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From Research to Policy: Evidence synthesis and valorisation in the field of air pollution research – the example of traffic-related air pollution

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Für meine wunderbarsten Unterstützer:innen

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In grosser Dankbarkeit

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[1]

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Methods Matter: A Comparative Review of Health Risk Assessments for Ambient Air Pollution in Switzerland [Review].
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ZUSAMMENFASSUNG

Public Health ist die Wissenschaft vom Schutz und der Förderung der öffentlichen Gesundheit. Das Konzept des Public-Health-Aktionszyklus veranschaulicht diesen konstanten Prozess mit den Schritten Problemdefinition, Strategieformulierung, Umsetzung und Bewertung. Dem Grundgedanken dieses Konzepts folgend, untersucht diese Dissertation die Risiken langfristiger verkehrsbedingter Luftverschmutzung (traffic-related air pollution TRAP) auf die kardiometabolischen Endpunkte Diabetes Typ 2 und Schlaganfall (Problemdefinition) und reflektiert Methoden zur Berechnung der Krankheitslast (Evaluation).

Ausgehend von einer systematischen Übersichtsarbeit des Health Effects Instituts, welche Auswirkungen der verkehrsbedingten Luftverschmutzung auf ausgewählte gesundheitliche Endpunkte untersuchte, beschreiben zwei Artikel dieser Dissertation die Ergebnisse unter Berücksichtigung neuerer Literatur. Diese wurde in den elektronischen Datenbanken PubMed und LUDOK für Diabetes bis Mai 2022 und für Schlaganfälle bis Januar 2022 gesucht. Kriterien für die Beurteilung der Belastung als verkehrsbedingt wurden in einem umfassenden Protokoll definiert. Wo möglich, wurden random-effects Meta-Analysen durchgeführt. Basierend auf dem Ansatz des Office for Health Assessment and Translation (OHAT) wurde das Vertrauen in die Qualität der Studienlage bewertet und der Grad des Vertrauens in das Vorhandensein eines Zusammenhangs unter der Berücksichtigung aller Studien in einer Gesamtbewertung beurteilt.

21 Studien wurden in die Diabetes- und 19 in die Schlaganfall-Analysen einbezogen. Alle metaanalytisch summierten Effektschätzer wiesen auf ein höheres Diabetes-Risiko bei höherer Belastung hin, insbesondere für die Diabetes-Prävalenz mit NO_2 (relatives Risiko RR 1.09; 95%-Konfidenzintervall: 1.02 bis 1.17 pro 10 µg/m^3). Das Vertrauen in die Evidenz wurde als mittel eingestuft, was nach Einbezug der fünf neueren Studien bestärkt wurde. Die Schlaganfall-Metaanalyse zeigte erhöhte Risiken mit Russ, PM_{10} und $PM_{2.5}$ und keine Zusammenhänge mit NO_x und NO_2. Das Vertrauen in die Qualität der Studienlage und in das Vorhandensein eines Zusammenhangs wurde als niedrig bzw. mittel eingestuft. Nach Einbezug der sechs zusätzlichen Studien war das Schlaganfallrisiko mit der $PM_{2.5}$-Belastung signifikant erhöht (RR 1.22; 1.03 bis 1.21) und mit NO_2 weiterhin nicht assoziiert (1.01; 0.96 bis 1.06), was mehr für einen Zusammenhang mit der verkehrsbedingten Feinstaubbelastung spricht.

Sogenannte Burden of Disease Studien zeigen, dass Luftverschmutzung der wichtigste umweltbedingte Risikofaktor für die Gesundheit ist. Anhand verschiedener Gesundheitsfolgenabschätzungen für die Schweiz wurden Unterschiede in der Methodik für die Berechnung der Krankheitslast durch Luftverschmutzung aufgezeigt und Auswirkungen auf die Resultate diskutiert, welche aufgrund unterschiedlicher Inputdaten stark variieren können. Beispielsweise reichte die berechnete Zahl der luftverschmutzungsbedingten Todesfälle von 16 bis 76 pro 100'000 Einwohner. Die Transparenz der Methoden ist wichtig, um die Glaubwürdigkeit zu gewährleisten und trotz unterschiedlicher Zahlen zu betonen, dass die Luftverschmutzung eine nicht zu vernachlässigende Ursache von Krankheits- und vorzeitigen Todesfällen ist, die von den politischen Entscheidungsträgern weltweit angegangen werden muss. Der Verkehr als wichtige Quelle der Luftverschmutzung mit nachgewiesenen Gesundheitsfolgen sollte mit integrierten Mobilitätskonzepten angegangen werden, die einen Zusatznutzen durch die Verringerung von Lärm und Treibhausgasemissionen, durch die Erhöhung von Grünflächen und körperlicher Aktivität sowie durch die Verbesserung der Umweltqualität insgesamt bringen.

EXECUTIVE SUMMARY

Public health is the science of protecting and improving the health of populations. The concept of the Public Health Action Cycle exemplifies this constant effort with the steps problem definition, strategy formulation, implementation and evaluation. Following the idea of the public health action cycle, this dissertation studies the harmfulness of long-term traffic-related air pollution (TRAP) on the cardiometabolic endpoints of diabetes type 2 and stroke and reflects on the methods of burden of disease calculations.

As part of a larger systematic review conducted by the Health Effects Institute on the effects of TRAP on key health outcomes published in 2022, the papers of this dissertation extend the interpretation of the reported results to include evidence published after completion of the original literature search in PubMed and LUDOK electronic databases up to May 2022 for diabetes and January 2022 for stroke. TRAP exposure was defined according to a comprehensive protocol. Random-effects meta-analyses were performed. Heterogeneity was assessed by the I^2 and investigated by various a priori subgroup analyses. Confidence assessments were based on a modified Office for Health Assessment and Translation (OHAT) approach, complemented with a broader narrative synthesis, which also included evidence from studies not entering meta-analysis.

21 and 19 studies were included in the diabetes and stroke-analyses, respectively. All meta-analytic estimates indicated higher diabetes risks with higher exposure, especially for the NO_2 prevalence analysis (relative risk RR 1.09; 95% confidence interval CI: 1.02; 1.17 per 10 µg/m^3). The overall confidence in the evidence was rated moderate, strengthened by the addition of 5 recently published studies. The stroke meta-analysis showed non-significantly elevated risks with EC, PM_{10} and $PM_{2.5}$ and null results with NO_x and NO_2 exposures. The confidence assessments regarding the quality of the body of evidence and separately regarding the presence of an association of TRAP with stroke considering all available evidence were rated low and moderate, respectively. The six additional studies resulted in slightly more robust adverse estimates for $PM_{2.5}$ (1.22; 95%-CI: 1.03-1.21) and a null association for NO_2 (1.01; 95%-CI: 0.96-1.06) making for a stronger case with particulate pollution from traffic.

The risks of air pollution translate into high burden of disease showing that air pollution is the most important environmental risk factor for health. The methodology of burden of disease or health risk assessment (HRA) calculations were discussed comparing different HRAs for Switzerland. They revealed variations in numbers of deaths due to air pollution ranging from 16 to 76 per 100,000 inhabitants. These are due to variations in input data such as the counterfactual scenario (TMREL), the year of analysis or the exposure-risk functions used. Transparency in methods is important to ensure credibility and stress that beyond different numbers, air pollution is an important source of premature death and morbidity that needs to be addressed by policy makers worldwide.

Traffic as an important source of air pollution should not only be addressed by technical solutions such as filter-technologies but with more integrated mobility concepts that have co-benefits by reducing noise, greenhouse gas emissions, increase green space, walkability and physical activity improving overall environmental quality.

LIST OF ABBREVIATIONS

33 CCHS	33 Communities Chinese Health Study
AAQD	Ambient air quality directive
ALSWH	Australian Longitudinal Study on Women's Health
AOC	Anthropogenic organic compounds
AP	Air pollution
AP-HRA	Air Pollution Health Risk Assessment
AQG	Air quality guideline
BaP	Benzo(a)pyrene
BC	Black carbon, measure of soot
BMI	Body mass index
BWHS	Black Women's Health Study
CAFEH	Community Assessment of Freeway Exposure and Health study
CANHEART	Cardiovascular Health in Ambulatory Care Research Team
CCZ	Congestion charging zones
CHAMPIONS	Calculating How Air Pollution Impacts Our Society Study
CI	Confidence interval
CM^3	Cubic Centimeter = milliliter
COPD	Chronic Obstructive Pulmonary Disease
CPRD	Clinical Practice Research Datalink
CRF	Concentration response function
CITIES	HRA for air pollution in around 1000 European urban areas (Khomenko et al.)
CRS	Concentration response function
CTM	Chemical Transport Model
CVD	Cardiovascular disease
DALY	Disability-adjusted life years
DDCH	Danish Diet, Cancer, and Health cohort
DE	Direct effect
DM	Diabetes mellitus
EC	Elemental carbon, a measure of soot
EEA	European Environment Agency
ELAPSE	Effects of Low-Level Air Pollution: A Study in Europe
ELISABET	Enquête Littoral Souffle Air Biologie Environnement study
EPA	Environmental Protection Agency
EPIC	European Prospective Investigation into Cancer and Nutrition (EPIC) study
ERF	Exposure risk function
ER-function	Exposure risk function
ESCAPE	European Study of Cohorts for Air Pollution Effects
ETS	Environmental tobacco smoke
EU	European Union

EURAD-CTM	EURopean Air pollution Dispersion-Chemical Transport Model
FCAH	(Swiss) Federal Commission of Air Hygiene
GBD	Global Burden of Disease study
GDM	Gestational diabetes mellitus
GOT-MONICA	Göteborg Monitoring Trends and Determinants in Cardiovascular Disease
GRADE	Grading of Recommendations Assessment, Development and Evaluation (approach)
HbA1c	Glycated hemoglobin A1c
HEI	Health Effects Institute
HIMS	Health In Men Study
HNR	Heinz Nixdorf Recall study
HOMA-IR	Homeostatic Model Assessment for Insulin Resistance
HR	Hazard ratio (or hazard risk)
HRA	Health risk assessment
HRAPIE	Health Risks of Ari Pollution in Europe
I^2	Statistic measure of heterogeneity between studies in meta-analysis
ICD	International classification of disease
IDF	International Diabetes Federation
IL-2	Interleukin-2
IMD	Index of multiple deprivation
IRR	Incidence rate ratio
iSES	individual socioeconomic status, measures of individual socioeconomic status such as education; income
JHS	Jackson Heart Study
JNK	c-Jun N-terminal kinase
km	Kilometer
km^2	Square kilometer
KPNC	Kaiser Permanente Northern California cohort
LEZ	Low emission zone
LUDOK	Literature database on health effects of ambient air pollution at the Swiss Tropical and Public Health Institute
LUR	Land Use Regression
m	Meter
m^3	Cubic meter
MESA	Multi-Ethnic Study of Atherosclerosis
MeSH	Medical Subject Headings (keywords set by PubMed)
mg	Milligram
min	Minute
mL	Milliliter
N	Number (of studies or participants)
NA	Not applicable
NAAQS	National ambient air quality standards
NIEHS OHAT	National Institute of Environmental Health Sciences Office of Health Assessment and Translation
Nm	Nanometer

NO	Nitric oxide
NO_2	Nitrogen dioxide
NOMAS	Northern Manhattan Study
NO_x	Nitrogen dioxide and nitric oxide
nSES	Neighborhood socioeconomic status, measures of neighborhood socioeconomic status such as mean household income
O3	Ozone
OHAT	Office of Health Assessment and Translation
ONPHEC	ONtario Population Health and Environment Cohort
OR	Odds ratio
PAF	Population attributable fraction
PAH	Polycyclic aromatic hydrocarbon
PECOS	Population, Exposure, Comparator, Outcome and Study
PM	Particulate matter
PM_{10}	Particulate matter with an aerodynamic diameter smaller or equal to 10 micrometer mass concentration
$PM_{2.5}$	Particulate matter with an aerodynamic diameter smaller or equal to 2.5 micrometer mass concentration
$PM_{2.5abs}$	Light absorption of $PM_{2.5}$, a measure of soot
$PM_{2.5coarse}$	Particulate matter with an aerodynamic diameter between 2.5 and 10 micrometer mass concentration
PNAM	Accumulation mode particle number concentration
PNC	Particle number count or concentration
ppb	Parts per billion
PPS	Primary Prevention Study
PRISMA	Preferred Reporting Items for Systematic Reviews and Meta-Analyses
RAD	Restricted activity person-days
RHINE	Respiratory Health in Northern Europe study
RoB	Risk of bias
RD	Respiratory disease
RR	Relative risk or risk ratio
SALIA	Study on the influence of Air pollution on Lung function, Inflammation and Ageing
SALSA	Sacramento Area Latino Study on Aging
SALT	Screening Across the Lifespan Twin Study
SAPALDIA	Swiss cohort study on Air Pollution and Lung Disease In Adults
SDPP	Stockholm Diabetes Prevention Programme cohort
SES	Socioeconomic status
SIXTY	Cohort of 60-year-olds
SNAC-K	Swedish National study on Aging and Care in Kungsholmen
SO_2	Sulfur dioxide
STE	Swiss assessments for Transport Externalities
T^2	Tau-squared, measure of heterogeneity
T1DM	Type 1 diabetes mellitus

T2DM	Type 2 diabetes mellitus
TMREL	Theoretical Minimum Risk Exposure Level
TRAP	Traffic-related air pollution
UFP	Ultrafine particles, with a diameter of equal to or less than 100nm
UK	United Kingdom
US	United States of America
USD	United States Dollar
Veg	Vegetable
VOC	volatile organic compounds
vs.	Versus
WHO	World Health Organization
YLD	Years lived with disability
YLL	Years of life lost
µg	Microgram
µm	Micrometer

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1. INTRODUCTION

1.1 Public health – a constant effort to improve health

Public health is the science of protecting and improving the health of populations – from neighborhoods to cities to countries to world regions – through education, promotion of healthy lifestyles, research toward prevention of disease and injury, and detecting, preventing, and responding to infectious diseases (CDC Foundation, 2023).

Epidemiology, the study of how often diseases occur in different groups of people and why (Coggon et al., 2009), as a scientific method brings evidence that bears directly on the health of the population (Samet, 2000). According to former director of the American Centers for disease control and prevention, Bill Foege, epidemiology has been the tool to “change the world” and not just “to study the world” (Frumkin, 2015). The term “consequential epidemiology” has been formed to describe this effort (Kim, 2019).

Environmental epidemiologist Jonathan A. Samet states that “research and policy-making are interactive and iterative, and policies may change as evidence evolves” (Samet, 2000). Thus, public health should be a constant effort to understand determinants of health and take measures to tackle or support them. In this context, the concept of the Public Health Action Cycle by Rosenbrock et al. (1995) seems illustrative stressing the constant cycle between problem definition or assessment, strategy formulation, implementation and evaluation in Public Health Policy making (see Fig. 1.1).

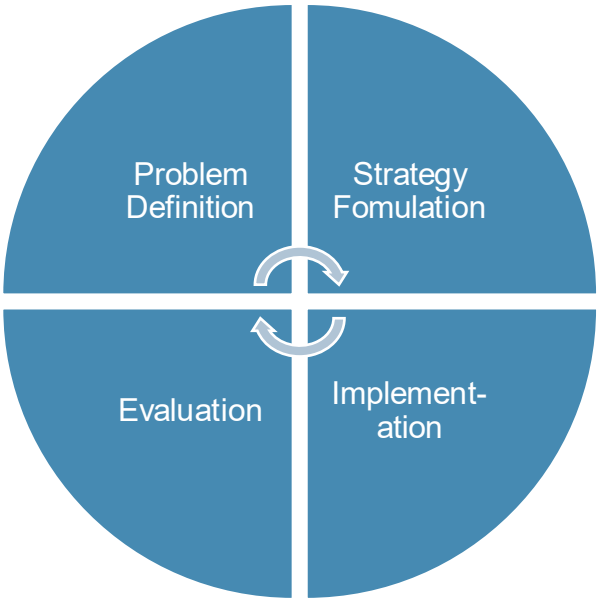

Fig. 1.1: Public Health Action Cycle (own figure).

Understanding the underlying problems and issues of public health is considered crucial, but equally important is strategically addressing them by formulating policies and ensuring their implementation and control. Additionally, evaluating the success or failure of such interventions is important.

Measles vaccination as an example of the public health action cycle in Switzerland

Tackling infectious diseases by immunization programs is one example of this ongoing public health action cycle. While infectious diseases in children used to be an important risk factor for child mortality and morbidity in Western countries (problem definition), immunization programs (strategy) in schools and through pediatricians (implementation) increased immunization rates and decreased disease numbers (evaluation). The example of measles in Switzerland showed that immunization rates remained below 70% in Switzerland till the early 80ies (evaluation / problem definition). However, when the vaccine was incorporated into a combination vaccine that provided immunization against mumps, measles, and rubella, and was additionally accompanied by a vaccination information campaign (strategy / implementation), vaccination rates increased (evaluation) (Rougemont et al., 1996). Yet, in 2007, Switzerland was the country with the highest measles incidence in Europe by far (problem definition) (Tarr et al., 2019). A national measles elimination program (strategy) increased vaccination rates. The program included the engagement of highest political bodies and health authorities, engagement of primary care and school doctors (strategy and implementation). This and the broad distribution of high-quality information have proven to be key success factors (Evaluation) (Bundesamt für Gesundheit, 2018). Still, more work needs to be done since measles vaccination rates vary

markedly between Swiss states (cantons) and only a minority of cantons have achieved >90% coverage, and most remain below the target rate of 95% (problem definition as part of the ongoing public health cycle) (Tarr et al., 2019). Since mandatory vaccination is not an option in Switzerland due to the constitutional right to self-determination (for now), a national research program (NFP74) to study vaccination hesitancy showed that vaccine hesitant carers are not opposed against vaccination per se but need more information and care addressing their concerns (Tarr, 2023). Thus, the constant effort to understand and tackle problems has led to better understanding of the needs and customized services around vaccination.

In the policy field of air pollution mitigation, the concept of the public health action cycle can be observed, too. This dissertation will focus on applying the public health action cycle in Europe, with particular attention to Switzerland and Germany.

1.2 Air pollution and public health

The great London Smog in 1952 killed approximately 4'000 people within a few days of extremely high air pollution levels and another 8'000 in the course of the following year (Bell & Davis, 2001) (problem definition). It led worldwide to the first air quality regulation, the UK Clean Air Act 1956, aiming at reducing ambient air pollution (Robson-Mainwaring, 2022). In 1987 the World Health Organization (WHO) published its first Ambient Air Quality Guidelines defining air quality values for short-term exposures (strategies). The taken policy measures concentrated on mitigation of smog situations and short-term peaks of pollution exposure (short-term meaning changes of levels within hours or days) (strategy and implementation) (U.S. EPA, 2023b).

Then, in 1993 the, US Harvard Six Cities study demonstrated a strong link between long-term air pollution and mortality risk (Dockery et al., 1993); with "long-term" indicating exposure spanning months or years. It was the first study of cohort design that prospectively followed-up people over 14 to 16 years including important confounding risk factors in the mortality analysis. This study showed a linear exposure-response relationship between long-term exposure to particulate matter and cardiopulmonary mortality. Hence, with increasing pollution, the mortality risk rose as well (Pope & Dockery, 2006). Thus, in addition to previous studies showing risks of short-term exposure to air pollution – over hours or days – it showed, that average long-term exposure of the duration of years contribute to excess mortality after ruling out common confounding risk factors, such as smoking or occupational exposure. It showed that deaths from cardiopulmonary diseases and also due to lung cancer – which was not shown in association with short-term exposure – seemed to be influenced by air pollution to a considerable extent on population level. Additionally, previously considered safe levels of particulate matter exposure

were shown to be hazardous for health. Long-term air pollution was identified as a new important risk factor at levels previously not considered to be hazardous (problem definition).

The 1987 national ambient air quality standard (NAAQS) for annual exposure to PM_{10} – referring to particles with an aerodynamic diameter of 10 micrometers (µm) or less – in the USA was set at 50 µg/m^3 (strategy) (U.S. EPA, 1996, 2023c), while the Harvard Six Cities study found effects for much lower levels. Effects started around 30-35 µg/m^3 in association with total particles, which entail even bigger particles than PM_{10}, and around 10-15 µg/m^3 in association with $PM_{2.5}$, which is part of PM_{10} and comprises particles with aerodynamic diameters of 2.5 or less µm (Dockery et al., 1993). Integrating these new findings into US EPA's integrated science assessments[2] (problem definition), the US EPA introduced a new air quality standard for $PM_{2.5}$ at 15 µg/m^3 in 1997 (U.S. EPA, 2022) (strategy formulation).

Once standards are set, policy makers need to implement measures to attain air quality standards (implementation). Thus, it is important to understand, which sources contribute most to (the toxicity of) air pollution and should be addressed by measures. Such measures should firstly prevent air pollution from being produced by reducing it at the source (e.g. by emission standards to be attained). Secondly, measures to mitigate air pollution from reaching the people should be taken (e.g. by city planning reducing traffic in residential areas). Finally, strategies to avoid exposure to air pollution on an individual level can be taken (e.g. wearing masks, avoiding polluted areas). Prevention of air pollution at the source should, however, be always the first step (Public Health England, 2019).

The last step in this cycle is evaluation. It should be evaluated, whether measures would be effective and worthwhile, e.g. to reduce air pollution and improve health, or whether new scientific evidence warrants new strategies or policies. A re-evaluation of health effects of air pollution and its impacts, e.g. with the integrated science assessments by the US EPA (Richmond-Bryant, 2020), is conducted regularly, followed by reformulation of policies. Today, ambient air pollution is recognized as the single biggest environmental risk factor for public health according to the Global Burden of Disease Study. In 2019, worldwide 4.2 million premature deaths and 124 million disability adjusted life years were attributed to ambient air pollution with increasing trends (Fuller et al., 2022; GBD 2019 Risk Factors Collaborators, 2020).

[2] The US EPA's integrated science assessment programme produces reports to accurately reflect the latest scientific knowledge useful in indicating the kind and extent of identifiable effects on public health and welfare which may be expected from the presence of a pollutant in the ambient air (U.S. EPA, 2023a). The integrated science assessments follow a transparent process of searching the literature, selecting studies for consideration, evaluating study quality, synthesizing and integrating the evidence, and characterizing the evidence for public health and welfare impacts of criteria air pollutants. Importantly information and evidence stem from various disciplines, such as atmospheric science, toxicology, epidemiology, and aquatic and terrestrial ecology. Evidence is evaluated within a discipline, e.g. environmental epidemiology, but also across scientific disciplines for related and similar health effects. It is synthesized, and integrated to develop conclusions and causality determinations (U.S. EPA, 2015).

Thus, it is worthwhile addressing this stressor for human health. So called accountability studies (Boogaard et al., 2017) or health impact assessments (Harris-Roxas & Harris, 2011) are tools to evaluate the impacts of policies and interventions, either retrospectively or prospectively. The benefits and costs of the US Clean Air Act have been calculated extensively. The latest report for the period 1990 to 2020 calculated costs of measures to reach the clean air targets at around 65 billion USD annually for the year 2020. However, the economic value of air quality improvements translating into lower numbers of death, disease and economic welfare and environmental conditions were estimated to reach almost 2 trillion USD for the year 2020. Benefits of reduced non-fatal health effects and improved visibility alone added up to 137 billion USD for the year 2020, which is still twice the estimated costs (U.S. EPA, 2011).

This dissertation uses the concept of the Public Health Action Cycle. It presents research regarding the elements problem definition and evaluation, which play an important role in the information of policy and consequential improvement of public health.

Important pollutants and sources of air pollution

Air pollution is a mixture of different chemicals stemming from various sources. The following pollutants are important markers of air pollution (EEA, 2022; WHO, 2023a):

Particulate matter (PM)

Particulate matter (PM) refers to inhalable particles, composed of sulfate, nitrates, ammonia, sodium chloride, black carbon, mineral dust or water. PM can be of different size and is generally defined by their aerodynamic diameter. PM_{10} refers to particles with an aerodynamic diameter of 10 micrometers (µm) or less, $PM_{2.5}$ comprise particles with aerodynamic diameters of 2.5 or less µm. The primary source of both PM_{10} and $PM_{2.5}$, is the energy consumption in the residential, commercial and institutional sector by burning (fossil) fuels. The road transport sector, is also a significant source of both pollutants, while agriculture is an important source of PM_{10}. Particulate matter can be emitted directly, and it can also be formed in the atmosphere. The gaseous precursor pollutants nitrogen oxides (NO_x), volatile organic compounds (VOCs), sulfur dioxides (SO_2), and ammonia (NH_3) contribute to the formation of such secondary fine particulates. Total suspended particles TSP is an older measure comprising airborne particles up to about 100 micrometers in diameter. Ultrafine particles (UFP) are defined as particles <100 nanometers (nm) or 0.1 µm. However, particles <1 µm are occasionally also referred to as ultrafine particles. The main source of UFP is combustion processes in transportation (e.g. vehicles, aviation, shipping), industrial and power plants and residential heating.

Black carbon (BC)

Black carbon is a major component of $PM_{2.5}$ and it is sometimes referred to as soot. Its main sources are from incomplete combustion of fossil fuels, biofuels and biomass. Thus the energy and transport sector are the most important sources. There are different metrics to measure soot such as elemental carbon, black smoke, and PM absorbance.

Nitrogen oxides (NO_x=NO and NO_2)

NO_x is a gas that is commonly released from the combustion of fuels in the transportation and industrial sectors. NO is a marker of freshly emitted traffic-related air pollution (TRAP) since it quickly reacts with oxygen to form NO_2 in the atmosphere.

Carbon monoxide (CO)

Carbon monoxide is a colorless, odorless and tasteless toxic gas produced by the incomplete combustion of carbonaceous fuels such as wood, petrol, charcoal, natural gas and kerosene. Energy consumption in the residential, commercial and institutional sector and the transportation sector are the main source of CO emissions.

Ozone (O_3)

Ozone at ground level – not to be confused with the ozone layer in the upper atmosphere – is one of the major constituents of photochemical smog and it is formed through the reaction with gases in the presence of sunlight. It is not a primary pollutant of traffic and thus not a marker of TRAP. However, NO_x are important precursors to ozone pollution.

