. Studies entering this review, including the newest available studies, comprised older adult populations (mean age >50 years) and have excluded persons with already manifest pollutant-dependent diabetes at baseline from the incidence analyses. Thus, a selection bias toward a healthier population might have compromised the ability to study associations with diabetes incidence. The subgroup analysis showed more robust results for studies with low risk of selection bias (**Supplementary Table S6**).

Another limitation refers to the possible underestimation and misclassification of diabetes. This may depend on the age of the study participants regarding results on incidence of diabetes or on study design and available data sources. Cohort studies with individual data or smaller cross-sectional studies show more rigorous outcome ascertainment with less risk of bias as opposed to the larger studies based on administrative data. Reliance on self-report or documented disease would miss 24% up to 50% of cases depending on the region, while in-depth study center examinations will have a much higher sensitivity due to the long oligosymptomatic prediagnostic phase of diabetes [2]. Non-differential outcome misclassification (independent from exposure status) related to incomplete case ascertainment might bias the results to the null [59, 60]. This was seen for prevalence studies in the sub-group analysis regarding risk of bias due to outcome ascertainment, but not incidence studies (**Supplementary Tables S6, S7**).

We were not able to distinguish between type 1 and type 2 diabetes. Since 90% of adult diabetes cases are type 2, and the vast majority of incident diabetes cases in adults are type 2 diabetes, we conclude that our results primarily refer to type 2 diabetes.

Future Research

In cities, where the majority of the world´s population resides, traffic remains an important source of air pollution. The majority of studies were from high-income countries in Europe and North America with generally lower levels of air pollution than in other world regions. However, the one study from China with mean exposure at the higher end of the exposure range (35.3 $\mu g/m^3$ NO_2) also showed increased risk of diabetes. The available evidence provides overall moderate evidence that TRAP increase diabetes risk. Large studies with rigorous case ascertainment are needed, including in low and middle income countries and other locations with higher exposures. Studies are also needed to assess the change in composition of TRAP due to diesel and gasoline fleet turnover to lower-emission vehicles with a rising share of non-tailpipe emissions in the overall share of traffic-related particulate matter (e.g., from SO_2 emissions). The interplay of TRAP with co-exposures in polluted spaces, most notably noise and green space, needs to be better understood for effective intervention [61].

Studies assessing critical windows of exposure, e.g., in younger populations and preclinical outcomes along the mechanistic path to clinically manifest disease are warranted. Evidence suggests that underlying pathology may be underway as early as childhood and adolescence [62]. Future experimental studies should provide more mechanistic evidence for a better understanding of the molecular and cellular actions of long-term exposure to NO_x and other TRAP on the cardiometabolic system.

Conclusion

In conclusion, we found moderate confidence in the evidence for an association of long-term exposure to traffic-related air pollution and diabetes, with higher effect estimates observed in prevalence studies. We observed increased risks in populations in various geographical regions and contexts and conclude, that TRAP is a risk factor for diabetes.

AUTHOR CONTRIBUTIONS

MKJ, BH, and ES were responsible for drafting the article; Panel members, MKJ, RK, and PH as well as AP, HB were responsible for the design and conduct of the broader systematic review on health effects of ambient air pollution, on which this work is based. ES and RA conducted formal analysis. ES conducted the extended analysis and prepared the figures on results of the meta-analyses. All authors were responsible for revising the article critically for important intellectual content. All authors contributed to the article and approved the submitted version.

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AUTHOR DISCLAIMER

The views expressed in this article are those of the authors and do not necessarily reflect the views of the Health Effects Institute or its sponsors.

CONFLICT OF INTEREST

Author FL was employed by the company Sonoma Technology, Inc.

The remaining authors declare that they do not have any conflicts of interest.

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SUPPLEMENTARY MATERIAL

The Supplementary Material for this article can be found online at: https://www.ssph-journal.org/articles/10.3389/ijph.2023.1605718/full#supplementary-material

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