Sulfur dioxide (SO_2)

SO_2 is a colorless gas with a sharp odor. It is produced from the burning of fossil fuels (coal and oil) and the smelting of mineral ores that contain sulfur. It is not a marker of TRAP.

Polycyclic aromatic hydrocarbons

Polycyclic aromatic hydrocarbons (PAHs) are present in the atmosphere in particulate form. They are a group of chemicals formed primarily from incomplete combustion of organic matter (e.g. cooking of meat) as well as fossil fuels in coke ovens, diesel engines and wood-burning stoves. Benzo(a)pyrene is considered a lead substance for other PAHs. Household stoves and fireplaces are among the largest group of polluters. Road traffic also emits benzo(a)pyrene through the combustion of fuels.

Important sources and sectors of air pollution

The main sectors contributing to emissions of air pollutants in Europe are transport, residential/ commercial and institutional energy supply, industry, agriculture and waste (management). In the urban context traffic is an important source of air pollution. In areas where biomass burning like wood combustion is wide-spread, households are important sources. People are exposed to air pollution in urban and rural areas. Depending on the pollutant, different sources are the main drivers of exposure and their contributions differs from country to country (see Fig. 1.2) contribution of emission sources for Europe and Germany (Fig. 1.3). Waste burning does not play an important role in Germany compared to the rest of the EU (e.g. black carbon BC), while the transport sector is a more important source of particulates and black carbon in Germany.

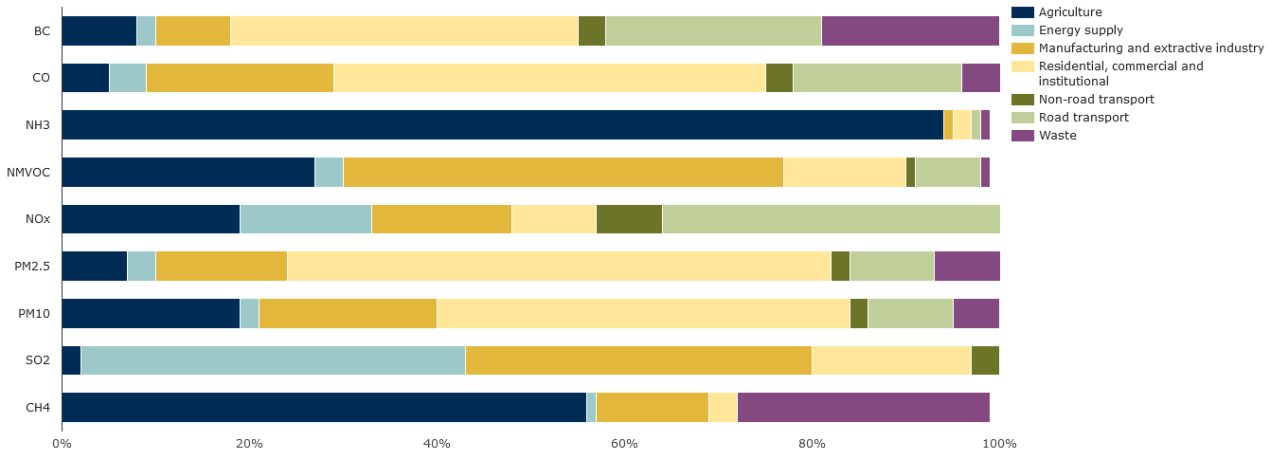

Fig. 1.2: Main source sectors of air pollution emissions in Europe (EU-27) in 2020 (publicly available from EEA, 2022).

Abbreviations: BC, black carbon (soot); CO, carbon monoxide, NH_3, ammonia; NMVOC, non-methane volatile organic compounds; NO_x, nitrogen dioxide and nitric oxide; $PM_{2.5}$, particulate matter with aerodynamic diameter ≤ 2.5 µm; PM_{10}, particulate matter with aerodynamic diameter ≤ 10 µm;SO_2, sulfur dioxide; CH_4, methane.

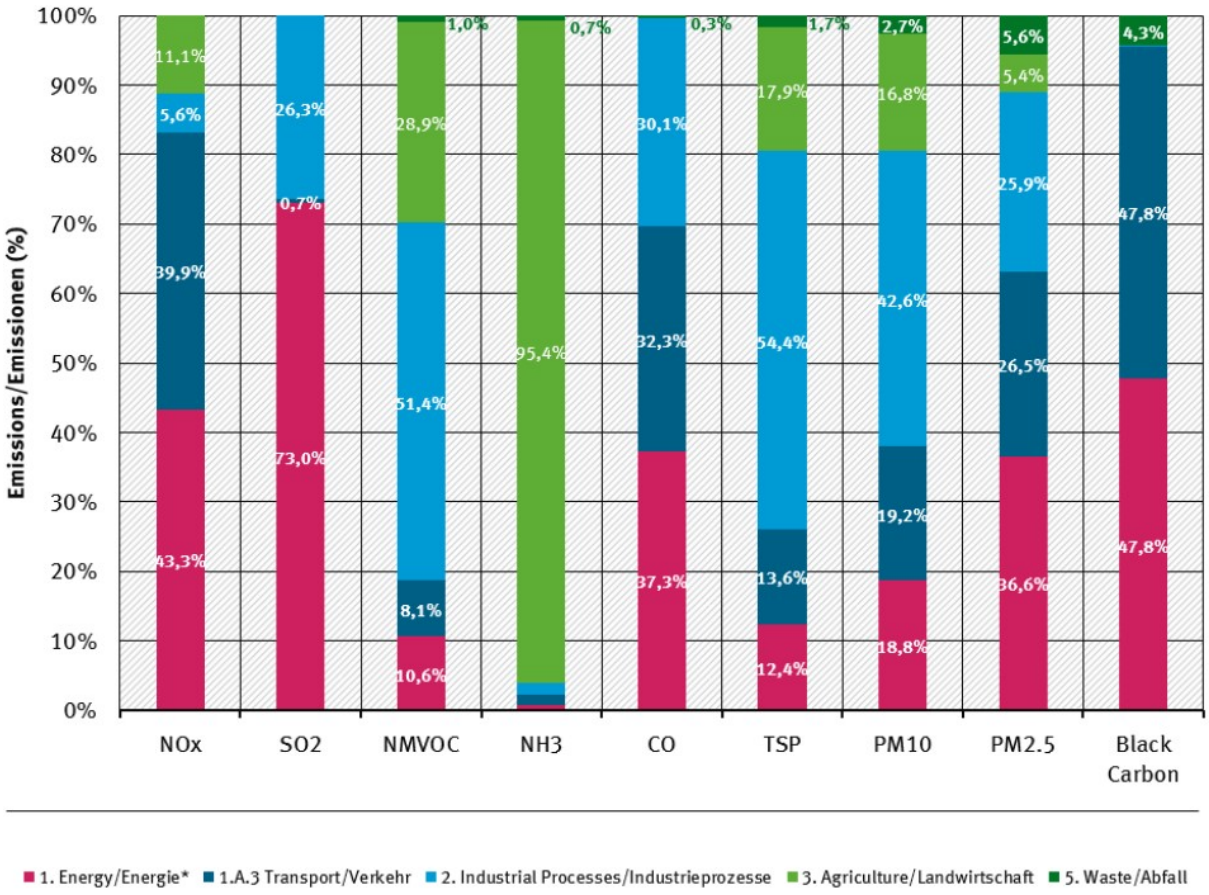

Fig. 1.3: Contribution of sources of air pollution to pollutant emissions Germany 2020 (publicly available from Umweltbundesamt, 2022).

* Without transport / ohne Verkehr (1.A.3)
Abbreviations: CO, carbon monoxide, NH_3, ammonia; NMVOC, non-methane volatile organic compounds; NO_x, nitrogen dioxide and nitric oxide; $PM_{2.5}$, particulate matter with aerodynamic diameter ≤ 2.5 µm; PM_{10}, particulate matter with aerodynamic diameter ≤ 10 µm;SO_2, sulfur dioxide; TSP, total suspended particulates.

Health effects of ambient air pollution

Research in the past 30 years has revealed that effects of air pollution extend to practically all organs (Thurston et al., 2017). Evidence for such effects stems from three sources: (1) toxicology, studying biological mechanisms and effects in cells and animals. (2) Experimental studies with humans that can show causal effects of exposure to specific pollutants in a controlled set-up. Such experiments can reveal short-term effects of exposures of hours and are often restricted to healthy adult populations or subclinical indicators due to ethical reasons. (3) Epidemiological studies give insights into effects of real-world exposures and mixes of pollutants within a population. Epidemiological studies examine entire populations and have the capacity to investigate susceptible subgroups such as pregnant women, newborns, children, elderly or patient groups. Additionally, they can study the health of populations over a long period giving insights into long-term effects of exposures over months or years.

The United States Environmental Protection Agency (US EPA) uses these knowledge sources to evaluate, synthetize and integrate the evidence within and across disciplines to develop scientific conclusions on the possible causal role of the pollutant in the observed health effect (U.S. EPA). According to the (U.S. EPA, 2016) mortality and several morbidity effects have been causally or likely-causally related to ambient air pollutants (U.S. EPA, 2010, 2016, 2017, 2019, 2020). These have been compiled by LUDOK (Kutlar Joss & Probst-Hensch, 2023) – the Swiss Literature Database on Air Pollution and Health – in an interactive figure, which is also available online (www.ludok.ch) (Fig. 1.4).

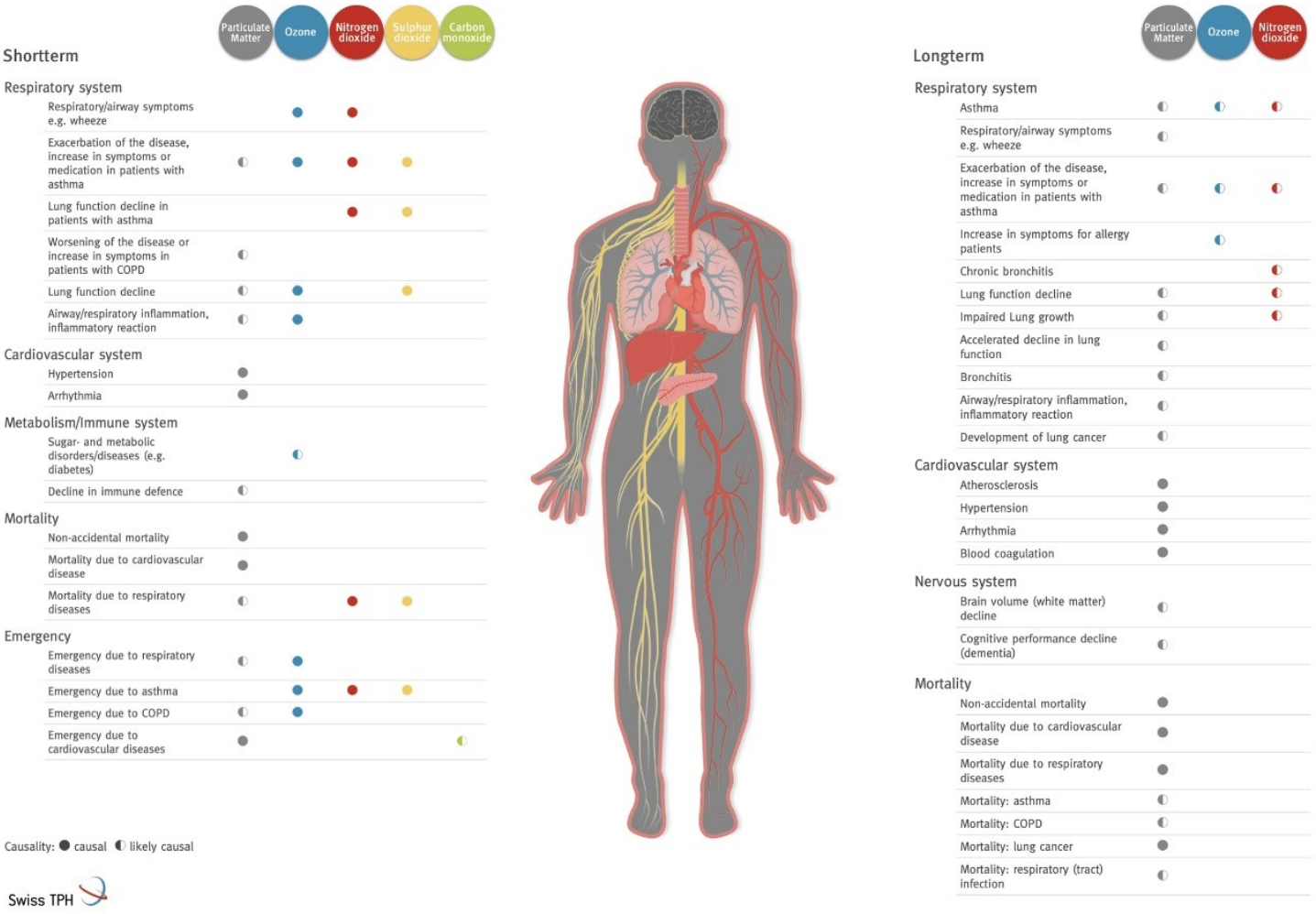

Fig. 1.4: Health effects of ambient air pollutants that have deemed to be causally (filled circles) or likely causally (half-filled circles) related to the short-term or long-term exposure to the respective pollutant by the US EPA (available from Swiss TPH, 2022).

Abbreviations: COPD, chronic obstructive pulmonary disease

Development of air pollution levels and policies

Air pollution policies have been successful to reduce air pollution levels over the last decades. The desulfurization of fuels and heavy oils have resulted in the most impressive drops in SO_2 exposure levels. Especially in areas, where coal is not an important energy source such as Switzerland, air quality standards and WHO air quality guideline values have been attained for a long time (Fig. 1.5).

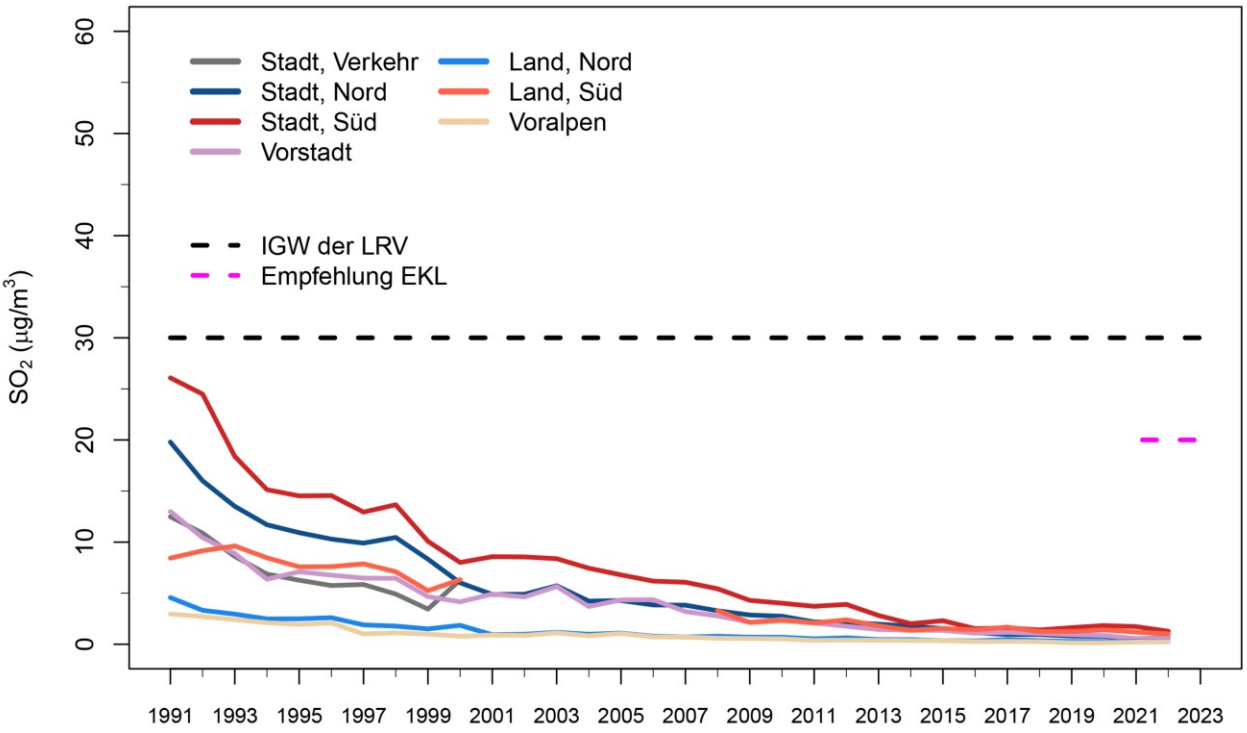

Fig. 1.5: Annual mean values of SO_2 1991-2023 at national monitors in Switzerland (available from Swiss Federal Office for the Environment in Eidgenössische Kommission für Lufthygiene (EKL), 2023).

The dotted black line indicates the Swiss air quality standard (IGW) and the pink line the WHO air quality guideline value. Red: Urban monitor in southern Switzerland, blue: urban monitor in northern Switzerland, light pink: agglomeration, grey: traffic monitor, orange: rural monitor in southern Switzerland, light blue: rural monitor in northern Switzerland, light brown: pre-alpine monitors

Abbreviations: EKL, Eidgenössische Kommission für Lufthygiene: Federal Commission on Air Hygiene; IGW, Immissionsgrenzwert: air quality standard; LRV, Luftreinhalteverordnung: Ordinance on Air Pollution Control, µg/m^3, microgram per cubic meter; WHO, World Health Organization.

While short-term peaks in exposures have generally been reduced, long-term levels of exposures have also declined slowly but steadily for all pollutants. For example in Germany, $PM_{2.5}$ and NO_2 levels in 2022 are well below the EU-standards of 25 and 40 µg/m^3, respectively (Fig. 1.6 and Fig. 1.7). The number of days with ozone levels above the target value of the 8-hour mean of 120 µg/m^3 have declined. However, in 2022 there were still 20 days on average with higher values (Fig. 1.8).

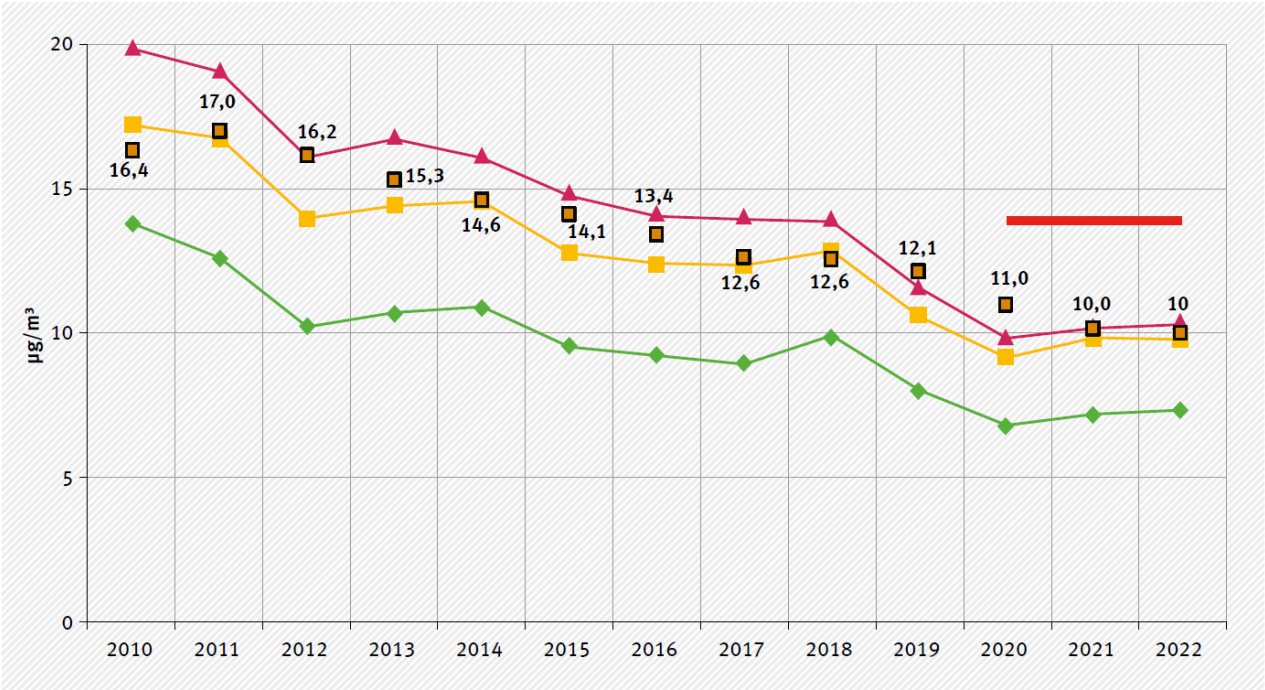

Fig. 1.6: Annual means of $PM_{2.5}$ 2010-2022, averaged over selected monitors in Germany (publicly available from Umweltbundesamt, 2023).

Green: rural background, yellow: urban background, red: urban traffic sites, orange box: average exposure indicator AEI (average exposure of the population calculated by the 3 year means of selected urban background sites), red line: reduction target of AEI
Abbreviations: µg/m³, microgram per cubic meter; $PM_{2.5}$, particulate matter with aerodynamic diameter ≤ 2.5 µm.

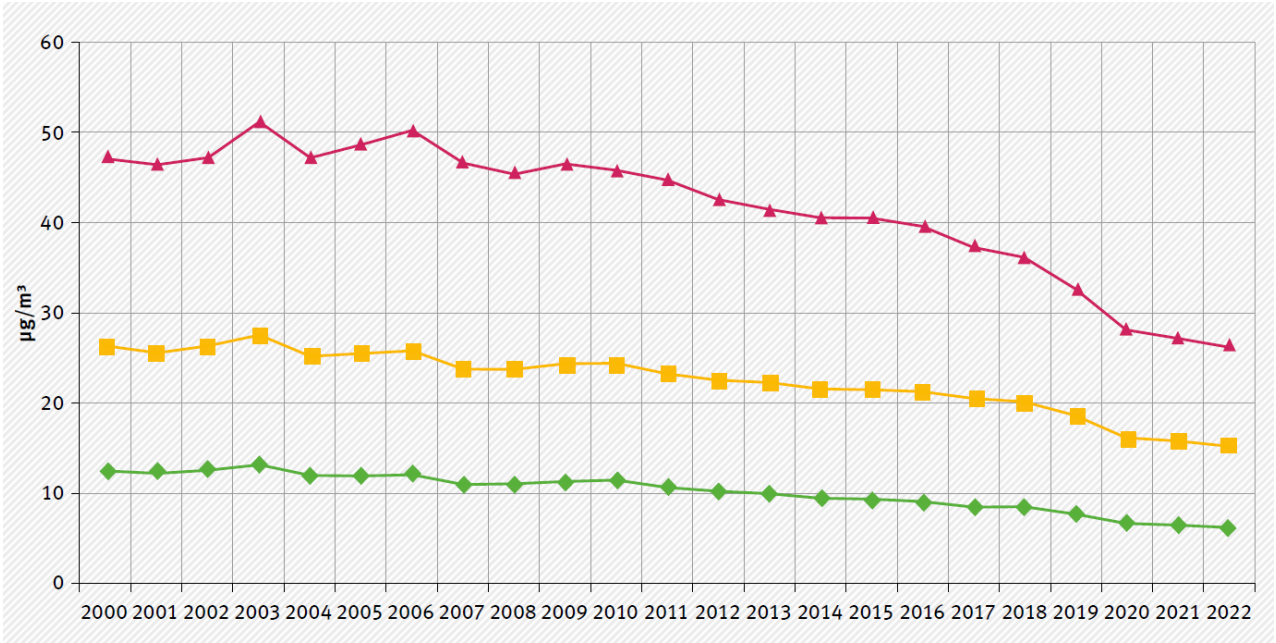

Fig. 1.7: Annual means of NO_2 2000-2022 averaged over selected monitors in Germany (publicly available from Umweltbundesamt, 2023).

Green: rural background, yellow: urban background, red: urban traffic sites. EU-limit value: 40 µg/m³, WHO air quality guideline value: 10 µg/m³
Abbreviations: µg/m³, microgram per cubic meter; NO_2; nitrogen dioxide.

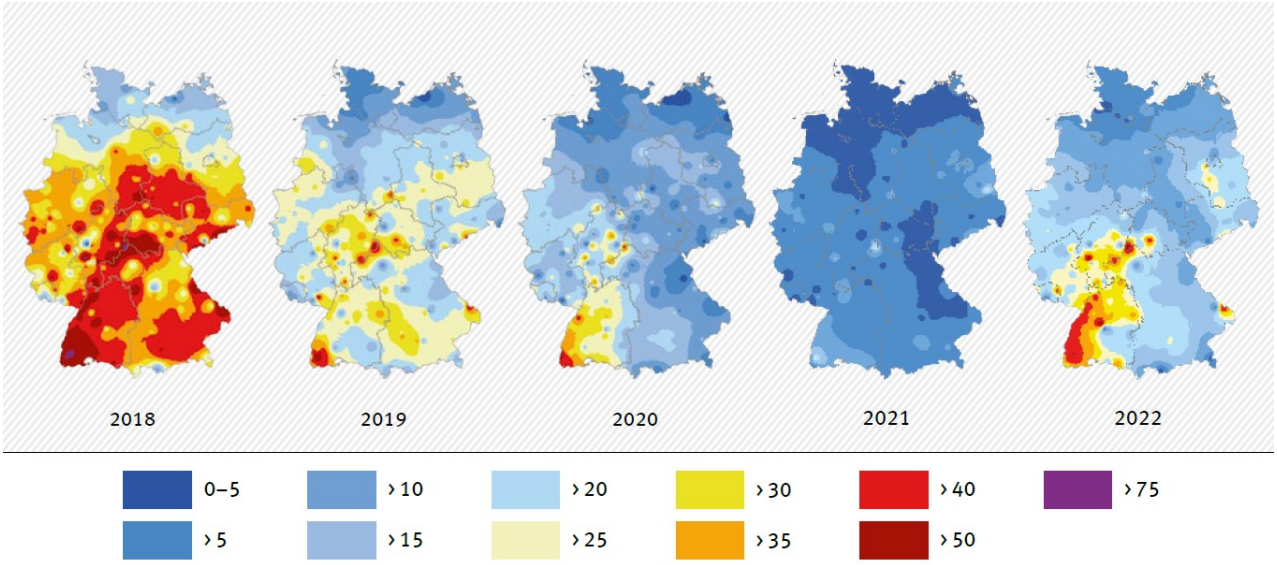

Fig. 1.8: Spatial distribution of days on which the long-term ozone target for health protection was exceeded (number of days with maximum 8-hour average values > 120 µg/m^3). Period 2018 to 2022, created from station measurements and geostatistical interpolation method. (publicly available from Umweltbundesamt, 2023)
Colors indicate the number days with exceedances.

A key element for successful air pollution policy making is to set air quality targets with national air quality standards or limit values that should not be exceeded (United Nations Environment Programme, 2021a, 2021b). In the past 40 years, WHO Europe has played a key role in defining health based recommendations regarding air quality with its ambient air quality guidelines (United Nations Environment Programme, 2021b). The values are set at pollutant levels, that either show a threshold, below which no adverse health effects are observed, or in absence of such a threshold the lowest level of air pollution at which health effects were still observed in epidemiological studies (World Health Organization, 2021). Due to advances in the study of health effects of ambient air pollution in epidemiological studies and a better understanding of its health effects and mechanisms, the WHO has further reduced its recommendations for the five “classical” air pollutants: Particulate Matter, Nitrogen Dioxide, Ozone, Sulfur Dioxide and Carbon Monoxide, with its latest update in 2021 (Table 1.1).

Table 1.1: Air quality guideline values set by the WHO for the pollutants particulate matter, ozone, NO_2, SO_2 and carbon monoxide from 1987-2021 (World Health Organization, 2021; World Health Organization. Regional Office for Europe, 1987, 2000, 2006).

Pollutant	Averaging time	WHO AQG 1987	WHO AQG 2000	WHO AQG 2005	WHO AQG 2021
Suspended particulates / particulate matter ($PM_{2.5}$), µg/m³	Annual average	-	Dose-response[a]	10	5
	24h mean value	-	Dose-response	25	15
Suspended particulates / particulate matter (PM_{10}), µg/m³	Annual average	-	Dose-response	20	15
	24h mean value	70 (thoracic)	Dose-response	50	45[b]
Ozone (O_3), µg/m³	Summer season[c]	-	-	-	60
	8h mean value	100-120	120	100	100[b]
Nitrogen dioxide (NO_2), µg/m³	Annual average	30 (vegetation[d])	40 (NO_x 30 vegetation)	40	10
	24h mean value	150	120 (8 h)	200 (1 h)	25[b]
Sulfur dioxide (SO_2), µg/m³	Annual average	50 (30 (vegetation)	50 (10-30 vegetation)	20	Not reviewed
	24h mean value	125	125	Not reviewed	40[b]
Carbon monoxide (CO), mg/m³	24h mean value	10 (8 h)	10 (8 h)		4[b]

Abbreviations: h, hour; WHO AQG, World Health Organization Air Quality Guideline Values, m^3, cubic meter; µg, microgram; $PM_{2.5}$, particulate matter with aerodynamic diameter ≤ 2.5 µm; PM_{10}, particulate matter with aerodynamic diameter ≤ 10 µm; SO_2, sulfur dioxide; NO_2, nitrogen dioxide

[a] Due to linear dose-response effects without a clear threshold level, the WHO did not formulate a guideline value: The available information does not allow a judgement to be made of concentrations below which no effects would be expected.

[b] 99th percentile (i.e. limit value may be exceeded three times per year).

[c] Average of daily maximum 8-hour mean ozone concentration in the six consecutive months with the highest six-month-running-average ozone concentrations.

[d] Guideline values set to protect ecosystems from adverse effects

The most important and effective measure to combat the burden of disease caused by air pollutants is the sustainable improvement of air quality by reducing emissions and setting binding air quality limits (United Nations Environment Programme, 2021a).

The biggest leverage to improve air quality is achieved, when either the biggest sources of air pollution or the source of the most toxic components of air pollution are tackled. Traffic-related air pollution (TRAP) is viewed as such a source, contributing a large share to NO_x and black carbon BC emissions (Fig. 1.3) and exposure to air pollution in cities and along busy roads.

1.3 Traffic-related air pollution

Automotive vehicular traffic is considered an important source of air pollution (traffic-related air pollution, TRAP), especially in urban environments, where a fraction of the population lives and works in close proximity to busy highways and roads (HEI (Health Effects Institute), 2010). Its harmfulness has been subject of studies and its regulation is key to reduce exposure to air pollution in urban environments.

Pollutants including nitrogen dioxide (NO_2) and nitrogen oxides (NO_x), elemental carbon (EC, soot), particulate matter (i.e. PM_{10} and $PM_{2.5}$) and ultrafine particles (UFPs) can be directly emitted through the vehicle exhaust after combustion of fuels (i.e. tailpipe emissions) or through resuspension of road dust, mechanical wear of brakes and tires, and abrasion of road surfaces (i.e. non-tailpipe emissions) (HEI (Health Effects Institute), 2010). Non-tailpipe emissions include PM trace metals such as copper (Cu), iron (Fe) and zinc (Zn) and microplastics from tire wear. In high-income countries, non-tailpipe emissions comprise over half of the PM from traffic (Piscitello et al., 2021).

Traffic contributes to PM pollution in cities by few percentages up to over 60% in cities worldwide. In Northwestern Europe traffic is still a major source of PM pollution in cities with a contribution between 12-20% (Heydari et al., 2020). In 2022 the contribution of traffic to emissions of PM_{10}, $PM_{2.5}$, NO_x, CO and Black Carbon in Germany were 19.2%, 26.5%. 39.9%, 32.3%, and 47.8% (Umweltbundesamt, 2022) (see Fig. 1.3). In Switzerland the contributions to emissions of PM_{10}, $PM_{2.5}$, NO_x, CO and Black Carbon are 31%, 23% 56% 43% and 23% (Eidgenössische Kommission für Lufthygiene (EKL), 2023).

Because of its ubiquity and proximity of the emissions to homes and businesses (HEI Panel on the Health Effects of Long-Term Exposure to Traffic-Related Air Pollution, 2022), policy makers have targeted the traffic sector among others to reduce air pollution (United Nations Environment Programme, 2021b). In the late 2000 years, the specific harmfulness of TRAP has raised research interest (Samet, 2007) and the Health Effects Institute compiled the evidence on TRAP and its health effects in a special report in 2010 (Traffic–Related Air Pollution: A Critical Review of the Literature on Emissions, Exposure, and Health Effects). The report aimed at drawing conclusions about whether the associations between TRAP exposure and health outcomes were causal. Except for some mortality and respiratory outcomes the evidence base was limited to draw firm conclusions (HEI (Health Effects Institute), 2010).

Since then, more studies have been published investigating the health effects of exposure to TRAP using more sophisticated methods to characterize air pollution from different sources such as dispersion modelling or land use regression modelling. A number of large cohort studies have

studied effects of TRAP with mortality, cardiovascular disease, respiratory disease, birth outcomes, and cancer.

Following its well-cited 2010 critical review, HEI appointed a new expert panel to systematically evaluate the epidemiological evidence regarding the associations between long-term exposure to TRAP and selected adverse health outcomes. The Panel consisted of 13 experts in epidemiology, exposure assessment, and statistics at institutions in North America and Europe. The Panel used a systematic approach to search the literature, select studies for inclusion in the review, assess study quality, summarize results, and reach conclusions about the confidence in the association between TRAP and a specific health outcome. Outcomes were selected based on evidence of causality (causal or likely causal) for general air pollution (broader than TRAP) from available authoritative integrated science assessments, and other considerations such as relevance for public health and policy, and resources available. The Panel selected clinical outcomes (rather than preclinical and biomarker measures), including birth outcomes (e.g., term low birth weight and preterm birth), respiratory outcomes (e.g., asthma onset), cardiometabolic outcomes (e.g., ischemic heart disease, stroke and diabetes), and all-cause and cause-specific (e.g., circulatory and respiratory) mortality (Boogaard, Atkinson, et al., 2023).

As a member of the contractor team hired to advice and execute certain parts of the review, the author of this thesis was involved in the development of the protocol, the bibliographic searches and data extraction as well as the separate articles on diabetes, stroke and mortality.

1.4 Air pollution and diabetes and stroke

A causal relationship between air pollution and diabetes or stroke is not firmly established (see Fig. 1.4 (U.S. EPA, 2016, 2019)). However, more recent studies indicate, that air pollution and possibly traffic-related air pollution could lead to the development of diabetes or stroke.

1.4.1 Diabetes

Diabetes mellitus (DM) is a chronic condition in which blood glucose (sugar) levels are elevated because the body can either no longer use insulin efficiently, no longer produces enough insulin, or no longer produces insulin at all (International Diabetes Federation, 2021). Insulin is an important hormone produced in the pancreas that facilitates the transfer of glucose out of the blood stream and into cells. There, glucose can either be used or stored. When this process fails to function properly, chronically high levels of blood glucose (hyperglycemia) can result in organ damage, with persons with diabetes commonly suffering from cardiovascular disease

(CVD), neuropathy, lowered kidney function or eye disease (International Diabetes Federation, 2021).

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. Diabetes is typically classified into three main types: type 1 diabetes (T1DM), type 2 diabetes (T2DM), and gestational diabetes (GDM). T1DM is an auto-immune disorder, in which the immune cells of a person's body incorrectly attack the beta cells in the pancreas. These are responsible for insulin production and their loss leads to a large or total deficiency in the amount of insulin able to be produced by the body (International Diabetes Federation, 2021). 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 (International Diabetes Federation, 2021). Gestational diabetes (GDM) is a condition that develops during pregnancy. As a result of placental hormone production insulin resistance is increased and leads to slightly elevated blood glucose levels (International Diabetes Federation, 2021). Diabetes does not only come with a higher risk for further disease and complications, it is also costly. Worldwide 11.5% of total global health spending was due to diabetes. The total diabetes-related health expenditure in Germany in 2021 was 41.3 billion USD, according to the IDF (International Diabetes Federation, 2021).

Apart from genetic factors that contribute to diabetes risk, the main risk factors for T2DM are unhealthy lifestyle, particularly obesity and lack of physical activity (World Health Organization, 2016). Environmental exposures, such as air pollution are also expected to play a role (Beulens et al., 2022).

Several mechanisms are proposed for the link between air pollution and the development of diabetes. Oxidative stress and subclinical inflammation that have been shown in animal studies to result in impaired insulin signaling and insulin resistance (Gorini et al., 2021). Some researches demonstrated that exposure to $PM_{2.5}$, PM_{10} and NO_2 might cause insulin resistance and reduced glucose tolerance, raising the risk of T2DM (Kelishadi et al., 2009; Rajagopalan and Brook, 2012; van der Pol et al., 2019). Also, oxidative stress is widely recognized as one of the key factors of linking air pollution and T2DM, which may generate a sequence of biological chemical events by inducing lipid peroxidation, activating pro-inflammatory factors and mediating inflammatory responses (Lim & Thurston, 2019). Indirectly, exposure to $PM_{2.5}$ can increase blood pressure and exacerbate hypertension, which are known to contribute to the development of type 2 diabetes (Kim et al., 2015).

Several systematic reviews have concluded that ambient air pollution is associated with diabetes mellitus (Liu et al., 2019; Yang et al., 2020), diabetes type 1 (Mozafarian et al., 2022) or

gestational diabetes mellitus (Ren et al., 2023). 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 (Wu et al., 2021).

Understanding how diabetes risk is affected by air pollution from specific sources informs useful air quality policies and other interventions. The sole systematic review to date evaluating the association of TRAP exposure with diabetes concluded, there was a positive association between the two (Alderete et al., 2018).

While T1DM and GDM are important public health problems with extensive overlap with T2DM, T2DM is the focus of this dissertation. Any subsequent allusions to “diabetes” or DM denote T2DM unless otherwise mentioned.

1.4.2 Stroke

A stroke occurs when a blood clot blocks blood supply to part of the brain or when a blood vessel in the brain bursts. A stroke can cause lasting brain damage, long-term disability, or even death (CDC, 2023). Stroke is a leading cause of death worldwide (Feigin et al., 2022). Two main categories of stroke are distinguished. Ischemic stroke, when blood clots or other particles block the blood vessels in the brain. And hemorrhagic stroke, when an artery in the brain leaks blood or ruptures. The leaked blood puts too much pressure on brain cells, which damages them (CDC, 2023). Depending on where the bleeding happens, the subtypes intracerebral, cerebral and subarachnoid hemorrhage exist (Sacco et al., 2013).

12.2 million people suffer a stroke annually and 6.5 million people die from stroke every year. Worldwide in 2019, 101 million people were living having experienced a stroke, some living with lasting disabilities. Stroke is the third leading cause of death and disability combined (Feigin et al., 2022).

Important risk factors for stroke morbidity and mortality include health states (e.g., high blood pressure, high fasting blood glucose, diabetes), behaviors that contribute to those states (e.g., smoking, features of the diet), and socioeconomic conditions that shape the former, and other factors influencing risk. Among these other factors are environmental pollutants. According to the GBD study, 20% of strokes are attributable to air pollution (GBD 2019 Stroke Collaborators, 2021). Also, it is estimated that 6% of global stroke mortality attributable to air pollution is traffic-related (McDuffie et al., 2021).

TRAP exposure is associated with mechanisms such as cerebrovascular dysfunction that appear to be manifested through several pathways that can increase stroke risk. These include inflammation and oxidative stress, endothelial dysfunction, blood pressure, atherosclerosis, pro-

coagulant changes, increased thrombogenicity, loss of vascular flexibility and alterations in autonomic nervous system balance (Landrigan et al., 2018; Miller, 2020). Most of these pathways have been causally attributed to PM exposure (see Fig. 1.4).

1.5 Burden of Disease

1.5.1 From small risks to large burden

On an individual level, the health risks of air pollution are small and other individual factors such as smoking can be a more important factor for the individual disease risk. However, since the entire population from young to old, healthy and sensitive are exposed to air pollution levels all the time, these small risks add up to a not negligible disease burden. This was convincingly shown in a comparative risk assessment by Nawrot et al. (2011). They compared triggers of myocardial infarction and calculated population attributable fractions (PAF) of disease based on the prevalence of the risk factors or triggers in the population. Even though cocaine use has a manifold risk triggering myocardial infarctions (odds ratio of 23.7) it has a much lower public health importance than air pollution with an odds ratio of 1.05 (per short-term increase of PM_{10} by 30 µg/m^3). The population attributable fraction is around 1% for the former and 5% for the latter (Nawrot et al., 2011). This stresses that despite small risk ratios of a few percentages of air pollution, its reach makes it an important risk factor for public health.

The burden of disease (BoD) analyses quantify the current level of population health and provide comprehensive overviews of the health status of a population group or countries. In BoD studies the comparative risk assessment (CRA) or health risk assessment (HRA) is commonly used to estimate the share of the burden attributable to risk factors. To reduce the disease burden and influence future health it is important to identify which risk factors are the key drivers of ill health. (Plass et al., 2022)

HRA[3] – another term for burden of disease studies – has been defined as “the scientific evaluation of potential adverse health effects resulting from human exposure to a particular hazard” (WHO, 2016). The general idea of the HRA is to compare a current harmful risk factor exposure level in the population against an alternative (or “counterfactual”) exposure situation where the selected risk factor is reduced to the so-called Theoretical Minimum Risk Exposure

[3] For the concept of HRA, alternative terms have been used in the literature, e.g. “assessments of the health burden”, “burden of disease assessment” or “health impact assessments”, although there can be some conceptual differences among them. For example, a health impact assessment focuses on the health impacts as a result of the implementation of a particular measure and comprise multiple policy steps World Health Organization. (2021). *WHO Global Air Quality Guidelines: Particulate Matter (PM2.5 and PM10), Ozone, Nitrogen Dioxide, Sulfur Dioxide and Carbon Monoxide*. World Health Organization. https://apps.who.int/iris/handle/10665/345329

Level (TMREL) (Plass et al., 2022). Therefore, it provides policymakers with compelling reasons to implement measures aimed at reducing exposure to a risk factor. It “evaluates” potential health gains. In so called accountability studies, health gains due to actual reductions of a risk factor (e.g. air pollution) after implementation of specific policies or measures are evaluated.

1.5.2 Methodology of Burden of Disease Studies

Methods for the estimation of the burden of disease due to air pollution were developed in the mid 1990s and became an inherent part of the global burden of disease calculations in this century (Cohen et al., 2005; Künzli et al., 2000; Künzli et al., 2001). According to the Global Burden of Disease Study, ambient air pollution is the single biggest environmental risk factor for public health, resulting in millions of premature deaths and years lived with disability (Fuller et al., 2022). In Western Europe with its improved air quality, it is still the number one environmental risk and the 10th important risk factor among behavioral and occupational risks (after smoking, high systolic blood pressure, high fasting plasma glucose, high BMI, dietary risks, alcohol use, high LDL cholesterol, occupational risks and kidney dysfunction) (GBD 2019 Risk Factors Collaborators, 2020).

HRA have been crucial in communicating and justifying the relevance of air pollution policy making for politicians, administrations, and the public. They have been specifically used to calculate cost–benefit analyses to compare the benefits of actions to reduce environmental burdens against their costs (Heroux et al., 2015). However, depending on the input data, results of health risk assessments can differ, challenging authorities with seemingly contradicting results (Künzli et al., 2023). For example, estimations for the number of premature deaths due to air pollution for the comparable area of European countries in 2019 was reported to be approximately 222’000 deaths in the Global Burden of Disease study (Central and Western European Countries combined plus Baltic states) (IHME, 2016) whereas the EEA calculated 412’000 (additionally including Kosovo) (European Topic Centre on Air pollution, 2020); almost double the number of the GBD.

It is important to understand the process of air pollution health risk assessments and differences in input data and their results to address concerns regarding their validity.

Fig. 1.9 shows the most relevant input data in AP-HRAs, which are:

- The difference between the population exposure, i.e. the modeled pollutant concentration to which population is exposed, and the counterfactual scenario, i.e. the minimum concentration considered in the AP-HRA to derive the overall impact.

- The concentration-response function (CRF) for selected adverse health effects, usually derived from a meta-analysis of epidemiological studies.
- The baseline health, i.e. prevalence or incidence of the disease data among the population at risk.

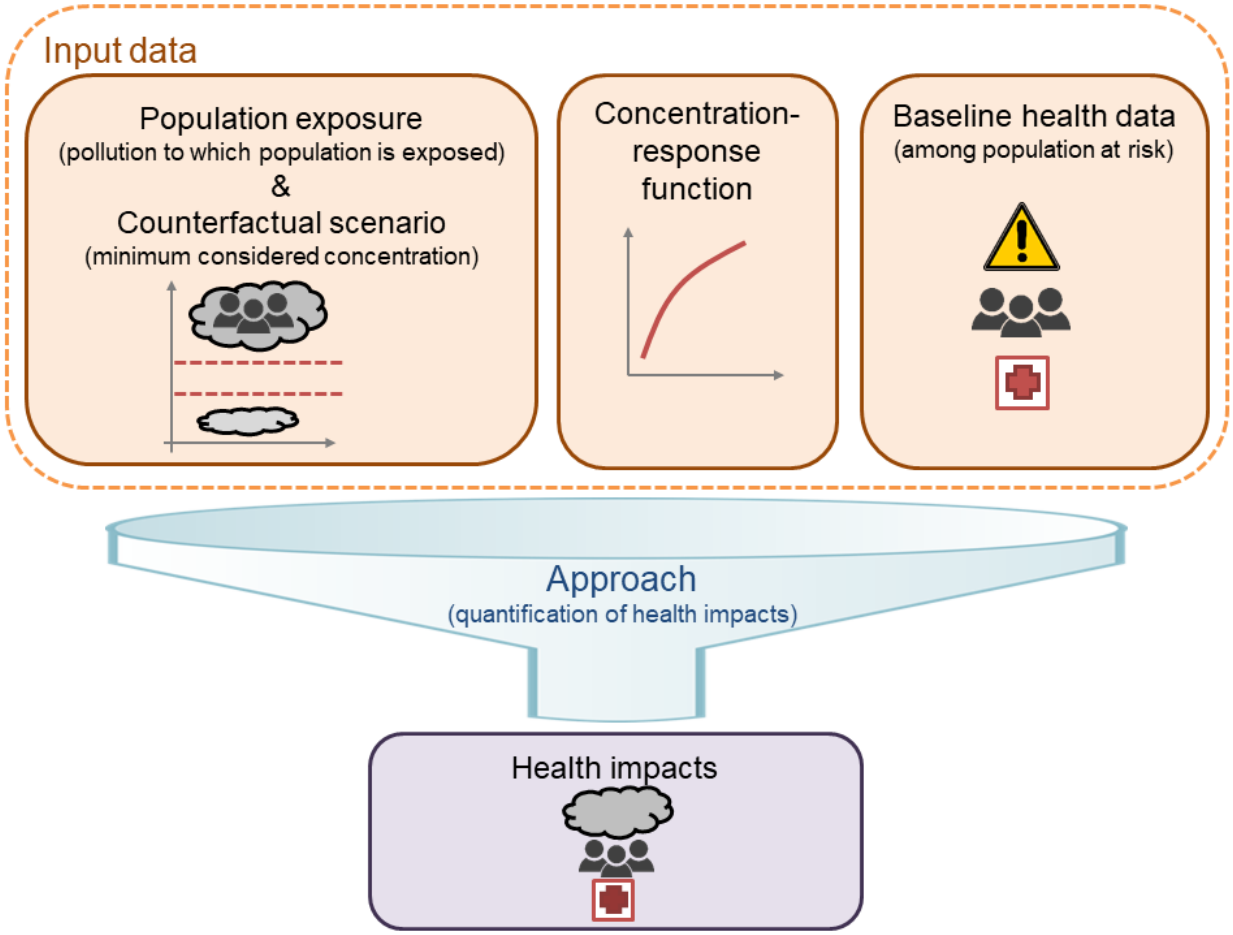

Fig. 1.9: General outline of relevant components of results of health impact assessments to derive the burden of health problems attributable to ambient air pollution (figure from (Castro et al., 2022) with kind permission of Alberto Castro).

Fig. 1.10 shows in more detail the general approach to quantify health impacts; including input data, intermediate results and calculations involved. Thus, to estimate health impacts, population attributable fraction (PAF) is multiplied by the baseline health data. The baseline health data is the annual number of cases of a health outcome (e.g. hospitalizations due to cardiovascular diseases) among the population at risk (defined by age and/or sex). The PAF can be defined as "the proportional reduction in *population* disease or mortality that would occur if exposure to a risk factor were reduced to an alternative ideal exposure scenario" (WHO, 2021). PAF can be calculated based on exposure-response functions (ERF) from the literature. They provide the relative risk for a specific difference between population exposure and counterfactual scenario. (Castro et al., 2022)

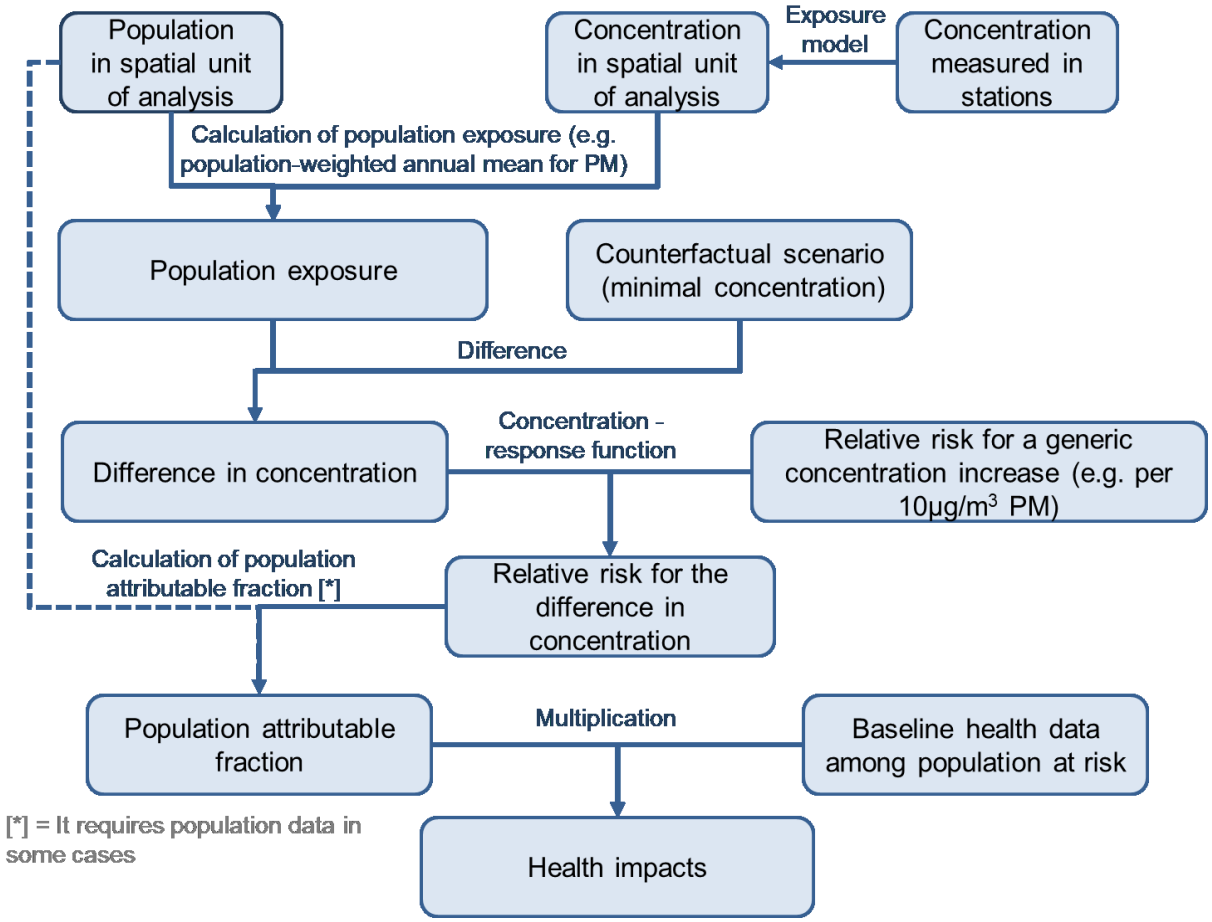

Fig. 1.10: General approach for the quantification of health impacts (own figure adapted from (Castro et al., 2022)).

For a risk factor to be included in such analyses, causality needs to be established between the risk factor (air pollution) and the health outcome. Concluding on causality is based on the strength of evidence that is brought by a variety of studies, each on its own not able to provide a definite answer. Finding a significant association in survey data does not suffice to assume that the risk factor was the cause of the health outcome. The gold standard for concluding on causality is often considered to be a randomized controlled trial (RCT). In reality, however, it is not always possible, due to ethical or practical constraints, to perform RCTs for many risk-outcome pairs (Plass et al., 2022). Especially environmental risk factors cannot or only rarely be studied in randomized controlled trials. Especially not, when long-term effects of exposure are to be judged. Concluding on causality is therefore based on the strength of evidence that is brought by a variety of studies, each on its own not able to provide a definite answer (Plass et al., 2022).

Despite the above-described rather common input data and general approach, the health impacts attributed to exposure to outdoor air pollution can be different across health risk

assessments. Differences in results of HRAs should not be dismissed as disagreement in science and uncertainty of effects, but rather as differences in input data such as the exposure data of the population, the selected health outcomes deemed to be causally related to the risk factor or the risks functions. Burden of disease studies or health risk assessments are part of the evaluation within the concept of the health action cycle.

1.6 Aims of the Thesis

In light of the public health action cycle, which defines public health as a constant process to gain understanding and knowledge of public health problems and introduce policies to tackle these problems, this dissertation addresses the question of the specific harmfulness of traffic-related air pollution (problem definition). While harmful effects of air pollution have been established (see Fig. 1.4), questions remain regarding effects on the cardiometabolic endpoints diabetes and stroke. The evidence in the last update of the integrated science assessment on particulate matter pollution in 2019 was not sufficient to infer causal relationships (U.S. EPA, 2019). Nonetheless, the Global Burden of Disease calculations have included Diabetes Type 2 and stroke into their burden of disease calculations (Health Effects Institute, 2020; Sang et al., 2022). Whether diabetes and stroke incidence and prevalence are related to TRAP is still under debate.

As part of a larger systematic review conducted by the Health Effects Institute on the effects of TRAP on key health outcomes published in 2022 (Boogaard et al.; HEI Panel on the Health Effects of Long-Term Exposure to Traffic-Related Air Pollution, 2022), this dissertation elaborates on the findings and confidence assessment on TRAP in relation to effects on diabetes and stroke in adults. The papers extend the interpretation of the reported results in the report to include evidence published after completion of the original literature search.

This dissertation also emphasizes the methodology for translating the findings of epidemiological studies concerning the risks associated with air pollution into meaningful numbers for effective communication (evaluation). This calculation of the burden of disease serves as a crucial tool in persuading policymakers of the importance of addressing air pollution to improve public health outcomes in the population. In light of different methodologies and resulting numbers, this dissertation will highlight the elements and input data of burden of disease studies using HRAs for Switzerland.

Therefore, this thesis aims to review

1. whether long-term exposure to TRAP is related to diabetes prevalence and incidence,
2. whether long-term exposure to TRAP is related to stroke incidence,
3. which elements of input data influence the results of different HRAs for Switzerland, and
4. how this should inform policy making in the context of the health action cycle.

1.6.1 Specific Objectives

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

The aim of Study I was to systematically evaluate the epidemiological evidence on long-term exposure to TRAP in relation to diabetes in adults and to elaborate in depth on the findings and confidence assessment on TRAP in relation to effects on diabetes in adults. It also aimed at highlighting the methodology developed by the expert Panel appointed by HEI for the "Systematic Review and Meta-analysis of Selected Health Effects of Long-Term Exposure to Traffic-Related Air Pollution". Results were not only quantitatively combined to evaluate the magnitude of the association, they were also assessed regarding the quality of the evidence and the level of confidence in the presence of an association taking into account studies that were not included in the meta-analyses. Results of the original report, which included studies up to July 2019, were discussed in light of new evidence with a sensitivity analysis of the original meta-analyses including more recent studies up to May 2022.

This study is part of the problem definition within the health action cycle.

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

The aim of Study II was to systematically evaluate the epidemiological evidence on long-term exposure to TRAP in relation to stroke in adults. Results were quantitatively combined to evaluate the magnitude of the association. Additionally, the quality of the evidence base and the level of confidence in the presence of an association between TRAP and stroke were assessed. In supplemental analyses results of the original report, which included studies up to July 2019, were discussed in light of new evidence including more recent studies up to January 2022.

This study is part of the problem definition within the health action cycle.

Study III: Methods Matter: A Comparative Review of Health Risk Assessments for Ambient Air Pollution in Switzerland

The aim of Study III was to analyze differences between different HRAs for Switzerland. In particular, national and international HRAs for Switzerland were analyzed and in a second step, their results were compared to the most recent “official” HRA, which calculates the Transport Externalities for Switzerland, i.e. the costs of traffic in Switzerland which includes cost calculations due to air pollution from traffic-related air pollution. Differences in the calculations are discussed regarding the assessed health impacts (selection of health endpoints) and their input data, namely the population exposure, counterfactual scenario, concentration-risk function and baseline health data.

This study refers to evaluation within the health action cycle.

2. PAPER I - LONG-TERM EXPOSURE TO TRAFFIC-RELATED AIR POLLUTION AND DIABETES: A SYSTEMATIC REVIEW AND META-ANALYSIS

Kutlar Joss, M., Boogaard, H., Samoli, E., Patton, A. P., Atkinson, R., Brook, J., Chang, H., Haddad, P., Hoek, G., Kappeler, R., Sagiv, S., Smargiassi, A., Szpiro, A., Vienneau, D., Weuve, J., Lurmann, F., Forastiere, F., & Hoffmann, B. H. (2023).

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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 $\mu g/m^3$), but less pronounced for diabetes incidence (RR 1.04; 95% CI: 0.96; 1.13 per 10 $\mu g/m^3$). 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

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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 $\mu g/m^3$, or mg/m^3 using standard WHO scaling factors (standardization of units). For example, 1 ppb NO_2 = 1.88 $\mu g/m^3$, 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 $\mu g/m^3$ 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^3[c] NO_x 1.02 (1.00, 1.04) per 11.4 μg/m^3[c] 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^3[c] 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^3[c]
[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

(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)
[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^3[c] NO_x 1.01 (1.00, 1.01) per 20 µg/m^3[c] $PM_{2.5abs}$ 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^3[c] 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^3[c] 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^3[c] $PM_{2.5}$ 0.98 (0.96, 1.00) per 5 µg/m^3[c] 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^3[c] PM_{10} 1.04 (0.86, 1.25) per 2 µg/m^3[c]
[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^3[c] 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^3[c]

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 DDOH.

[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

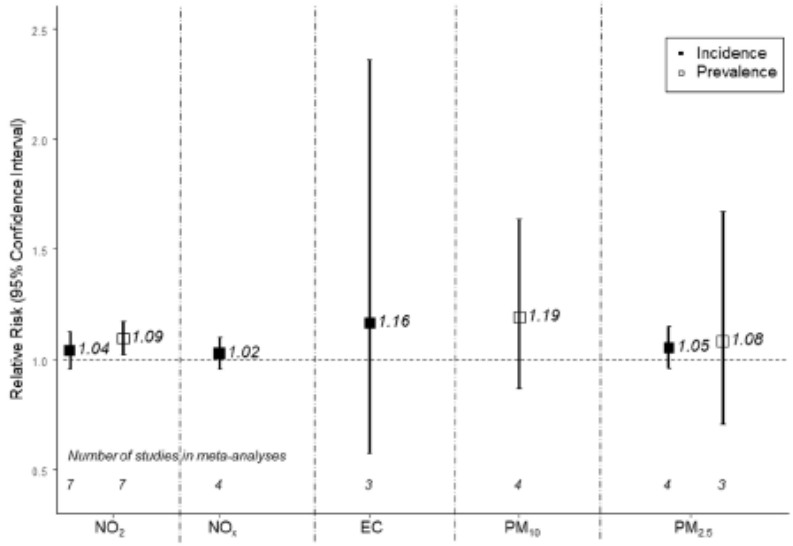

FIGURE 1 | Meta-analysis of associations between traffic-related air pollutants and diabetes prevalence (empty squares) and incidence (filled squares) (Global 2022). The following increments were used: 10 μg/m^3 for NO_2, 20 μg/m^3 for NO_x, 1 μg/m^3 for EC, 10 μg/m^3 for PM_{10}, and 5 μg/m^3 for $PM_{2.5}$.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

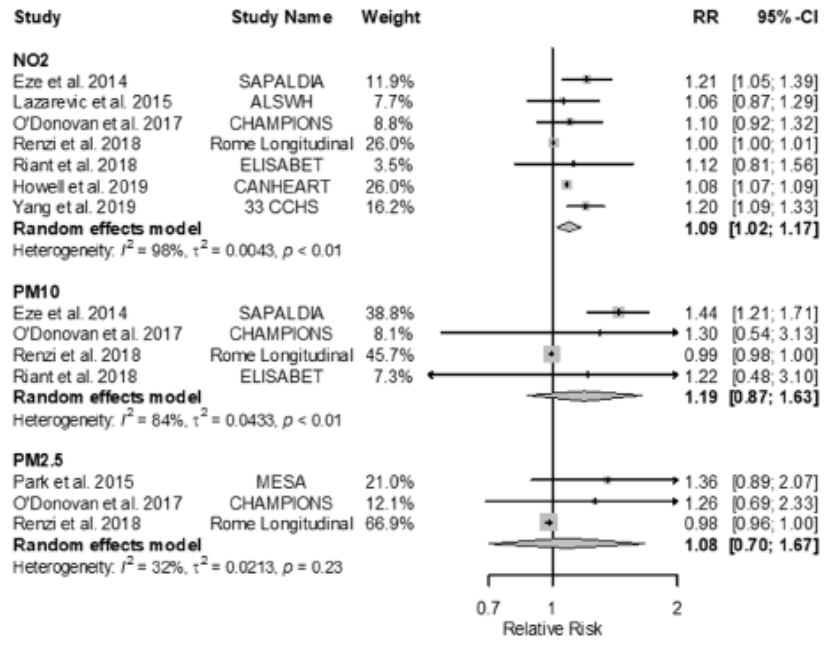

FIGURE 2 | Forest plots of adjusted RRs (95% CIs) for diabetes prevalence with NO_2, PM_{10}, and $PM_{2.5}$ (Global 2022). The size of the grey squares represents the weight of the study in the meta-analysis. The following increments were used: 10 μg/m^3 for NO_2, 20 μg/m^3 for NO_x, 1 μg/m^3 for EC,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

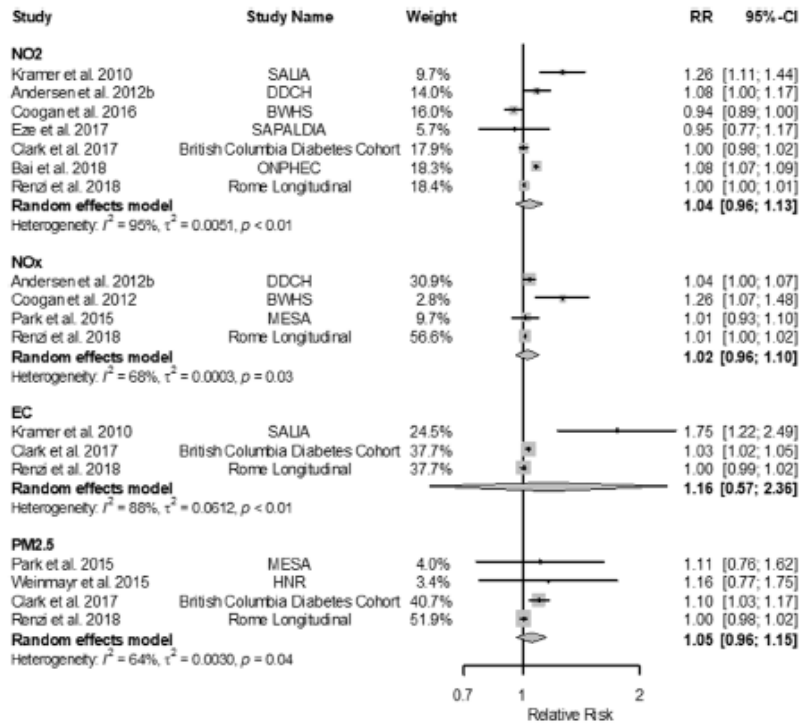

FIGURE 3 | Forest plots of adjusted RRs (95% CIs) for diabetes incidence with NO_2, NO_x, EC and $PM_{2.5}$ (Global 2022). The size of the grey squares represents the weight of the study in the meta-analysis. The following increments were used: 10 μg/m^3 for NO_2, 20 μg/m^3 for NO_x, 1 μg/m^3 for EC, 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 Rationale	+++ (N = 7) Cohort design initially rated as moderate	0 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	0 No formal evaluation possible	+ Two influential studies show monotonic ERF (Andersen, 2012b; Bai, 2018)	0 Confounding in both directions possible	0 Too few studies to evaluate	++ (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
	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 Rationale	+++ (N = 4) Cohort design initially rated as moderate	0 One study high RoB, but increased estimate after exclusion	0 Moderate heterogeneity (I^2 = 68%) mostly due to magnitude not direction	- Sample size met, but confidence interval wide and includes unity	0 No formal evaluation possible	0 No evidence of plausible shape of ERF	0 Confounding in both directions possible	0 Too few studies to assess robustness across populations	++ (Low)	NA
EC	Cohort Rationale	+++ (N = 3) Cohort design initially rated as moderate	0 Elevated estimate based on one study with moderate RoB. Two studies with high RoB show effect closer to the null	0 High heterogeneity (I^2 = 88%) due to magnitude not direction	- Sample size met, but confidence interval wide and includes unity	0 No formal evaluation possible	0 No evidence of plausible shape of ERF.	0 Confounding in both directions possible	0 Insufficient evidence for robustness across populations	++ (Low)	NA

(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^3[b] 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^3[b] 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^3[b] 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^3[b] 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^3[b] 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^3[b] 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^3[b]

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 DDOH.

[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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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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2.1 Paper I – Publication Appendix

Contents

List of Abbreviations

ALSWH	Australian Longitudinal Study on Women's Health
BaP	Benzo(a)pyrene
BWHS	Black Women's Health Study
CAFEH	Community Assessment of Freeway Exposure and Health study
CANHEART	Cardiovascular Health in Ambulatory Care Research Team

CHAMPIONS	Calculating How Air Pollution Impacts Our Society Study
CI	confidence interval
DDCH	Danish Diet, Cancer, and Health cohort
EC	elemental carbon, a measure of soot
ELISABET	Enquête Littoral Souffle Air Biologie Environnement Study
ERF	Exposure risk function
GRADE	Grading of Recommendations Assessment, Development and Evaluation (approach)
HEI	Health Effects Institute
HNR	Heinz Nixdorf Recall study
HR	Hazard risk
ICD	International classification of disease
IDF	International Diabetes Federation
IDF	international diabetes federation
IRR	Incidence rate ratio
iSES	individual socioeconomic status, measures of individual socioeconomic status such as education; income
JHS	Jackson Heart Study
LUDOK	Literature database on health effects of ambient air pollution
MESA	Multi-Ethnic Study of Atherosclerosis
NA	Not applicable
NIEHS OHAT	National Institute of Environmental Health Sciences Office of Health Assessment and Translation
NO	nitrous oxide
NO2	nitrogen dioxide
NOx	nitrogen dioxide and nitrous oxide
NOx	oxides of nitrogen
nSES	neighborhood socioeconomic status, measures of neighborhood socioeconomic status such as mean household income, BMI: body mass index, area
ONPHEC	ONtario Population Health and Environment Cohort
PAH	Polycyclic aromatic hydrocarbon
PM10	particulate matter with an aerodynamic diameter smaller or equal to 10 micrometer
PM2.5	particulate matter with an aerodynamic diameter smaller or equal to 2.5 micrometer
PM2.5abs	Light absorption of PM2.5, a measure of soot
PM2.5coarse	particulate matter with an aerodynamic diameter between 2.5 and 10 micrometer
RoB	risk of bias
RR	Relative risk or risk ratio
SALIA	Study on the influence of Air pollution on Lung function, Inflammation and Ageing
SALSA	Sacramento Area Latino Study on Aging
SAPALDIA	Swiss cohort study on Air Pollution and Lung Disease In Adults
33 CCHS	33 Communities Chinese Health Study
TRAP	traffic-related air pollution
UFP	Ultrafine particles, with a diameter of equal to or less than 100nm
WHO	World Health Organization

Table S1 Pollutants and metrics considered as TRAP

Exposure Metric	Consideration
NO_2, NO_x, 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
$PM_{2.5}$, PM_{10}, and PM_{coarse}	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, such as Cu, Fe and Zn	Increased interest because of reduction of tailpipe emissions
UFP, PNC, 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 upon 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), British Smoke (BS), and PM Absorption (PM_{abs}) are referred to as EC throughout this report. These carbonaceous pollutants are defined by operational measurement techniques rather than by fundamental chemical properties alone.

Table S2 Exposure framework eligibility criteria matrix

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[1]
All pollutants from Table S2	Dispersion or CTM models of traffic emissions or traffic-specific source-tracking/apportionment (method 3-4 in Table 6.3)	≤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 Table S2	Dispersion or CTM models of all sources (method 3 in Table 6.3)	≤5 km	≤5 km	Residential address as exact address, neighborhood, census tract, zip code acceptable (city or county not acceptable)	Judgement needed (e.g., required area adjustment in epidemiological analysis if spatial extent of the study area was >10,000 km^2, determination of whether exposures met long-term criteria)
All pollutants from Table S2	LUR models that contain at least one traffic predictor (e.g., traffic intensity or road density) or broader surrogate of traffic (e.g., address density, household density, population density, impervious surface) (method 5 in Table 6.3)	≤5 km	≤5 km	Residential address as exact address, neighborhood, census tract, zip code acceptable (city or county not acceptable)	Judgement needed (e.g., required area adjustment if spatial extent of the study area was >10,000 km^2, determining whether exposures met long-term criteria)
$PM_{2.5}$ PM_{10} PM_{coarse}	Surface, satellite and personal monitoring (methods 6-8 in Table 6.3)	Excluded	Excluded	Excluded	Excluded
Indirect traffic measures (metrics based upon distance or traffic density)	Objective (methods 1-2 in Table 6.3)	≤1000 m from a highway or a major road	≤100 m	Residential address as exact address or detailed zip code (i.e., street segment)	Assumed by method

[1]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 (see text for additional considerations). The spatial resolution of a pollution surface was selected based on its capacity to identify within-city contrasts in ambient air pollution.

Table S3 Search terms

The comprehensive search strategy was following the PECOS research questions, which can be translated to the diabetes search as: “In the general ADULT population (P), what is the increase in risk of DIABETES (O) for a change (C) in long–term exposure to traffic–related air pollution (E), observed in epidemiologic studies relevant for the health outcome and exposure duration of interest (S)?”

Search terms for the whole review – diabetes related outcomes highlighted in bold letters in PubMed

PECOS		Search Terms for Pubmed
Population		adult[tiab] OR adults[tiab] OR child[tiab] OR children[tiab] OR pupils[tiab] OR preschooler[tiab] OR preschoolers[tiab] OR student[tiab] OR students[tiab] OR adolescent[tiab] OR adolescents[tiab] OR infant[tiab] OR infants[tiab] OR toddler[tiab] OR toddlers[tiab] OR newborn[tiab] OR baby[tiab] OR babies[tiab] OR person[tiab] OR persons[tiab] OR human[tiab] OR humans[tiab] OR people[tiab] OR man[tiab] OR men[tiab] OR woman[tiab] OR women[tiab] OR elderly[tiab] OR boy[tiab] OR boys[tiab] OR girl[tiab] OR girls[tiab] OR patients[tiab] OR population[tiab] OR populations[tiab] OR survivor[tiab] OR survivors[tiab] OR spouse[tiab] OR spouses[tiab] OR wife[tiab] OR husband[tiab] OR smoker[tiab] OR smokers[tiab] OR resident[tiab] OR residents[tiab] OR veteran[tiab] OR mother[tiab] OR mothers[tiab] OR father[tiab] OR fathers[tiab] OR “population based”[tiab] OR “cohort”[tiab] OR (("persons"[Mesh] OR "humans"[Mesh]) NOT (animals[Mesh] NOT humans[Mesh]))
Exposure	General Terms to be combined with pollutants	("Environmental Exposure"[Mesh] OR "Environmental Pollution"[Mesh] OR "Air Pollutants"[Mesh] OR "Air Pollution"[Mesh] OR "air pollution"[tiab] OR "air pollutants"[tiab] OR "polluted atmosphere"[tiab] OR "atmospheric pollution"[tiab] OR "polluted air"[tiab] OR "ambient air"[tiab] OR "Inhalation Exposure/adverse effects"[Mesh] OR "Motor Vehicles"[Mesh] OR "Vehicle Emissions"[Mesh] OR "traffic-related"[tiab]) OR ((traffic OR transport) AND air)
NOx	Different Pollutants to be combined with OR	((("Nitrogen Oxides"[Mesh] OR "Nitrogen dioxide"[tiab] OR "NO2"[tiab] OR "NO(2)"[tiab] OR "NOx"[tiab] OR "NO(x)"[tiab] OR "Nitrogen oxide"[tiab] OR "nitrogen oxides"[tiab]))) OR "oxides of nitrogen"[tiab]
CO		"Carbon Monoxide"[Mesh] OR "carbon monoxide"[tiab]
Traffic PM		"Particulate Matter"[Mesh:NoExp] OR "Smog"[Mesh] OR “smog”[tiab] OR "Particle Size"[Mesh] OR "PM10"[tiab] OR PM2.5[tiab] OR PM10-2.5[tiab] OR PM2.5-10[tiab] OR PM1[tiab] OR “fine particulate”[tiab] OR "PM10"[tiab] OR "PM2.5"[tiab] OR "PM10-2.5"[tiab] OR "PM2.5-10"[tiab] OR "PM1"[tiab] OR "PM(10)"[tiab] OR "PM(2.5)"[tiab] OR "PM(10-2.5)"[tiab] OR "PM(2.5-10)"[tiab] OR "PM(1)"[tiab] OR "particulate matter"[tiab] OR "PMcoarse"[tiab] OR "PMcoarse"[tiab]
Non-tailpipe emissions and metals		resuspended dust[tiab] OR re-suspended dust[tiab] OR road dust[tiab] OR brake dust[tiab] OR tire dust[tiab] OR tyre dust[Text Word] OR brake wear[tiab] OR tire wear[tiab] OR tyre wear[tiab] OR road wear[tiab] OR debris dust[tiab] OR fugitive dust[tiab] OR diffuse dust[tiab] OR wear dust[tiab] OR non-exhaust[tiab] OR source

		apportionment[tiab] OR windblown dust[tiab] OR non-tailpipe[tiab] OR mineral dust[tiab] (nickel[tiab] OR Ni[tiab] OR Copper[tiab] OR Cu[tiab] OR aluminium[tiab] OR aluminum[tiab] OR Al[tiab] OR zinc[tiab] OR Zn[tiab] OR barium[tiab] OR Ba[tiab] OR iron[tiab] OR Fe[tiab] OR copper[tiab] OR Cu[tiab] OR Antimon[tiab] OR Sb[tiab] OR Tinn[tiab] OR Sn[tiab] OR Zirconium[tiab] OR Zr[tiab] OR "trace metals"[tiab] AND ("Particulate Matter"[Mesh:NoExp] OR "Smog"[Mesh] OR "smog"[tiab] OR "Particle Size"[Mesh] OR "PM10"[tiab] OR PM2.5[tiab] OR PM10-2.5[tiab] OR PM2.5-10[tiab] OR PM1[tiab] OR "fine particulate"[tiab] OR "PM10"[tiab] OR "PM2.5"[tiab] OR "PM10-2.5"[tiab] OR "PM2.5-10"[tiab] OR "PM1"[tiab] OR "PM(10)"[tiab] OR "PM(2.5)"[tiab] OR "PM(10-2.5)"[tiab] OR "PM(2.5-10)"[tiab] OR "PM(1)"[tiab] OR "particulate matter"[tiab] OR "PMcoarse"[tiab] OR "PMcoarse"[tiab]))
UFPs		"submicron"[tiab] OR "surface area"[tiab] OR "ultrafine"[tiab] OR "ultrafine particles"[tiab] OR "ultrafine particle"[tiab] OR "nano particle"[tiab] OR "nano particles"[tiab] OR "nanoparticles"[tiab] OR "nanoparticle"[tiab] OR PM0.1[tiab] OR "PM0.1"[tiab] OR "PM(0.1)"[tiab] OR PM0.25[tiab] OR "PM(0.25)"[tiab] OR "PM0.25"[tiab] OR "quasi-ultrafine"[tiab] OR "quasi ultrafine"[tiab] OR "PNC"[tiab] OR "accumulation mode"[tiab] OR "particle number"[tiab] OR "number of particles"[tiab] OR "aitken mode"[tiab]
Soot/BC		"Soot"[Mesh] OR soot[tiab] OR "PM2.5 absorbance"[tiab] OR "PM2.5absorbance"[tiab] OR "PM2.5abs"[tiab] OR "black carbon"[tiab] OR "carbon black"[tiab] OR "organic carbon"[tiab] OR "elemental carbon"[tiab] OR "black smoke"[tiab]
PAHs		"Polycyclic Aromatic Hydrocarbons"[Mesh:NoExp] OR "polycyclic aromatic hydrocarbons"[tiab] OR PAH[tiab] OR "PAH's"[tiab] OR PAHs[tiab] OR "benzo(a)pyrene"[tiab] OR benzopyrene[tiab]
Benzene		"benzene"[Mesh] OR benzene[tiab] OR BTEX[tiab]
Proxy measures for traffic incl. OHAT traffic terms		((((traffic[tiab]) NOT ("Accidents, Traffic"[Mesh] OR safety[tiab] OR accident[tiab] OR accidents[tiab] OR injur*[tiab] OR collision*[tiab] OR crash*[tiab])) OR "traffic intensity"[tiab] OR "traffic density"[tiab] OR "traffic load"[tiab] OR "traffic count"[tiab] OR "road length"[tiab] OR ((proximity[tiab] OR near[tiab] OR distance[tiab] OR nearest[tiab] OR next[tiab] OR close[tiab] OR closest[tiab]) AND (road*[tiab] OR highway*[tiab] OR freeway*[tiab] OR motorway*[tiab] OR interstate[tiab] OR expressway[tiab]))))) OR ((vehicle[tiab] OR vehicles[tiab] OR vehicular[tiab] OR auto[tiab] OR automobile[tiab] OR bus[tiab] OR buses[tiab] OR car[tiab] OR truck[tiab] OR trucker[tiab] OR trucks[tiab] OR engine[tiab] OR transport[tiab] OR traffic[tiab]) AND (emissions[tiab] OR exhaust[tiab] OR fume*[tiab]))
	Measures of effect	"risk"[Mesh] OR "risk"[tiab] OR "risks"[tiab] OR "incidence"[Mesh] OR "incidence"[tiab] OR "incident"[tiab] OR "Prevalence"[Mesh] OR "prevalence"[tiab] OR "prevalent"[tiab] OR "Risk Factors"[Mesh] OR "risk factor"[tiab] OR "Odds Ratio"[Mesh] OR "odds"[tiab] OR "onset"[tiab] OR "associated"[tiab] OR "association"[tiab] OR "cause"[tiab] OR "causes"[tiab] OR "caused"[tiab] OR "develop"[tiab] OR "developed"[tiab] OR "prevent"[tiab] OR "prevents"[tiab] OR "prevented"[tiab] OR "increase"[tiab] OR "increased"[tiab] OR "increases"[tiab] OR "effect"[tiab] OR "effects"[tiab] OR "affect"[tiab] OR "affects"[tiab] OR "affected"[tiab] OR "protective"[tiab] OR

		“protect”[tiab] OR “protected”[tiab] OR “harm”[tiab] OR “harms”[tiab] OR “harmed”[tiab] OR “harmful”[tiab] OR “hazard”[tiab] OR “hazardous”[tiab] OR "Proportional Hazards Models"[Mesh] OR "proportional hazard"[tiab]
Outcome		**Specific Outcomes / Diseases**
	Mortality	("Mortality"[Mesh] OR "mortality"[MeSH Subheading] OR "Cardiovascular Diseases/mortality"[Mesh] OR "Myocardial Ischemia/mortality"[Mesh] OR "Respiratory Tract Diseases/mortality"[Mesh] OR "Respiratory Tract Infections/mortality"[Mesh] OR "Respiration Disorders/mortality"[Mesh] OR "Lung Neoplasms/mortality"[Mesh] OR "Pulmonary Disease, Chronic Obstructive/mortality"[Mesh]) OR (("cause-specific"[tiab] OR "all-cause"[tiab] OR "non-accidental"[tiab] OR "natural"[tiab] OR "natural-cause"[tiab] OR "cardiovascular"[tiab] OR "respiratory"[tiab] OR "cardiorespiratory"[tiab] OR "cardio respiratory"[tiab] OR "lung cancer"[tiab] OR "COPD"[tiab]) AND (mortality[tiab] OR death[tiab] OR "deadly"[tiab] OR died[tiab] OR fatal*[tiab] OR surviv*[tiab])) OR ("mortality"[tiab] OR "death"[tiab])
	Respiratory Effects	"Pulmonary Ventilation"[Mesh] OR "Respiratory Function Tests"[Mesh] OR “spirometry”[tiab] OR "plethysmography"[tiab] OR “forced expiratory”[tiab] OR “FEV”[tiab] OR “FVC”[tiab] OR “FEF25-75”[tiab] OR “MEF”[tiab] OR “expiratory flow”[tiab] OR “expiration flow”[tiab] OR “small airway”[tiab] OR “impulse oscillometry”[tiab] OR “FOT”[tiab] OR “peripheral airway”[tiab] OR (("pulmonary"[tiab] OR "respiratory"[tiab] OR "lung"[tiab]) AND ("volume"[tiab] OR "function"[tiab] OR "ventilation"[tiab] OR "capacity"[tiab])) OR "Asthma"[Mesh] OR asthma[tiab] OR asthmatic[tiab] OR wheezing[tiab] OR wheeze[tiab] OR whistle[tiab] OR whistling[tiab] OR "bronchial hyperreactivity"[tiab] OR "Bronchial Hyperreactivity"[Mesh] OR "bronchial hyperresponsiveness"[tiab] OR "airway hyperresponsiveness"[tiab] OR ISAAC[tiab] OR "Respiratory Hypersensitivity/chemically induced"[Mesh] OR bronchiodilat*[tiab] OR "bronchial dilation"[tiab] OR "bronchial dilatation"[tiab] OR bronchioconstrict*[tiab] OR salbutamol*[tiab] OR "methacholine"[tiab] OR "mannitol"[tiab] OR "Breath Tests"[Mesh] OR “exhaled nitric oxide”[tiab] OR “FeNO”[tiab] OR “fractional exhaled NO”[tiab] OR "Acute lower respiratory infection"[tiab] OR "Acute lower respiratory tract infection"[tiab] OR "ALRI"[tiab] OR ("respiration tract"[tiab] AND "infection"[tiab]) OR "Pneumonia"[Mesh] OR "pneumonia"[tiab] OR "Bronchiolitis"[tiab] OR "Bronchitis"[Mesh] OR "Bronchitis"[tiab] OR "Pulmonary Disease, Chronic Obstructive"[Mesh] OR COPD[tiab] OR ((“chronic obstructive”[tiab]) AND (bronchitis[tiab] OR “bronchopulmonary disease”[tiab] OR “lung disorder”[tiab] OR “pulmonary disease”[tiab] OR “pulmonary disorder”[tiab] OR “respiratory disease”[tiab] OR disease[tiab])) OR "emphysema"[tiab] OR "chronic airway obstruction"[tiab] OR "chronic airflow obstruction"[tiab]
	Cardiovascular effects	*This search term includes the general term “cardiorespiratory” which will also be relevant for the mortality studies* (“cardiovascular”[Title/Abstract] OR “cardiorespiratory”[Title/Abstract] OR “cardio-respiratory”[Title/Abstract]) OR

		("Myocardial Ischemia"[Mesh] OR ((myocardial[tiab] OR myocard[tiab] OR heart[tiab] OR cardiac[tiab] OR cardial[tiab] OR myocardium[tiab]) AND (infarct[tiab] OR infarction[tiab] OR attack[tiab] OR failure[tiab] OR disease[tiab])) OR "Heart Failure"[Mesh] OR “fatal MI”[tiab] OR “coronary event”[tiab] OR “coronary syndrome”[tiab] OR “coronary syndrom”[tiab] OR “cardiac death”[tiab] OR “revascularization”[tiab] OR “revascularisation”[tiab]) OR ("Stroke"[Mesh] OR "Stroke"[tiab] OR "acute cerebrovascular lesion"[tiab] OR "cerebral vasculopathy"[tiab] OR "brain attack"[tiab] OR "cerebral apoplexy"[tiab] OR "brain ischemic attack"[tiab] OR (("cerebrovascular"[tiab] OR "cerebro vascular"[tiab] OR cerebral[tiab]) AND (insufficiency[tiab] OR "accident"[tiab] OR arrest[tiab] OR "failure"[tiab] OR "injury"[tiab] OR "attack"[tiab]))) ("Arteriosclerosis"[Mesh] OR “atherosclerosis”[tiab] OR “arteriosclerosis”[tiab] OR “vascular sclerosis”[tiab] OR "Carotid Intima-Media Thickness"[Mesh] OR “CIMT”[tiab] OR "aorta wall thickness"[tiab] OR "aortic thickness"[tiab] OR "aortic wall thickness"[tiab] OR "arterial thickness"[tiab] OR "artery thickness"[tiab] OR "artery wall thickness"[tiab] OR "carotid intima media thickness"[tiab] OR "carotid intima-media thickness"[tiab] OR "carotid intimamedia thickness"[tiab] OR "intima-media thickness"[tiab] OR "intimal medial thickness"[tiab] OR "intimamedia thickness"[tiab]) OR "Ankle Brachial Index"[Mesh] OR “ankle-brachial index”[tiab] OR "ankle brachial pressure index"[tiab] OR "ankle brachial ratio"[tiab] OR "Pulse Wave Analysis"[Mesh] OR "pulse wave velocity"[tiab] OR "pulse wave analysis"[tiab] OR "augmentation pressure"[tiab] OR "augmentation index"[tiab] OR "vascular reactivity"[tiab] OR "vascular function"[tiab] OR "Vascular Stiffness"[Mesh] OR ((aorta[tiab] OR arterial[tiab] OR aortic[tiab] OR artery[tiab] OR vascular[tiab]) AND (stiffness[tiab] OR stiffening[tiab])) OR "Calcinosis"[Mesh] OR "artery calcification"[tiab] OR "aortic calcification"[tiab] OR ("Blood Pressure"[Mesh] OR “blood pressure”[tiab] OR “systolic pressure”[tiab] OR “diastolic pressure”[tiab] OR "Hypertension"[Mesh] OR “hypertension”[tiab] OR “intravascular pressure”[tiab] OR “vascular pressure”[tiab] OR “blood tension”[tiab] OR “normotension”[tiab] OR “hypertensive”[tiab]) OR ("Plaque, Atherosclerotic"[Mesh] OR "plaque area"[tiab] OR “atherosclerotic plaque”[tiab] OR “arteriosclerotic plaque”[tiab] OR "atheromatous plaque”[tiab] OR "intima plaque”[tiab])
	Diabetes	**"Diabetes Mellitus, Type 2"[Mesh] OR "diabetes"[tiab] OR "diabetic"[tiab] OR T2DM[tiab] OR "type 2 DM"[tiab] OR "fasting blood glucose"[tiab] OR "fasting glucose"[tiab] OR "glucose metabolism"[tiab] OR "glucose homeostasis"[tiab] OR Hba1c[tiab] OR IDDM[tiab] OR NIDDM[tiab] OR HOMA-IR[tiab] OR hyperglycemia[tiab]**
	Cancer: Childhood Leukaemia	(("Leukemia"[Mesh] OR "Leukemia"[tiab] OR "Leukaemia"[tiab] OR leucemia[tiab] OR leucaemia[tiab] OR "childhood cancer"[tiab] OR hemoblastoma[tiab]) AND ("Child"[Mesh] OR "Adolescent"[Mesh] OR "Young Adult"[Mesh] OR "Infant"[Mesh] OR "children"[tiab] OR "childhood"[tiab] OR child[tiab] OR preschooler[tiab] OR preschoolers[tiab] OR pupil[tiab] OR pupils[tiab] OR student[tiab] OR students[tiab] OR adolescent[tiab] OR adolescents[tiab] OR infant[tiab] OR infants[tiab] OR toddler[tiab] OR toddlers[tiab] OR newborn[tiab] OR newborns[tiab] OR baby[tiab] OR babies[tiab] OR boy[tiab] OR boys[tiab] OR girl[tiab] OR girls[tiab]))

	Birth Outcomes	"Fetal Growth Retardation"[Mesh] OR "Birth Weight"[Mesh] OR "Infant, Low Birth Weight"[Mesh] OR "Premature Birth"[Mesh] OR “intrauterine growth restriction”[tiab] OR "Fetal Development"[Mesh] OR “fetal development”[tiab] OR “foetal development”[tiab] OR “intrauterine growth retardation”[tiab] OR "birth weight"[tiab] OR “small for gestational age”[tiab] OR “preterm birth”[tiab] OR “premature birth”[tiab] OR "birth outcome"[tiab] OR "pregnancy outcome"[tiab] OR “neonatal weight”[tiab] OR “newborn weight”[tiab] OR “fetal growth”[tiab] OR “foetal growth”[tiab] OR “foetus growth”[tiab] OR “fetus growth”[tiab] OR “foetal growth restriction”[tiab] OR “foetal growth retardation”[tiab] OR “in utero growth retardation”[tiab] OR “in utero growth restriction”[tiab] OR “congenital hypotrophy”[tiab] OR “prenatal growth retardation”[tiab] OR “prenatal growth restriction”[tiab] OR “retarded intrauterine growth”[tiab] OR “premature childbirth”[tiab] OR “premature birth”[tiab] OR “small for date”[tiab] OR “low birth weight”[tiab] OR (LBW[tiab] AND (infant[tiab] OR baby[tiab] OR newborn[tiab] OR child[tiab])) OR (premature[tiab] AND (infant[tiab] OR baby[tiab] OR newborn[tiab] OR child[tiab])) OR (“preterm”[tiab] AND (infant[tiab] OR baby[tiab] OR newborn[tiab] OR child[tiab]))
	Pregnancy outcomes	"Diabetes, Gestational"[Mesh] OR "Hypertension, Pregnancy-Induced"[Mesh] OR "Gestational Hypertension"[tiab] OR "pregnancy-induced hypertension"[tiab] OR (pregnan*[tiab] AND hypertens*[tiab]) OR pre-eclampsia[tiab] OR preeclampsia[tiab] OR (pregnan*[tiab] AND toxemia*[tiab])
	Neuro outcomes Children	"Cognition Disorders"[Mesh] OR cognition[tiab] OR cognitive[tiab] OR neurobehavio*[tiab] OR neuropsych*[tiab] OR "Mental Processes"[Mesh] OR memory[tiab] OR "mental recall"[tiab] OR (verbal[tiab] OR language[tiab] OR reading[tiab] AND (comprehension[tiab])) OR “language”[tiab] OR learning[tiab] OR perception[tiab] OR perceptual[tiab] OR neurodevelop*[tiab] OR intelligen*[tiab] OR intellect*[tiab] OR “IQ”[tiab] OR behavior[Mesh:NoExp] OR Child behavior[Mesh] OR Adolescent behavior[Mesh] OR Behavioral symptoms[Mesh] OR Spatial behavior[Mesh] OR executive function[tiab] OR “academic achievement”[tiab] OR “academic performance”[tiab] OR "Neurodevelopmental Disorders"[Mesh] OR attention[tiab] OR inattenti*[tiab] OR hyperactiv*[tiab] OR "impulsive behavior"[Mesh] OR impulsive[tiab] OR impulse-control[tiab] OR impulsivity[tiab] OR “response inhibition”[tiab] OR “inhibitory control”[tiab] OR “vigilance”[tiab] OR “social-behavior”[tiab] OR “social-behaviour”[tiab] OR “social skills”[tiab] OR aggression[tiab] OR aggressive[tiab] OR “ADDH”[tiab] OR “ADHS”[tiab] OR “ADHD”[tiab] OR “ADH”[tiab] OR "Autism Spectrum Disorder"[Mesh] OR autistic[tiab] OR autism[tiab] OR “Tic-disorder”[tiab] OR Asperger*[tiab] OR “communication-disorder*”[tiab] OR language[tiab] OR agraphia[tiab] OR dyslexi*[tiab] OR dyscalculia[tiab] OR speech[tiab] OR aphasia[tiab] OR echolalia[tiab] OR “stereotyp*”[tiab] OR “Pervasive Developmental Disorder”[tiab] OR “social cognition”[tiab] OR “social communication”[tiab] OR “social reciprocity”[tiab] OR “repetitive behavior*”[tiab] OR “repetitive behaviour”[tiab] OR “restricted interests”[tiab] OR “maladaptive behavior”[tiab] OR “maladaptive behaviour”[tiab] OR “adaptive behavior”[tiab] OR “behavioral regulation”[tiab]
	Additional search terms for adult outcomes	"Aging"[Mesh] OR "Cognitive Dysfunction"[Mesh] OR “dementia”[Mesh] OR dementia[tiab] OR alzheime*[tiab] OR neurotox*[tiab] OR “Neurodegenerative Diseases”[Mesh] OR

		neurodegenerat*[tiab] OR neurodisease*[tiab] OR Parkinson*[tiab] OR neuropsycholog*[tiab]
Filter		NOT ((((((("shortterm"[ti] OR "short-term"[ti] OR “time series”[ti] OR time-series[ti]) AND (("shortterm"[ti] OR "short-term"[ti] OR “time series”[ti] OR time-series[ti]) NOT ("longterm"[tiab] OR "long term"[tiab] OR "medium term"[tiab] OR "intermediate term"[tiab] OR “chronic”[tiab])))))) OR ("Clinical Trial"[Publication Type] OR "Treatment Outcome"[MeSH] OR "Cross-Over Studies"[Mesh] OR "case cross over"[tiab])) OR ("Air Pollutants, Occupational"[Mesh] OR "Accidents, Traffic"[Mesh] OR "Protective Devices"[Mesh])) OR (mouse[Title/Abstract] OR mice[Title/Abstract] OR rat[Title/Abstract] OR rats[Title/Abstract]) AND English[Language] AND ("1980/01/01"[Date - Publication] : "3000"[Date - Publication])
Search terms for the LUDOK database		
		(Sterblichkeit[methods] AND 7L) OR (road[methods] AND 7L) OR (traffic[methods] AND 7L) OR (schwangerschaft[methods] AND 7L) OR (geburt[methods] AND 7L) OR (arteriosklerose[methods] AND 7L) OR (diabetes[methods] AND 7L) OR (leukämie[methods] AND 7L) OR (4O AND 7L) OR (4I AND 7L)

Note 7L is the code for long-term studies, 4O code for outcomes related to pregnancy and prenatal development, 4I outcomes related to outcomes regarding neurocognitive outcomes, 4B = lung function, 4E = acute respiratory outcomes, 4H = cardiovascular outcomes like stroke, blood pressure, 4F = chronic respiratory outcomes, [] indicates the fields searched in the database. the [methods]-field is where LUDOK saves the keywords.

Table S4 List of excluded diabetes studies with reasons (Global 2022 and Global 2023)

Author	**year**	**Title**	**Reasons for exclusion during full text analysis**
Requia et al. [5]	2017	Association of PM with diabetes, asthma, and high blood pressure incidence in Canada: A spatiotemporal analysis of the impacts of the energy generation and fuel sales	spatial scale too crude (pollution surface), nationwide/statewide study with no or insufficient area-specific adjustments
Strak et al. [6]	2017	Long-term exposure to particulate matter, NO and the oxidative potential of particulates and diabetes prevalence in a large national health survey	nationwide/statewide study with no or insufficient area-specific adjustments
Orioli et al. [7]	2018	Association between PM10, PM2.5, NO2, O3 and self-reported diabetes in Italy: A cross-sectional, ecological study	spatial scale too crude (pollution surface)
Hazlehurst et al. [8]	2018	Individual and Neighborhood Stressors, Air Pollution and Cardiovascular Disease	spatial scale too crude (pollution surface), nationwide/statewide study with no or insufficient area-specific adjustments

Bowe et al. [9]	2018	The 2016 global and national burden of diabetes mellitus attributable to PM air pollution	nationwide/statewide study with no or insufficient area-specific adjustments
Gandini et al. [10]	2018	Long term effect of air pollution on incident hospital admissions: Results from the Italian Longitudinal Study within LIFE MED HISS project	spatial scale too crude (pollution surface), nationwide/statewide study with no or insufficient area-specific adjustments
Shin et al. [11]	2019	Association between long-term exposure of ambient air pollutants and cardiometabolic diseases: A 2012 Korean Community Health Survey	nationwide/statewide study with no or insufficient area-specific adjustments
Lao et al. [12]	2019	Long-term exposure to ambient fine particulate matter (PM) and incident type 2 diabetes: a longitudinal cohort study	nationwide/statewide study with no or insufficient area-specific adjustments
Qiu et al. [13]	2018	Long-term exposure to fine particulate matter air pollution and type 2 diabetes mellitus in elderly: A cohort study in Hong Kong	spatial scale too crude (pollution surface): PM satellite data
Hansen et al. [14]	2016	Long-term exposure to fine particulate matter and incidence of diabetes in the Danish Nurse Cohort	nationwide/statewide study with no or insufficient area-specific adjustments
Liang et al. [15]	2019	Long-term exposure to ambient fine particulate matter and incidence of diabetes in China: A cohort study.	spatial scale too crude (pollution surface)
Jørgensen et al. [16]	2019	Long-Term Exposure to Road Traffic Noise and Incidence of Diabetes in the Danish Nurse Cohort.	nationwide/statewide study with no or insufficient area-specific adjustments
Liu et al. [17]	2019	Gut microbiota partially mediates the effects of fine particulate matter on type 2 diabetes: Evidence from a population-based epidemiological study.	nationwide/statewide study with no or insufficient area-specific adjustments
Kloog et al. [18]	2012	Acute and chronic effects of particles on hospital admissions in New-England	spatial scale too crude (pollution surface)
Sørensen et al. [19]	2013	Long-term exposure to road traffic noise and incident diabetes: a cohort study	other: no relevant exposure metric
Liu et al. [20]	2016	Associations between long-term exposure to ambient particulate air pollution and type 2 diabetes prevalence, blood glucose and glycosylated hemoglobin levels in China	spatial scale too crude (pollution surface)
Hart et al. [21]	2015	Effect Modification of Long-Term Air Pollution Exposures and the Risk of Incident Cardiovascular Disease in US Women	nationwide/statewide study with no or insufficient area-specific adjustments
Coogan et al. [22]	2016	PM2.5 and Diabetes and Hypertension Incidence in the Black Women's Health Study	nationwide/statewide study with no or insufficient area-specific adjustments
Hellack et al. [23]	2017	Land use regression modeling of oxidative potential of fine particles, NO2, PM2.5 mass and association to type two diabetes mellitus	review, methodological, HIA, or similar paper (no primary data)
Heidemann et al. [24]	2014	Residential traffic and incidence of Type 2 diabetes: the German Health Interview and Examination Surveys	other: self-reported exposure
Meo et al. [25]	2015	Effect of environmental air pollution on type 2 diabetes mellitus	review, methodological, HIA, or similar paper (no primary data)
Brook et al. [26]	2008	The relationship between diabetes mellitus and traffic-related air pollution	Very selective subgroup

Weaver et al. [27]	2019	Neighborhood sociodemographic effects on the associations between long-term PM exposure and cardiovascular outcomes and diabetes.	Very selective subgroup
Yang et al. [28]	2018	Ambient fine particulate pollution associated with diabetes mellitus among the elderly aged 50 years and older in China	no within-area or spatial contrast exploited
Excluded studies from updated search with reasons			
Thacher et al.[29]	2021	Long-Term Exposure to Transportation Noise and Risk for Type 2 Diabetes in a Nationwide Cohort Study from Denmark	no or insufficient area-specific adjustments
Jalali et al. [30]	2021	Long-term exposure to PM2.5 and cardiovascular disease incidence and mortality in an Eastern Mediterranean country: findings based on a 15-year cohort study	Other: traffic related measures did not end up in the final model
Meroni et al. [31]	2021	The relationship between air pollution and diabetes: A study on the municipalities of the Metropolitan City of Milan	Geographic study, spatial scale too crude (pollution surface)
Sørensen et al. [32]	2022	Air pollution, road traffic noise and lack of greenness and risk of type 2 diabetes: A multi-exposure prospective study covering Denmark	nationwide/statewide study with no or insufficient area-specific adjustments
Ye et al. [33]	2021	Association of long-term exposure to PM2.5 with hypertension and diabetes among the middle-aged and elderly people in Chinese mainland: a spatial study	spatial scale too crude (pollution surface)
Zhang et al. [34]	2021	Associations of long-term exposure to ambient nitrogen dioxide with indicators of diabetes and dyslipidemia in China: A nationwide analysis	nationwide/statewide study with no or insufficient area-specific adjustments
Paul et al. [35]	2021	The impact of air pollution on the incidence of diabetes and survival among prevalent diabetes cases	nationwide/statewide study with no or insufficient area-specific adjustments
Liu et al. [36]	2019	Gut microbiota partially mediates the effects of fine particulate matter on type 2 diabetes: Evidence from a population-based epidemiological study	nationwide/statewide study with lack of detail on the area adjustment
Li et al. [37]	2019	Association Between Long-term Exposure to PM2.5 and Incidence of Type 2 Diabetes in Taiwan: A National Retrospective Cohort Study	nationwide/statewide study with no or insufficient area-specific adjustments
Klompmaker et al. [38]	2019	Associations of Combined Exposures to Surrounding Green, Air Pollution, and Road Traffic Noise with Cardiometabolic Diseases	nationwide/statewide study with no or insufficient area-specific adjustments
Jorgensen et al. [16]	2019	Long-Term Exposure to Road Traffic Noise and Incidence of Diabetes in the Danish Nurse Cohort.	nationwide/statewide study with no or insufficient area-specific adjustments
Dimakakou et al. [39]	2020	Is Environmental and Occupational Particulate Air Pollution Exposure Related to Type-2 Diabetes and Dementia? A Cross-Sectional Analysis of the UK Biobank	nationwide/statewide study with no or insufficient area-specific adjustments
Li et al. [40]	2021	Obesity and the relation between joint exposure to ambient air pollutants and incident type 2 diabetes: A cohort study in UK Biobank	nationwide/statewide study with no or insufficient area-specific adjustments

Equation S1 For conversion of effect estimates to a standardized increment of exposure

For the re-scale, we assumed a log-linear shape of the CRF, as used in a recent air pollution health risk assessment by Khomenko et al. [41]), applying Equation:

$RR_E = e^{\ln(RR_U)*\frac{C_E}{U}}$	**RR_U = Relative risk for a concentration D as in original literature.** **U = Unit of concentration of the relative risk as in the original literature (e.g. 10 in µg/m^3 $PM_{2.5}$).** **C_E = Desired increment of exposure, e.g. per 5 in µg/m^3 $PM_{2.5}$**

We converted to a common exposure units, that reflect a realistic range: per 10 µg/m3 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 $PM_{2.5}$.

Figure S1 Assessing confidence in the quality of the body of evidence following OHAT [42]

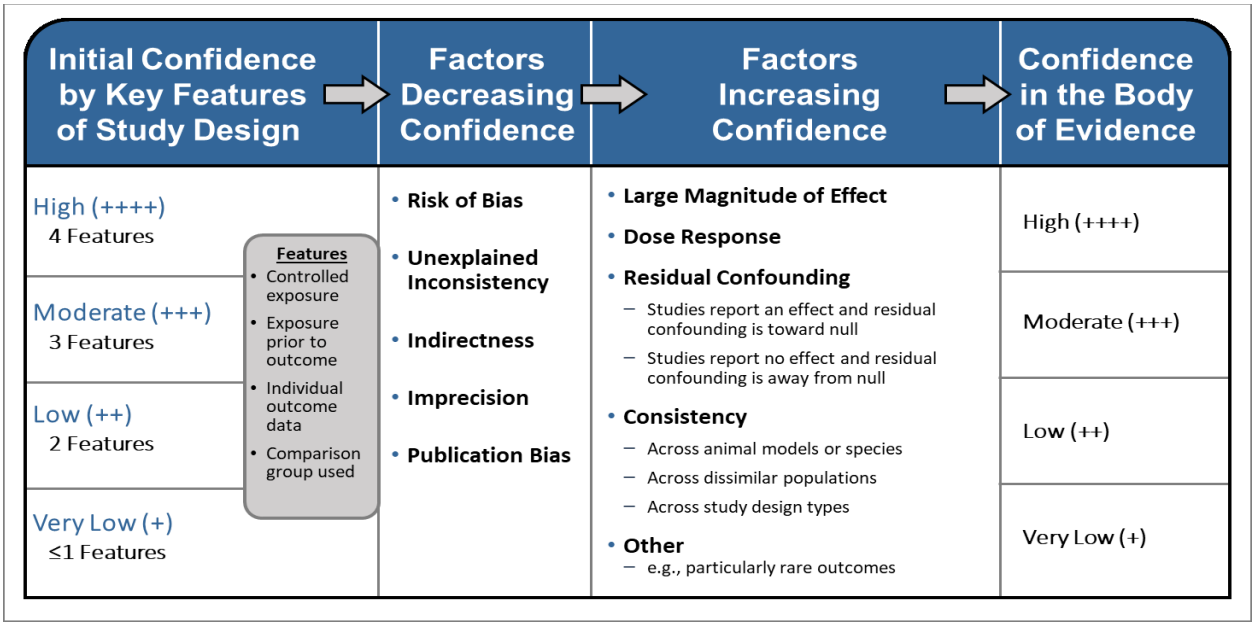
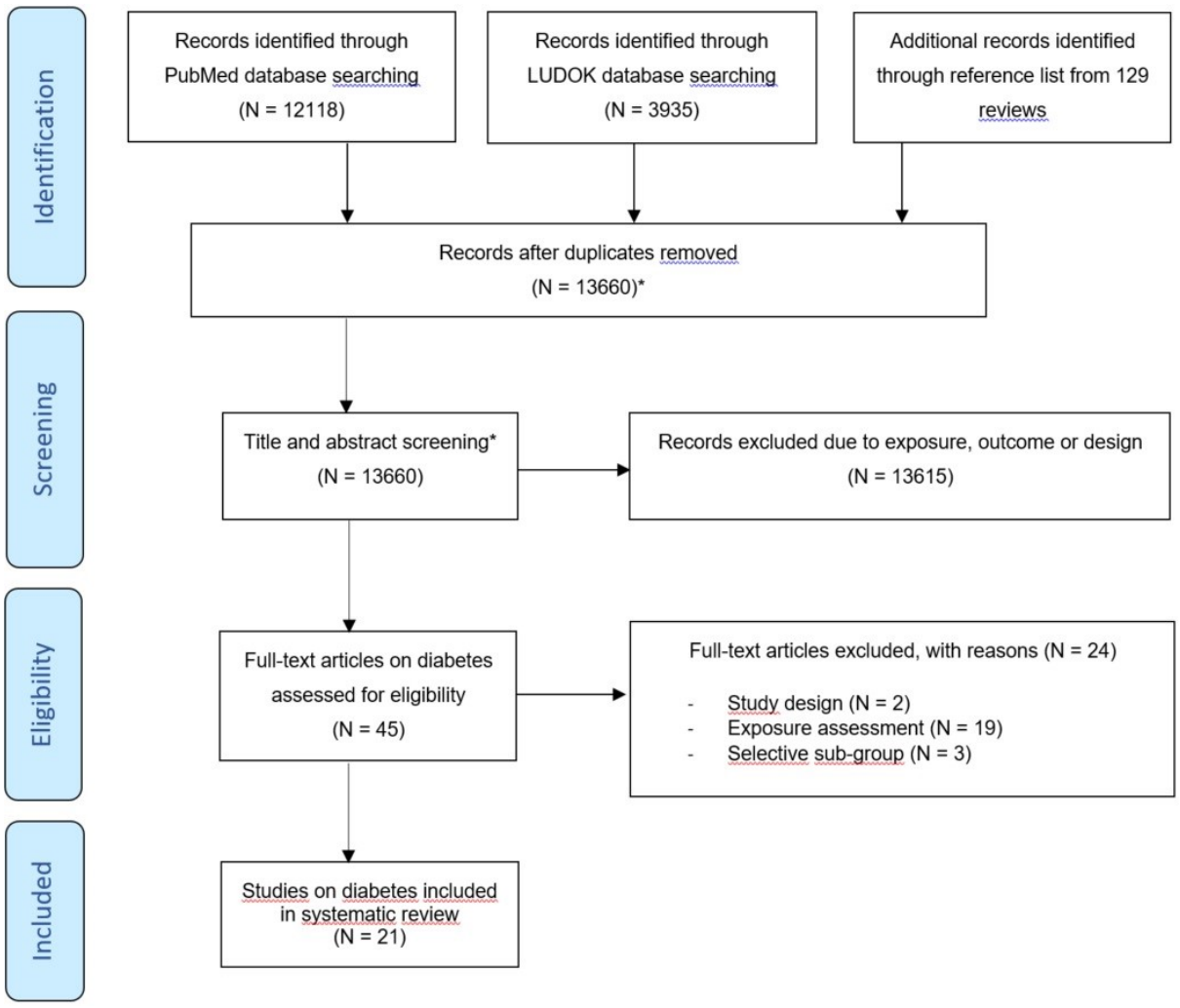


Figure S2 Preferred Reporting Items For Systematic Reviews and Meta-Analysis (PRISMA) flow diagram for the search of the comprehensive review on the association of TRAP with various health outcomes with the focus on diabetes, search up to July 2019. (Global. 2022)



*Results of the comprehensive search including mortality, respiratory diseases, birth outcomes, and cardiometabolic health effects

Figure S3 Forest-plot of the associations between distance measures and diabetes. (Global. 2022)

*SALIA estimates correspond to low and high education correspondingly

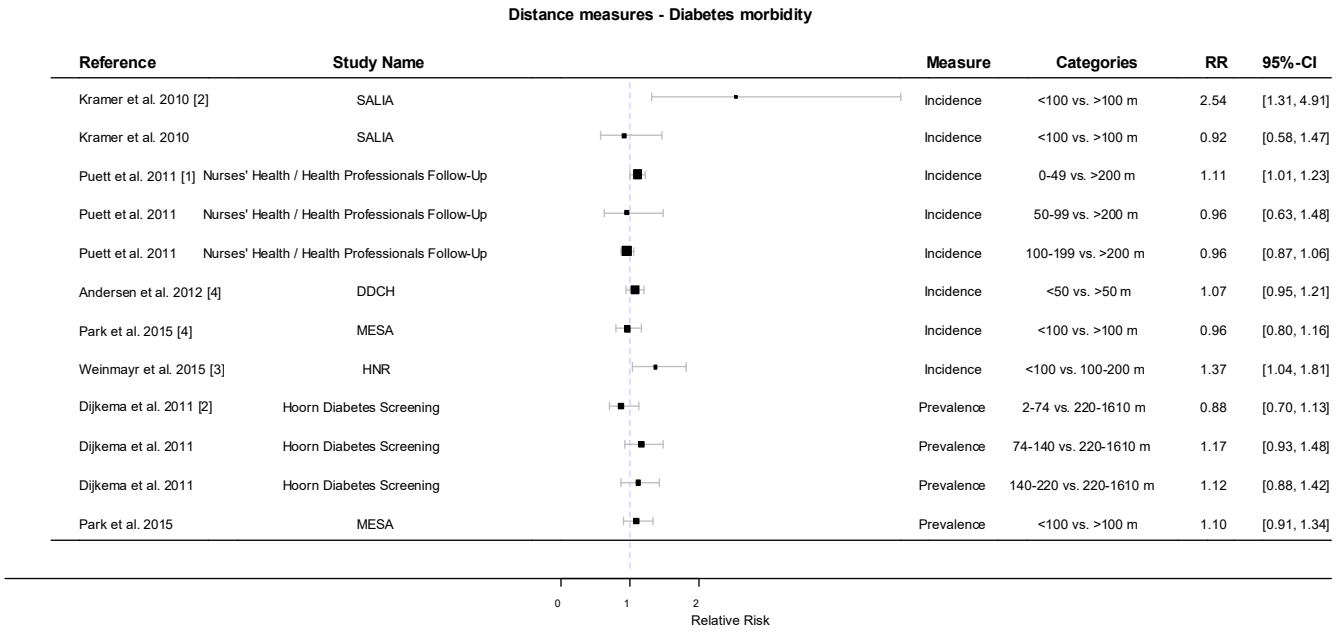


Figure S4 Forest-plot of the associations between traffic density measures and diabetes. (Global. 2022)

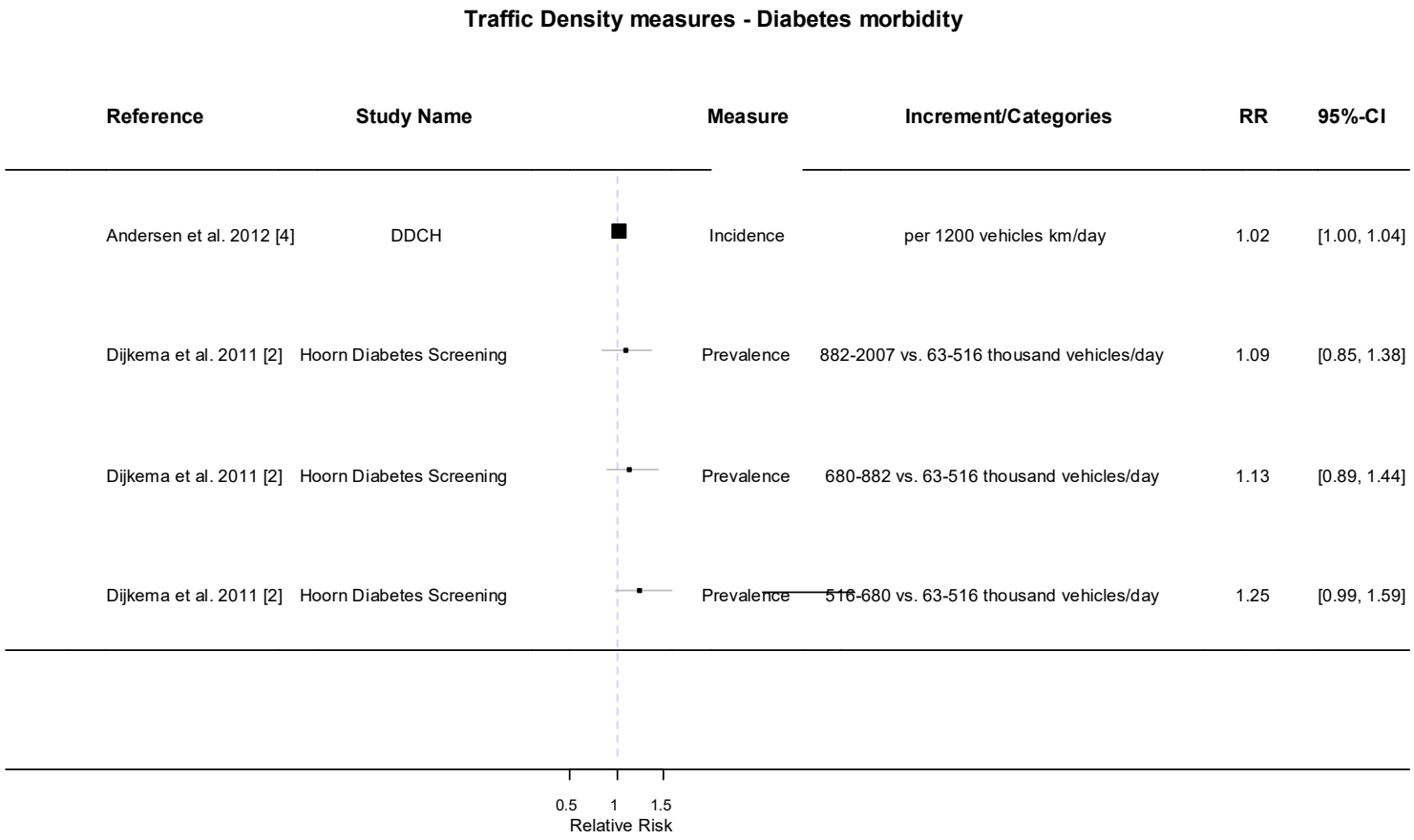


Table S5 Risk of bias assessment for studies included in meta-analysis: diabetes. (Global. 2022)

Reference	Study Name	Confounding	Selection Bias	Exposure Assessment	Outcome Measurement	Missing Data	Selective Reporting
Andersen, 2012 [4]	DDCH	Low	Low	Mod	Low	Low	Low
Bai, 2018 [43]	ONPHEC	High	Low	Mod	Low	Low	Low
Clark, 2017 [44]	British Columbia Diabetes Cohort	High	Low	Low	Low	Low	Low
Coogan, 2012 [45]	BWHS	Mod	Low	Low	Mod	Low	Low
Coogan, 2016 [46]	BWHS	Low	Low	Low	Mod	Mod	Low
Eze, 2014 [47]	SAPALDIA	Low	Mod	Low	Low	Low	Low
Eze, 2017 [48]	SAPALDIA	Low	High	Low	Low	Low	Low
Howell, 2019 [49]	CANHEART	High	Low	Low	Low	Low	Low
Kramer, 2010 [50]	SALIA	Mod	Low	Mod	Low	Mod	Low
Lazarevic, 2015 [51]	ALSWH	Low	Mod	Low	Mod	Low	Low
O'Donovan, 2017 [52]	CHAMPIONS	Low	Mod	Low	Low	Low	Low
Park, 2015 [53]	MESA	Low	Low	Mod	Low	Low	Low
Renzi, 2018 [54]	Rome Longitudinal	High	Low	Low	Low	Low	Low
Riant, 2018 [55]	ELISABET	Low	Low	Low	Low	Low	Low
Weinmayr, 2015 [3]	HNR	Low	Low	Low	Low	Low	Low
Yang, 2019 [56]	33 CCHS	Low	Low	Low	Low	High	Low

Table S6 Results of the subgroup and sensitivity analysis for the diabetes prevalence. (Global. 2022)

Analysis were only conducted when three or more studies were available.

		Prevalence of Diabetes								
		NO_2			PM_{10}			$PM_{2.5}$		
Stratification by		No. of studies	HR/OR (95%-CI)	Heterogeneity I2; T2; P-value	No. of studies	HR/OR (95%-CI)	Heterogeneity I2; T2; P-value	No. of studies	HR/OR (95%-CI)	Heterogeneity I2; T2; P-value
None		**7**	**1.09 [1.02; 1.17]**	**98%; 0.0043; p<0.01**	**4**	**1.19 [0.87: 1.63]**	**84%; 0.0433; p<0.01**	**3**	**1.08 [0.70; 1.67]**	**32%; 0.0213; p=0.23**
Region	North America	1	1.08 [1.07; 1.09]	NA				1	NA	
	Western Europe	4	1.08 [0.94; 1.25]	64%; 0.0067; p=0.04	4	1.19 [0.87: 1.63]	84%; 0.0433; p<0.01	2	NA	
	Asia	1	1.20 [1.09; 1.33]	NA						
	Australia/NZ	1	1.06 [0.87; 1.29]	NA						
Traffic Specificity	high	6	1.07 [1.00; 1.15]	98%; 0.0030, p<0.01				0		
	moderate	1	1.20 [1.09; 1.33]	NA	4	1.19 [0.87: 1.63]	84%; 0.0433; p<0.01	3	1.08 [0.70; 1.67]	32%; 0.0213; p=0.23
Selection bias	low	4	1.08 [0.95; 1.23]	99%; 0.055, p<0.01	2	0.99 [0.96;1.03]	0%; 0.0; p=0.67	2	NA	
	moderate/high	3	1.14 [0.96; 1.36]	0%, 0; p=0.50	2	1.43 [1.12; 1.83]	0%; 0.0; p=0.82	1		
Smoking adjustment	yes	5	1.17 [1.09; 1.25]	0%; 0, p=0.74	3	1.43 [1.28; 1.59]	0%; 0; 0.92	2	NA	

	No	2	1.04 [0.64; 1.70]		1	0.99 [0.98; 1.00]	NA	1		
Missing data RoB	low	6	1.07 [1.00; 1.15]	98%; 0.0030; p<0.01	4	1.19 [0.87: 1.63]	84%; 0.0433; p<0.01		NA	
	high	1	1.20 [1.09; 1.33]	NA						
Confounding	low/moderate	5	1.17 [1.09; 1.25]	0%; 0, p=0.74	3	1.43 [1.28; 1.59]	0%; 0; 0.92	2	NA	
	high	2	1.04 [0.64; 1.70]		1	0.99 [0.98; 1.00]	NA	1		
RoB exposure assessment	low		NA			NA		2	NA	
	moderate							1		
RoB outcome assessment	low	6	1.10 [1.01; 1.19]	98%; 0.0050; p<0.01		NA		2	NA	
	moderate	1	1.06 [0.87; 1.29]	NA				1		

The following increments were used: 10 µg/m3 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.

Table S7 Results of the subgroup and sensitivity analysis for the diabetes incidence. (Global. 2022)

Analysis were only conducted when three or more studies were available.

		Incidence of Diabetes											
		NO_2			NO_x			EC			$PM_{2.5}$		
Stratification by		No. of studies	HR/OR (95%-CI)	Heterogeneity I2; T2; P-value	No. of studies	HR/OR (95%-CI)	Heterogeneity I2; T2; P-value	No. of studies	HR/OR (95%-CI)	Heterogeneity I2; T2; P-value	No. of studies	HR/OR (95%-CI)	Heterogeneity I2; T2; P-value
None		**7**	**1.04 [0.96; 1.17]**	**98%; 0.0051; p<0.01**	**4**	**1.02 [0.96; 1.10]**	**68%; 0.0003; p<0.03**	**3**	**1.16 [0.57; 2.36]**	**88%; 0.0612; p<0.01**	**4**	**1.05 [0.96; 1.15]**	**64%, 0.0030, p=0.04**
Region	North America	3	1.01 [0.85; 1.19]	96%; 0.0042; p<0.01	2	NA		1	NA		2	NA	
	Western Europe	4	1.07 [0.89; 1.29]	81%; 0.0089; p<0.01	2	NA		2	NA		2	NA	
	Asia	0											
	Australia/NZ	0											
Traffic Specificity	high	6	1.05 [0.97; 1.15]	96%; 0.0038, p<0.01	4	1.02 [0.96; 1.10]	68%; 0.0003; p<0.03	3	1.16 [0.57; 2.36]	88%; 0.0612; p<0.01	0		
	moderate	1	0.94 [0.89; 1.00]	NA	0			0			4	1.05 [0.96; 1.15]	64%, 0.0030, p=0.04
Selection bias	low	6	1.04 [0.95; 1.15]	96%; 0.0057; p<0.01	6	1.04 [0.95; 1.15]	96%; 0.0057; p<0.01	3	1.16 [0.57; 2.36]	88%; 0.0612; p<0.01	0		
	moderate/high	1	0.95 [0.77; 1.17]	NA	1	0.95 [0.77; 1.17]	NA	0			4	1.05 [0.96; 1.15]	64%, 0.0030, p=0.04
Smoking adjustment	yes	4	1.05 [0.85; 1.31]	85%; 0.0146; p<0.01	3	1.07 [0.82; 1.40]	67%; 0.0069; p<0.05	1	NA		2	1.13 [0.84; 1.53]	0%, 0, p=0.87
	No	3	1.03 [0.92; 1.15]	98%; 0.0019; p<0.01	1	1.01 [1.00; 1.02]	NA	2	NA		2	1.04 [0.59; 1.85]	87%, 0.0036, p<0.01
Missing data RoB	low	7	1.04 [0.96; 1.17]	98%; 0.0051; p<0.01	4	1.02 [0.96; 1.10]	68%; 0.0003; p<0.03	3	1.16 [0.57; 2.36]	88%; 0.0612; p<0.01	0		

		Incidence of Diabetes											
		NO_2			NO_x			EC			$PM_{2.5}$		
Stratification by		No. of studies	HR/OR (95%-CI)	Heterogeneity I2; T2; P-value	No. of studies	HR/OR (95%-CI)	Heterogeneity I2; T2; P-value	No. of studies	HR/OR (95%-CI)	Heterogeneity I2; T2; P-value	No. of studies	HR/OR (95%-CI)	Heterogeneity I2; T2; P-value
	high	0			0			0			4	1.05 [0.96; 1.15]	64%, 0.0030, p=0.04
Confounding	low/moderate	4	1.05 [0.85; 1.31]	85%; 0.0146; p<0.01	3	1.07 [0.82; 1.40]	67%; 0.0069; p<0.05	1	NA		2	1.13 [0.84; 1.53]	0%, 0, p=0.87
	high	3	1.03 [0.92; 1.15]	98%; 0.0019; p<0.01	1	1.01 [1.00; 1.02]	NA	2	NA		2	1.04 [0.59; 1.85]	87%, 0.0036, p<0.01
RoB exposure assessment	low	4	1.00 [0.99; 1.02]	40%; 0.0; p=0.17	2	1.11 [0.27; 4.51]	86%; 0.0214; p<0.01	2	NA		3	1.05 [0.90; 1.21]	75%, 0.0033; p=0.02
	moderate	3	1.11 [0.93; 1.34]	62%; 0.0028; p=0.07	2	1.03 [0.92; 1.15]	0%; 0.0; p=0.060	1	NA		1	1.11 [0.76; 1.62]	NA
RoB outcome assessment	low	5	1.03 [0.98; 1.09]	96%; 0.0016; p<0.01	3	1.01 [0.98; 1.05]	4%; 0.0001; p=0.35		NA			NA	
	moderate	2	1.08 [0.17; 6.90]	94%; 0.0398; p<0.01	1	1.26 [1.07; 1.48]	NA					NA	

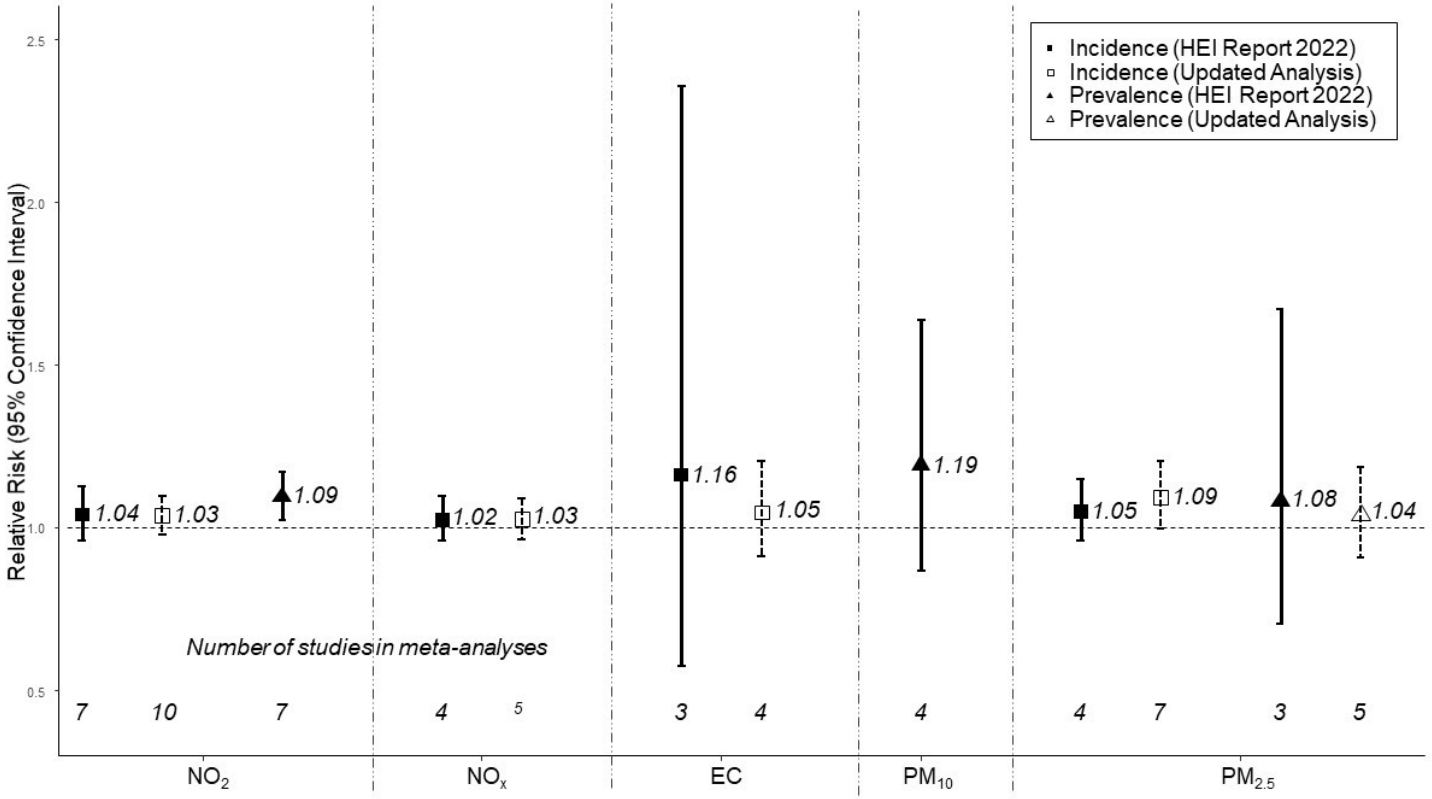
The following increments were used: 10 µg/m3 for NO_2, 20 µg/m^3 for NO_x, 1 µg/m^3 for EC, 10 µg/m^3 for PM_{10}, and 5 µg/m^3 for $PM_{2.5}$. Effect estimates cannot be directly compared across the different traffic-related pollutants because the selected increments do not necessarily represent the same contrast in exposure.

Table S8 Multi-pollutant analyses in diabetes studies considering noise. (Global. 2022)

Reference	Study Name	Pollutant	Incidence or prevalence	Effect measure	Increment	Single pollutant results	Noise adjusted
Clark, 2017 [44]	British Columbia Diabetes Cohort	NO	Incidence	odds ratio (OR)	13.13 μg/m^3	1.04 (1.01, 1.05)	1.01 (1.00, 1.04)
Clark, 2017 [44]	British Columbia Diabetes Cohort	$PM_{2.5\ abs}$	Incidence	odds ratio (OR)	0.9 1e-5/m	1.03 (1.01, 1.04)	1.01 (0.99, 1.03)
Clark, 2017 [44]	British Columbia Diabetes Cohort	$PM_{2.5}$	Incidence	odds ratio (OR)	1.6 μg/m^3	1.03 (1.01, 1.05)	1.03 (1.02, 1.05)
Dzhambov, 2016 [57]	Plovdiv Diabetes Survey	PAH (BaP)	Prevalence	odds ratio (OR)	>6 vs. <6 ng/m3	1.76 (0.52, 5.98)[1]	1.76 (0.52, 5.98)[1]
Dzhambov, 2016 [57]	Plovdiv Diabetes Survey	$PM_{2.5}$	Prevalence	odds ratio (OR)	>25 vs. <25 μg/m^3	1.32 (0.28, 6.24)[1]	1.32 (0.28, 6.24)[1]
Eze, 2014 [47]	SAPALDIA	NO_2	Prevalence	odds ratio (OR)	10 μg/m^3	1.21 (1.05, 1.39)	1.19 (1.03, 1.38)
Eze, 2014 [47]	SAPALDIA	PM_{10}	Prevalence	odds ratio (OR)	10 μg/m^3	1.44 (1.21, 1.71)	1.40 (1.17, 1.67)
Eze, 2017 [48]	SAPALDIA	NO_2	Incidence	relative risk (RR)	15 μg/m^3	0.92 (0.67, 1.26)	0.86 (0.61, 1.22)
Renzi, 2018 [54]	Rome Longitudinal	NO_2	Incidence	hazard ratio (HR)	10 μg/m^3	1.00 (1.00, 1.01)	1.00 (0.99, 1.01)
Renzi, 2018 [54]	Rome Longitudinal	NO_2	Prevalence	odds ratio (OR)	10 μg/m^3	1.00 (1.00, 1.01)	1.01 (1.00, 1.02)
Renzi, 2018 [54]	Rome Longitudinal	NO_x	Incidence	hazard ratio (HR)	20 μg/m^3	1.01 (1.00, 1.01)	1.01 (1.00, 1.02)
Renzi, 2018 [54]	Rome Longitudinal	NO_x	Prevalence	odds ratio (OR)	20 μg/m^3	1.01 (1.00, 1.01)	1.02 (1.01, 1.02)
Renzi, 2018 [54]	Rome Longitudinal	PM_{10}	Incidence	hazard ratio (HR)	10 μg/m^3	1.00 (0.99, 1.02)	1.00 (0.98, 1.02)
Renzi, 2018 [54]	Rome Longitudinal	PM_{10}	Prevalence	odds ratio (OR)	10 μg/m^3	0.99 (0.98, 1.00)	1.00 (0.99, 1.02)
Renzi, 2018 [54]	Rome Longitudinal	$PM_{2.5\ abs}$	Incidence	hazard ratio (HR)	1 1e-5/m	1.00 (0.98, 1.02)	1.00 (0.98, 1.02)
Renzi, 2018 [54]	Rome Longitudinal	$PM_{2.5\ abs}$	Prevalence	odds ratio (OR)	1 1e-5/m	0.98 (0.96, 0.99)	0.98 (0.97, 1.00)
Renzi, 2018 [54]	Rome Longitudinal	$PM_{2.5}$	Incidence	hazard ratio (HR)	5 μg/m^3	1.00 (0.98, 1.02)	1.00 (0.97, 1.02)
Renzi, 2018 [54]	Rome Longitudinal	PM2.5 mass	Prevalence	odds ratio (OR)	5 μg/m^3	0.98 (0.96, 1.00)	0.92 (0.97, 1.01)
Renzi, 2018 [54]	Rome Longitudinal	PMcoarse mass	Incidence	hazard ratio (HR)	10 μg/m^3	0.99 (0.97, 1.02)	0.98 (0.95, 1.01)
Renzi, 2018 [54]	Rome Longitudinal	PMcoarse mass	Prevalence	odds ratio (OR)	10 μg/m^3	0.96 (0.94, 0.98)	0.97 (0.95, 0.99)

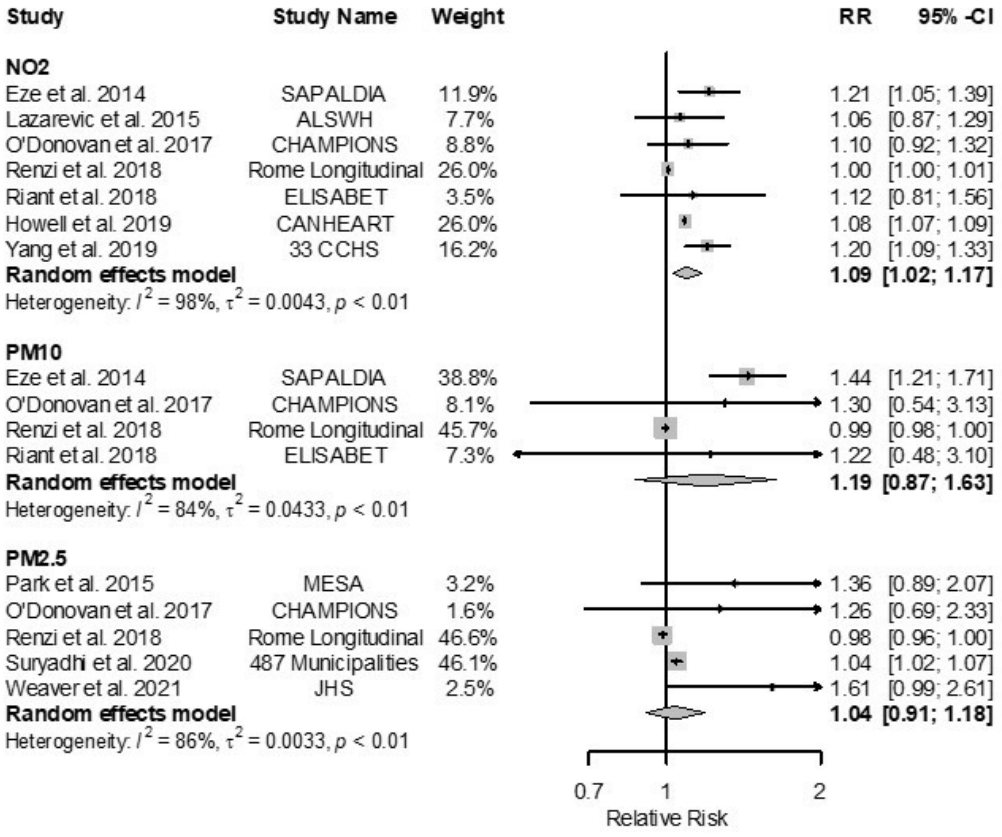
[1]The single pollutant results also corrected for noise; hence the two columns are similar.

Figure S5 Comparison of meta-analytic results of associations between traffic-related air pollutants and diabetes prevalence and incidence from original analyses including studies up to July 2019 (squares) and the updated analysis (triangles) including studies up to May 2022. (Global. 2023)



The following increments were used: 10 µg/m³ for NO_2, 20 µg/m³ for NO_x, 1 µg/m³ for EC, 10 µg/m³ for PM_{10}, and 5 µg/m³ 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. No new studies were added from the update for the prevalence analysis with NO_2 and PM_{10}.

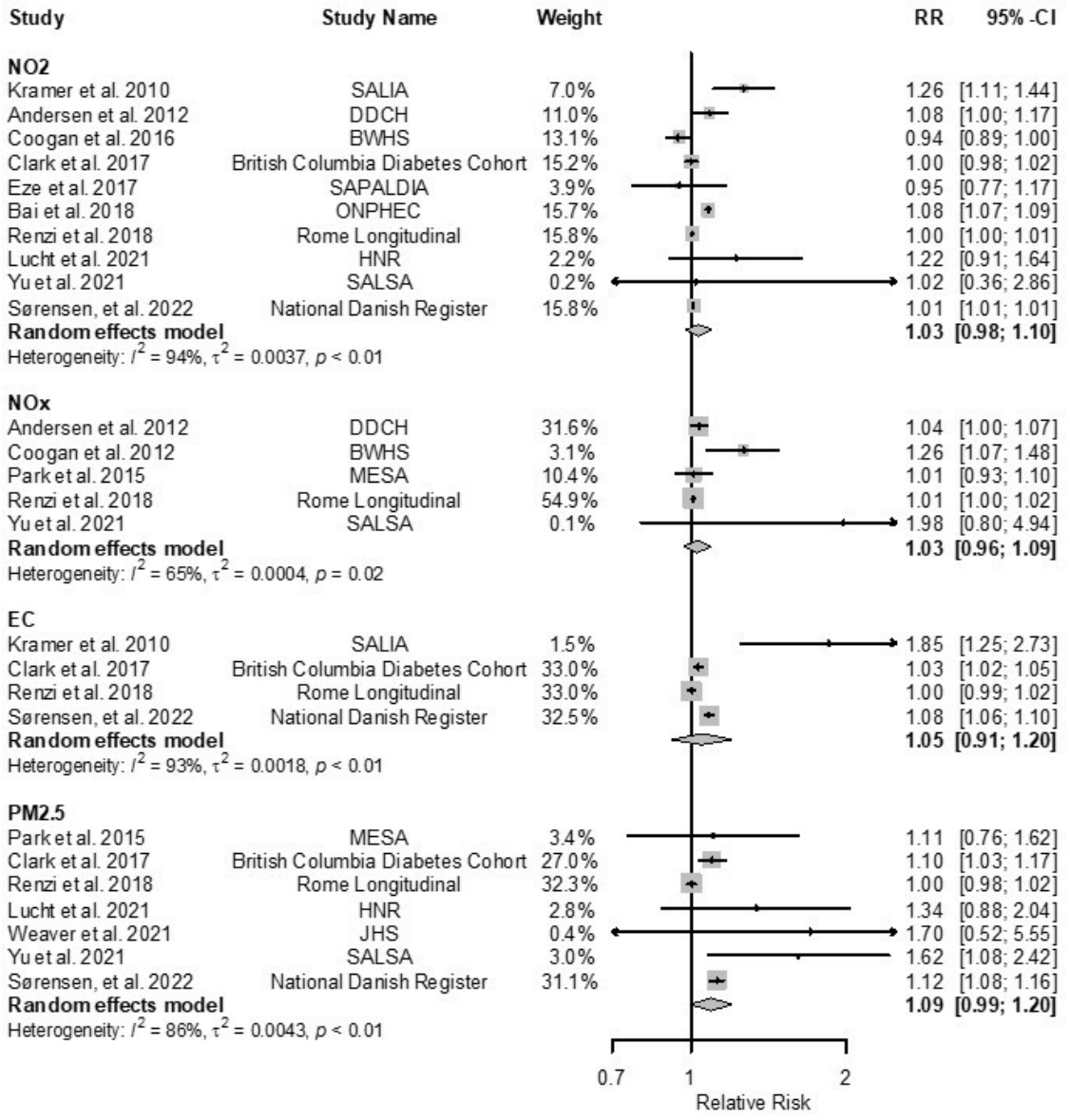
Figure S6 Forest plots of adjusted RRs (95%-CIs) for diabetes prevalence with NO_2, PM_{10} and $PM_{2.5}$ from the updated analysis including studies up to May 2022. (Global. 2023)



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 NOx, 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.

New study references Lucht [58], Yu [59], Sorensen [60], Weaver [61]

Figure S7 Forest plots of adjusted RRs (95%-CIs) for diabetes prevalence with NO_2, NO_x, EC, and $PM_{2.5}$ from the updated analysis including studies up to May 2022. (Global. 2023)



Note: only PM2.5 was updated

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 NOx, 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.

New study reference Suryadi [62], Weaver [61]

Table S9 Comparison of effect estimates with previously published reviews on diabetes prevalence and incidence with ambient air pollution.

Prevalence						
Authors	$PM_{2.5}$ per 10 µg/m^3	Number of studies	PM_{10} per 10 µg /m^3	Number of studies	NO_2 per 10 µg/m^3	Number of studies
HEI 2022 [63]	1.16 (0.49-2.79)* original: 1.08 (0.70-1.67)	3	1.19 (0.87-1.63)	4	**1.09 (1.02-1.17)**	7
Liu 2019 [64]	**1.09 (1.05-1.13)**	11	**1.12 (1.06-1.13)**	7	**1.05 (1.03-1.08)**	12
Yang 2020 [65]	**1.08 (1.04-1.12)**	11	**1.10 (1.03-1.17)**	6	**1.07 (1.04-1.11)**	11
Incidence						
Authors	$PM_{2.5}$ per 10 µg /m^3	Number of studies	PM_{10} per 10 µg /m^3	Number of studies	NO_2 per 10 µg/m^3	Number of studies
HEI 2022 [63]	1.10 (0.92-1.32)* original 1.05 (0.96-1.15)	4	-		1.04 (0.96-1.13)	7
Liu 2019 [64]	**1.10 (1.04-1.16)**	12	1.05 (0.98-1.13)	4	1.02 (0.99-1.05)	9
Yang 2020 [65]	**1.10 (1.04-1.17)**	11	**1.11 (1.00-1.22)**	**6**	1.01 (0.99-1.02)	7

* For the re-scale, we assumed a log-linear shape of the CRF, as recent AP-HRAs (e.g. Khomenko et al. [41]), applying Equation:

$RR_E = e^{\ln(RR_U)*\frac{C_E}{U}}$	**RR_U = Relative risk for a concentration D as in literature.** **U = Unit of concentration of the relative risk as in the literature (e.g. 10 in µg/m^3 PM).** **C_E = Desired increment of exposure**

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3. PAPER II LONG-TERM EXPOSURE TO TRAFFIC-RELATED AIR POLLUTION AND STROKE: A SYSTEMATIC REVIEW AND META-ANALYSIS

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

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ABSTRACT

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

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

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

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

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1. Introduction

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

Important risk factors for stroke morbidity and mortality include health states (e.g., high blood pressure, diabetes), behaviours that contribute to those states (e,g., smoking, features of the diet), and socioeconomic conditions that shape the former, and other factors influencing risk. Among these other factors are environmental pollutants. Air pollution, in particular, is of interest because of its adverse association

Abbreviations

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

with several cardiovascular outcomes (Franklin et al., 2015; Kaufman et al., 2020; Newman et al., 2020). Also, it is estimated that 6% of global mortality attributable to air pollution is traffic-related (McDuffie et al., 2021).

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

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

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

2. Methods

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

2.1. Search strategy

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

2.2. Eligibility criteria

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

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

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

2.3. Exposure framework

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

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

2.4. Study selection and data extraction

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

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

2.5. Meta-analysis

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

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

2.6. Overall assessment of the evidence

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

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

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

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

3. Results

3.1. Study selection

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

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

3.2. Study characteristics

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

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

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

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

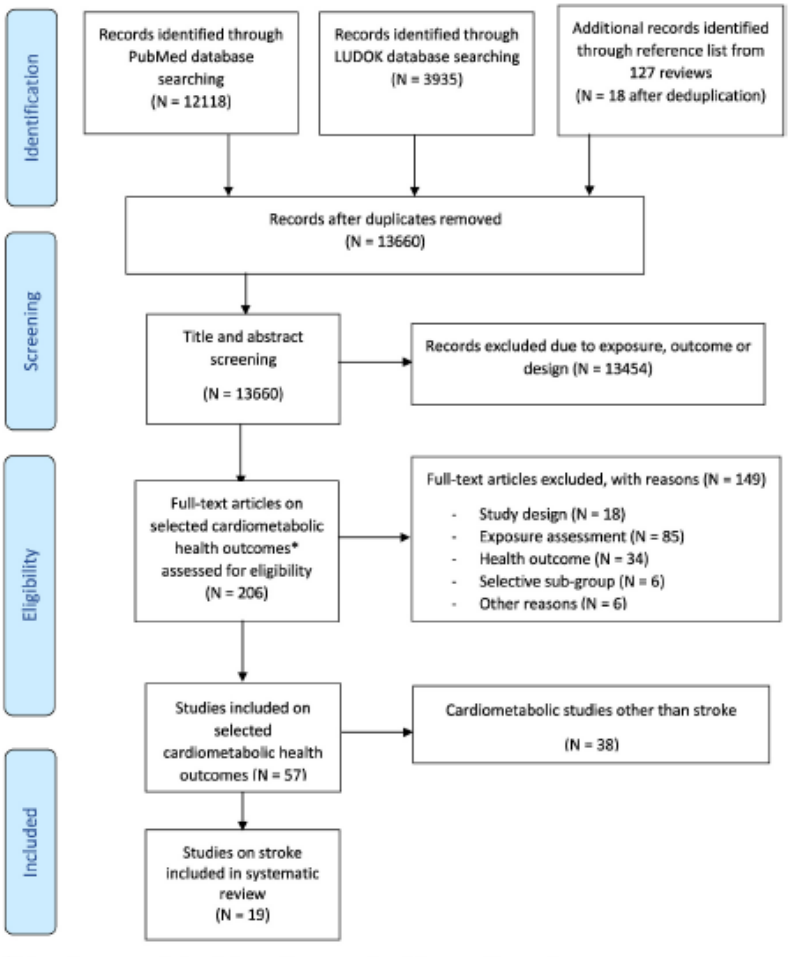

Fig. 1. Study Selection Flow Chart
*Selected outcomes: ischemic heart disease, stroke, diabetes mellitus and coronary events.

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

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

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Table 1 (*continued*)

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

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Table 1 (*continued*)

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

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Table 1 (*continued*)

Reference	Study Name	Location	Study period	Study design and Sample size	Exposure Assessment	Age at baseline	Sex	Stroke outcome ascertain-ment	Confounder adjustment	Results (estimate[a], 95% CI, increment)
				556912						NO_x 0.87 (0.73, 1.03) 30–60 vs. <10 μg/m³ NO_x 0.97 (0.90, 1.05) 10–20 vs. <10 μg/m³ NO_x 0.95 (0.86, 1.06) 20–30 vs. <10 μg/m³
Oudin et al., 2011	Scania Stroke	Scania, Sweden	2001–2006	Case-control 6302	Dispersion and CTM	Birth year: 1923–1965	Males and Females	Cases: hospital admissions from national stroke register	Sex, marital status, country of birth, smoking, co-morbidities[b], physical inactivity	**Non-fatal (prevalence) ischemic stroke (OR)** NO_x[c] 0.93 (0.82, 1.95) 10 μg/m³
Pindus et al., 2016	RHINE Tartu	Tartu, Estonia	2011–2012	Cross sectional 905	Dispersion and CTM	Mean age: 50	Males and Females	Self-reported	Gender, age, BMI, education, smoking, ETS	**Non-fatal (prevalence) all stroke (OR)** $PM_{10\ traffic}$ 1.21 (0.53, 2.77) per 2.2 μg/m³
Qin et al., 2015	33 CCHS	Shenyang and Anshan and Jinzhou, China	2009–2009	Cross sectional 14646: normal weight, 1435: obese, 8764: overweight	Surface monitoring	Age Range: 18-74	Males and Females	Self-reported	Age, sex, race, education, income, smoking, drinking, exercise, diet, sugar, family co-morbidities[b], study district	**Non-fatal (per weight category; prevalence) all stroke (OR)** NO_2 1.01 (0.84, 1.22) per 9 μg/m³ NO_2 1.15 (0.64, 2.07) per 9 μg/m³ NO_2 1.22 (0.98, 1.51) per 9 μg/m³
Sørensen et al., 2014	DDCH	Copenhagen and Aarhus, Denmark	1993–2009	Cohort 51569	Dispersion and CTM	Age Range: 50-64	Males and Females	National registries, medical records	Sex, length of school attendance, nSES, smoking, fruit/veg, alcohol, coffee, physical activity, BMI, calendar year, noise[d]	**Fatal and non-fatal all stroke (IRR)** NO_2[c] 1.08 (1.01, 1.16) per 10 μg/m³ NO_x[c] 1.02 (0.98, 1.07) per 20 μg/m³ **Fatal all stroke (IRR)** NO_2 1.47 (1.21, 1.80) per 10 μg/m³ NO_x 1.17 (1.05, 1.31) per 20 μg/m³
Stafoggia et al., 2014	ESCAPE	Multiple cities, Multiple countries	1992–2010	Cohort 99446	LUR and density measures	Mean Age range: 44–74	Males and Females	Self-reported, medical record, death certificates	Sex, calendar year, marital status, education, occupation, smoking, area level SES, noise[d]	**Fatal and non-fatal all stroke (HR)** $PM_{2.5\ abs}$[c] 1.08 (0.83, 1.41) per 1 1e-5/m NO_2[c] 0.99 (0.89, 1.11) per 10 μg/m³ NO_x[c] 0.98 (0.89, 1.07) per 20 μg/m³ $PM_{10\ mass}$[c] 1.11 (0.90,

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Table 1 (*continued*)

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

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

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

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

3.3. Meta-analyses and sensitivity analyses

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

3.4. NO_2

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

3.5. NO_x

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

3.6. EC

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

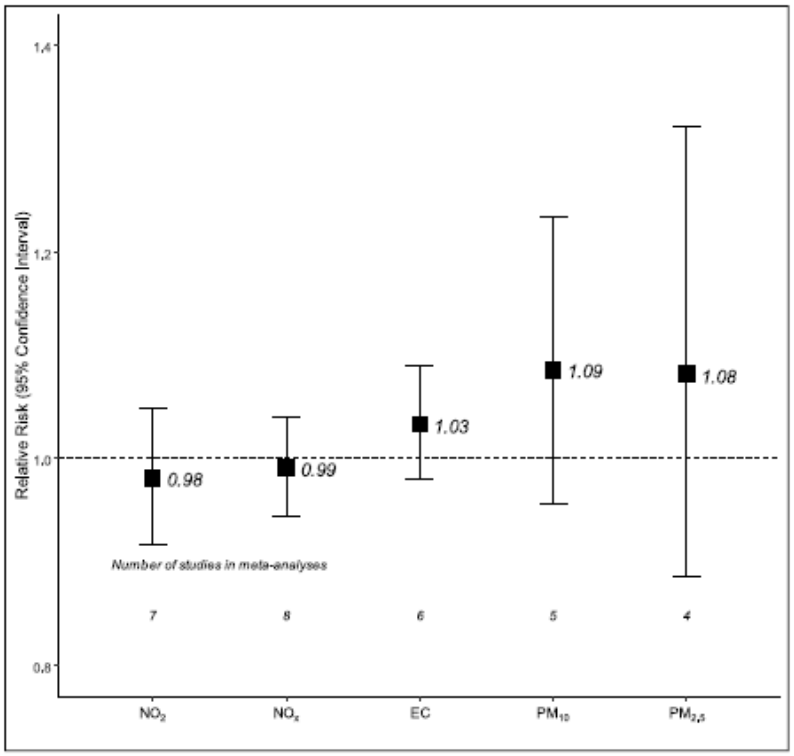

Fig. 2. Meta-analysis of associations between TRAP and incidence of stroke.

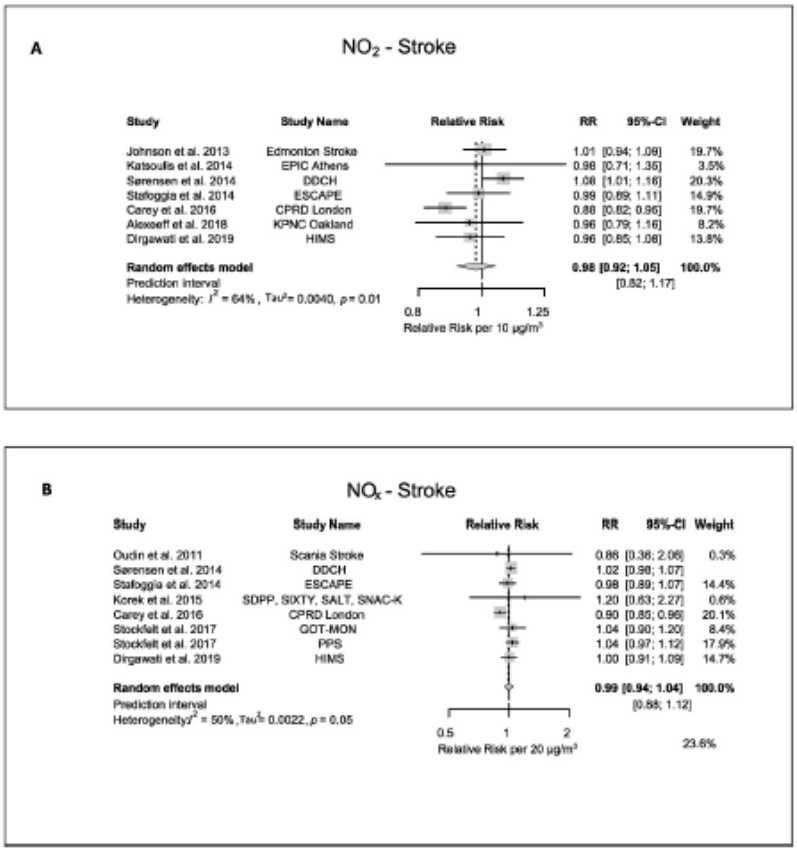

Fig. 3. Associations between gaseous traffic-related pollutants (NO_2 (A) and NO_x (B)) and incidence of stroke: Meta-analysis.

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

3.7. PM_{10}

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

3.8. $PM_{2.5}$

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

3.9. Results of studies not entering meta-analyses

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

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

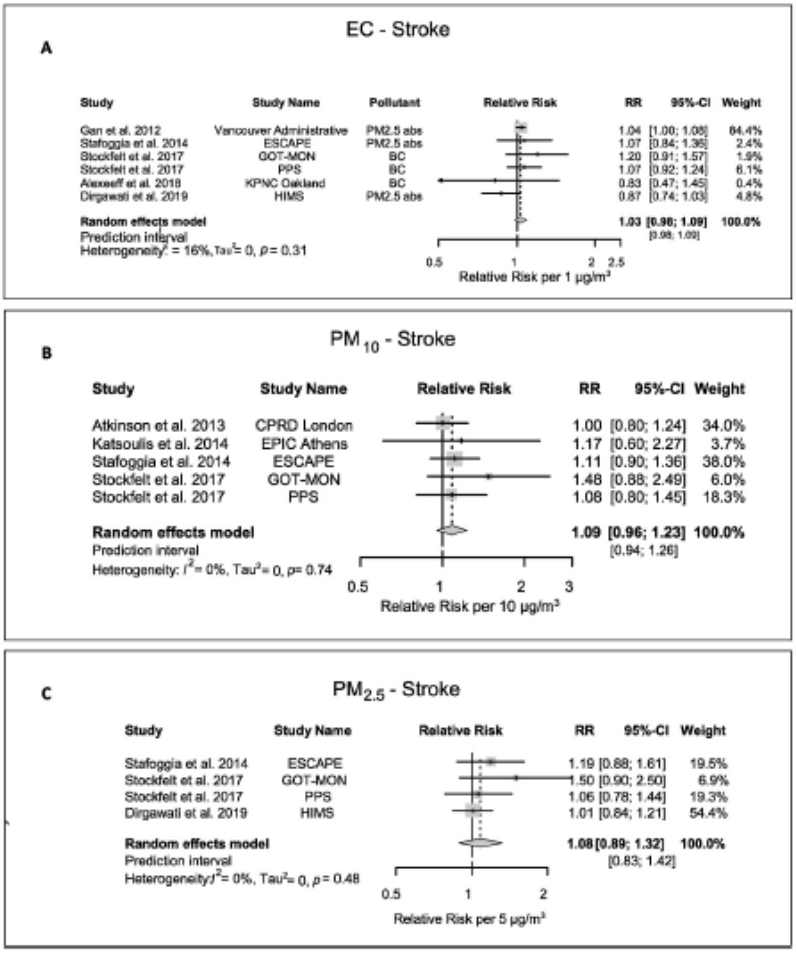

Fig. 4. Associations between particulate pollutants (EC (A), PM_{10} (B) and $PM_{2.5}$ (C)) and incidence of stroke: Meta-analysis.

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

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

3.10. Overall assessment

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

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

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

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

Table 2
Confidence rating for TRAP and stroke incidence.

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

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

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

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

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

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

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

4. Discussion

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

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

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

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

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

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

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

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

5. Conclusions

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

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

Reference	Study Name Location	Study period	Study design and sample size	Exposure Assessment	Age at baseline, sex	Stroke outcome ascertainment	Monotonic ER-function	Confounder adjustment	Results (estimate, 95% CI, increment)	Results (estimate, 95% CI, increment) Adjusted for road traffic noise
Magnoni et al. (2021)	Data collected by the Agency for Health Protection (ATS) Milan, Italy	2011–2018	Cohort 1,087,110	LUR model	Mean Age: 54, both	Medical record	No	Age, sex, citizenship, Italian Deprivation Index	**Fatal and non-fatal ischemic (HR)** NO_2 0.99 (0.96, 1.03) per 10 μg/m³ **Fatal and non-fatal heamorrahgic (HR)** NO_2 0.99 (0.92, 1.06) per 10 μg/m³	**Fatal and non-fatal ischemic (HR)** NO_2 0.98 (0.94, 1.02) per 10 μg/m³ **Fatal and non-fatal heamorrahgic (HR)** NO_2 0.96 (0.90, 1.04) per 10 μg/m³
Amini et al. (2020)	Danish Nurse Study Denmark, nationwide	1993–2014	Cohort 23, 423	Danish air pollution modeling system, called DEHM/UBM/AirGIS	Mean Age: 52.6, female	National patient registry	Yes	Age, year of entry, calendar year, income, degree of urnabanicity, physical activity, alcohol, smoking, marital status, fruit consumption	**Fatal and non-fatal (all stroke) (HR)** $PM_{2.5}$ 1.12 (1.05, 1.25) per 3.9 μg/m³ PM_{10} 1.05 (0.97, 1.13) per 3.3 μg/m³ NO_2 1.05 (0.97, 1.13) per 8.0 μg/m³ NO_x 1.02 (0.99, 1.06) per 11.0 μg/m³	**Fatal and non-fatal (all stroke) HR** $PM_{2.5}$ 1.13 (1.01, 1.25) per 3.9 μg/m³ PM_{10} 1.05 (0.97, 1.13) per 3.3 μg/m³ NO_2 1.05 (0.97, 1.15) per 8.0 μg/m³ NO_x 1.03 (0.99, 1.06) per 11.0 μg/m³
Andersson et al. (2020)	PPS Gothenburg, Sweden	1970–2011	Cohort 6304	High resolution dispersion model	Age range: 47–55; men	Hospital discharge register, Swedish national death register	No	Calendar year, marriage/cohabitation, SES, smoking, BMI, cholesterol, stress, heredity, diabetes, physical activity, age	**Fatal and non-fatal (all stroke) (HR)** NO_x 1.02 (0.97, 1.07) per 10 μg/m³ **Fatal and non-fatal (all stroke) (HR) categorized** NO_x 1.14 (0.93, 1.40) 36.1–44.1 versus <36.7 μg/m³ NO_x 1.05 (0.85, 1.3) 44.1–53.3 versus <36.7 μg/m³ NO_x 1.05 (0.85, 1.30) 53.3–64.8 versus <36.7 μg/m³ NO_x 1.25 (1.02, 1.54) >64.8 versus <36.7 μg/m³	**Results only for categories of exposure** NO_x 1.14 (0.93, 1.41) 36.1–44.1 versus <36.7 μg/m³ NO_x 1.06 (0.85, 1.31) 44.1–53.3 versus <36.7 μg/m³ NO_x 1.04 (0.83, 1.32) 53.3–64.8 versus <36.7 μg/m³ NO_x 1.20 (0.93, 1.56) >64.8 versus <36.7 μg/m³
Vivanco-Hidalgo et al. (2019)	Barcelona, Spain	2005–2014	Cross-sectional 2786	LUR model	Mean age: 75; both	BASICMAR database	no	Age, sex, smoking status, nSES, comorbidities[a]	**Severe Ishemic stroke (OR)** $PM_{2.5}$ Q2 1.01 (0.80, 1.26) $PM_{2.5}$ Q3 0. 93 (0.74, 1.17) $PM_{2.5}$ Q4 1.04 (0.83, 1.31)	**Severe Ishemic stroke (OR)** $PM_{2.5}$ Q2 0.97 (0.77, 1.21) $PM_{2.5}$ Q3 0.88 (0.70, 1.11) $PM_{2.5}$ Q4 0.95 (0.75, 1.20) **Adjusted for noise and green space**

(continued on next page)

Table 3 (*continued*)

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

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

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

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Declaration of competing interest

No author declares a conflict of interest.

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

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

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

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

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Appendix A. Supplementary data

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3.1 Paper II – Publication Appendix

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 analyzed, 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
NO_2, NO_x, 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
PM_{10}, PM_{coarse}, and $PM_{2.5}$	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 (PM_{abs}) 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

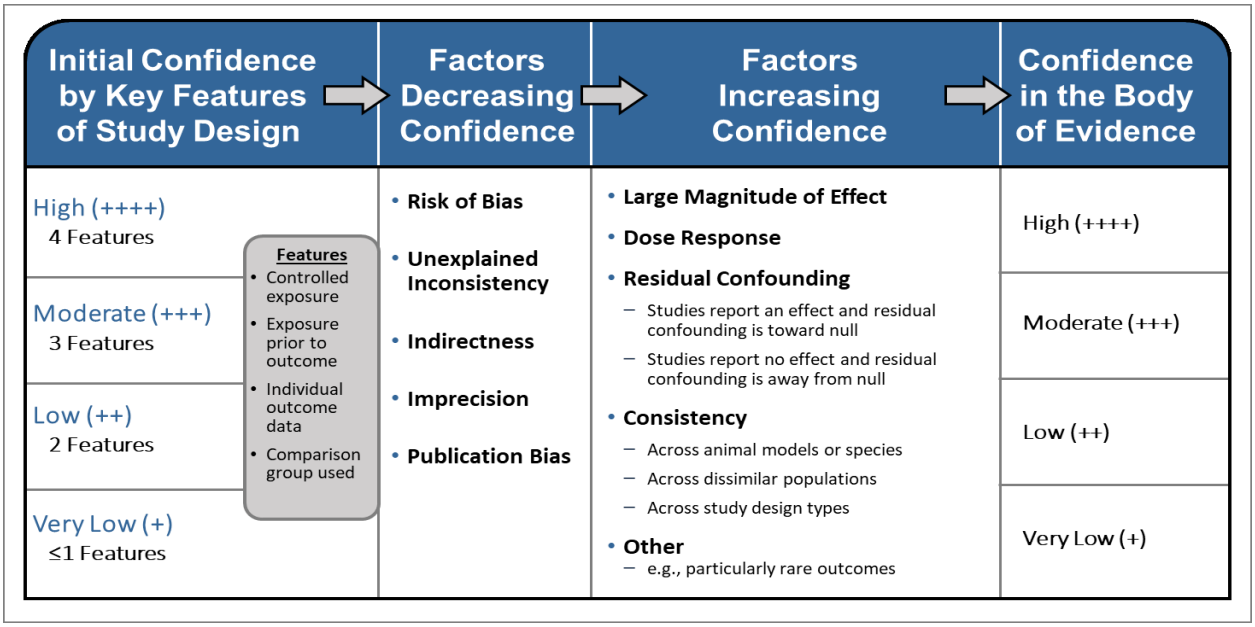
Exposure metric	Exposure assessment methods	Spatial resolution "pollution surface"	Spatial resolution address	Spatial resolution address for study identification	Traffic contribution to exposure and other considerations*
All pollutants from Supplementary Table 2	Dispersion / CTM models of traffic emissions 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 km^2, 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 km^2, determining whether exposures met long-term criteria)
All pollutants from Supplementary Table 2 except PM_{10}, PM_{coarse} and $PM_{2.5}$	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)
PM_{10}, PM_{coarse}, $PM_{2.5}$	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 metaanalytic 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.

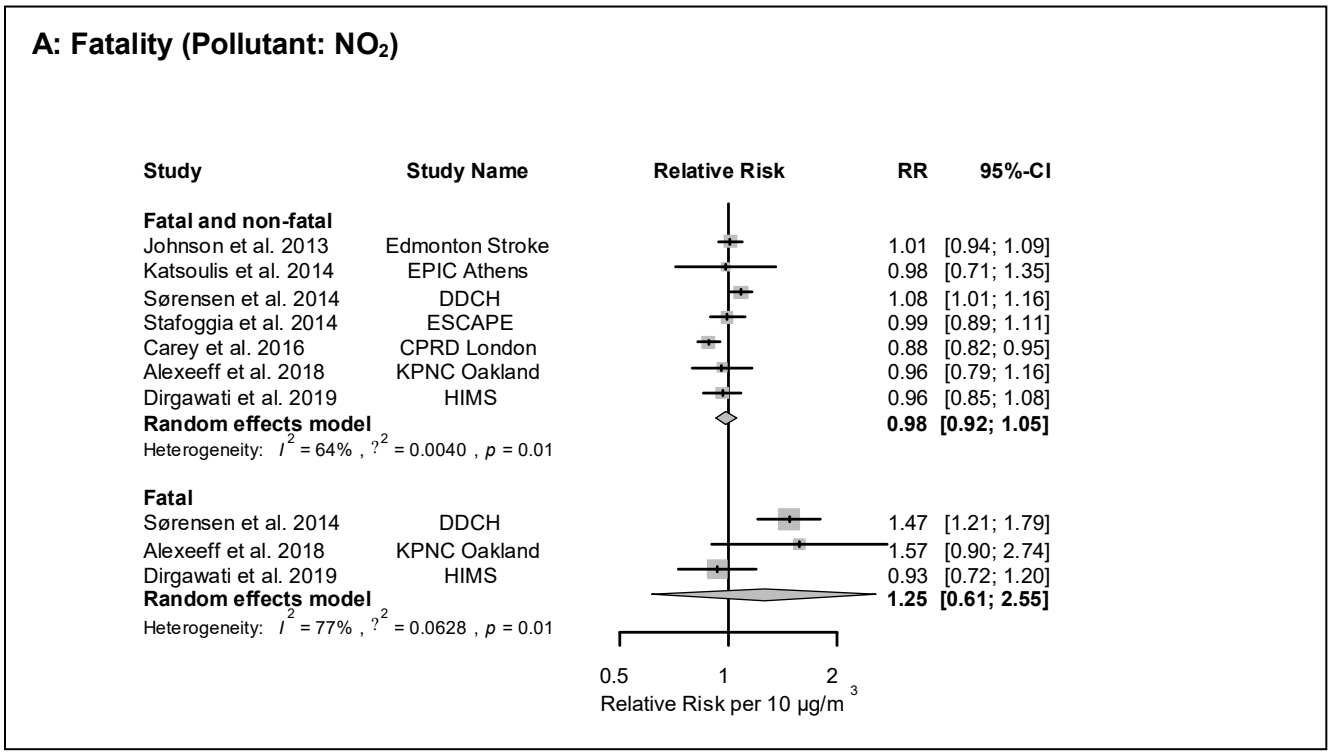
*The overall assessment of the association of each health outcome with long-term exposure to TRAP is a combination of the narrative assessment and the modified OHAT assessment. The descriptors are modified from OHAT (2019) and U.S. EPA (2015).

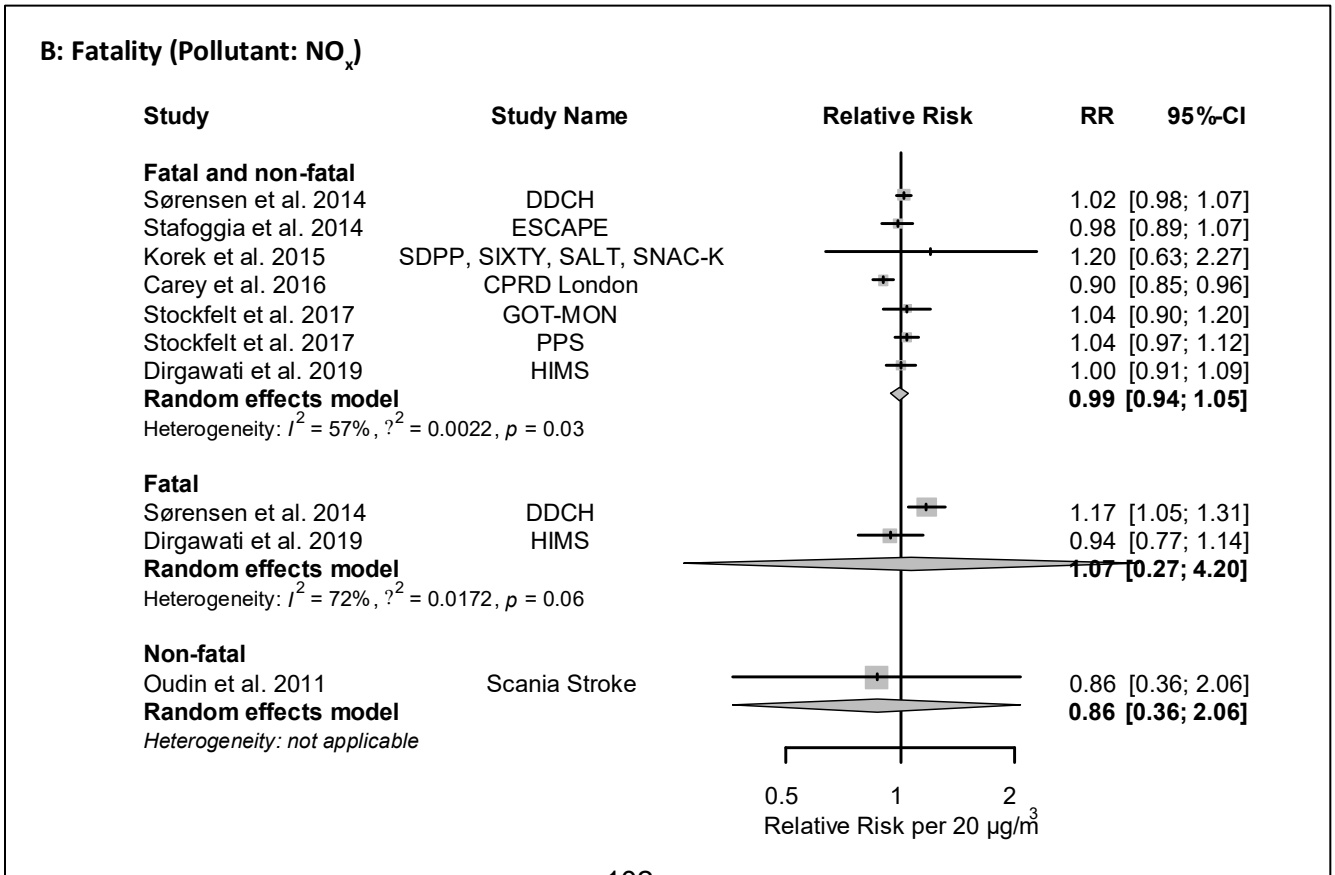
Supplementary Table 7 List of Excluded Citations with Justification

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)

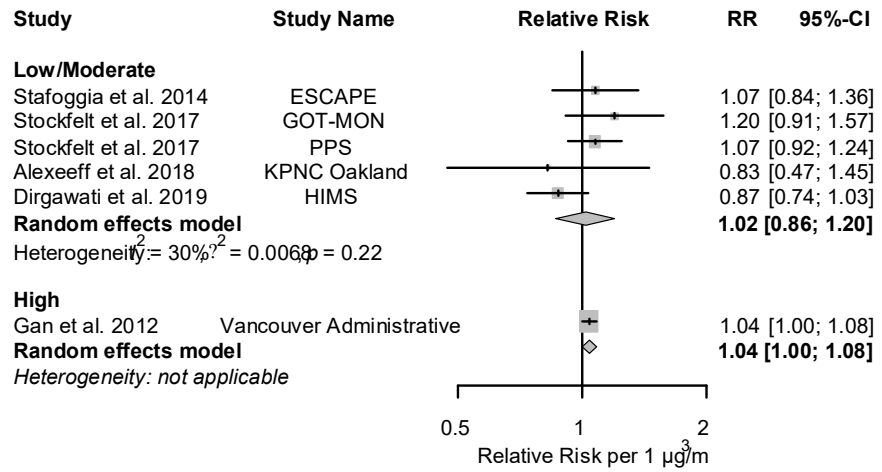
Title	Authors, Year	Reason behind exclusion
Particulate matter exposures, mortality, and cardiovascular disease in the health professionals follow-up study	Puett et al, 2011	Exposure assessment (main reason: nationwide study with no or insufficient area-specific adjustments)
Fine particulate matter exposure 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)

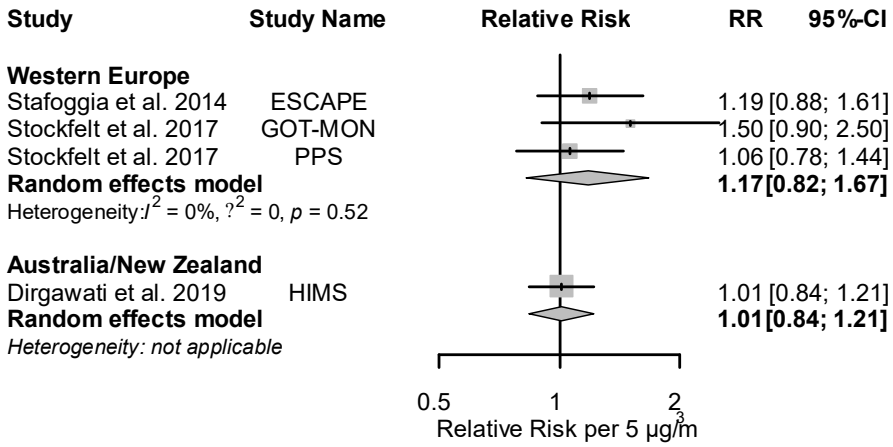


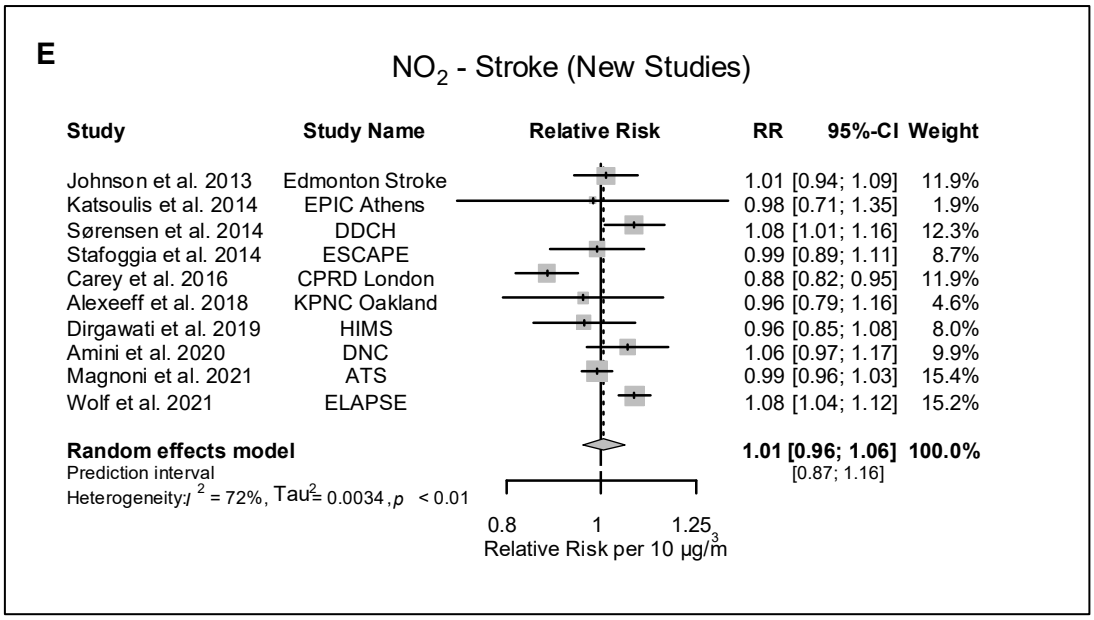


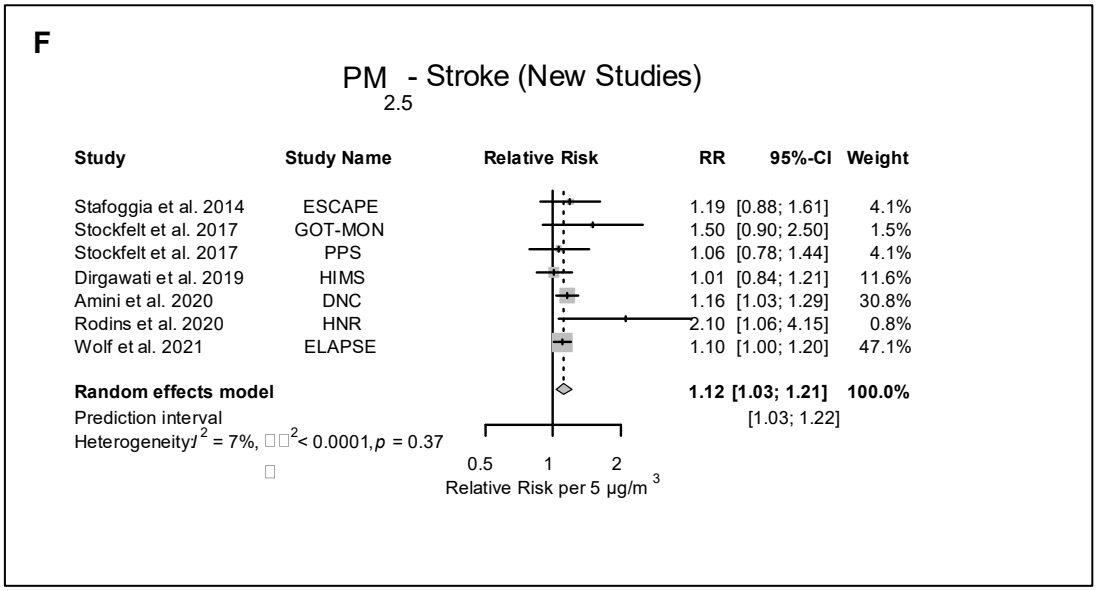
C: Risk of Bias (Pollutant: EC)



D: Region (Pollutant: $PM_{2.5}$)







A. Forest plot of the association between NO_2 and stroke by fatality, **B**. Forest plot of the association between NO_x 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 $PM_{2.5}$ and stroke by region, **E.** Forest plot of the association between $PM_{2.5}$ and stroke by the inclusion of the new studies from the updated search, **F.** Forest plot of the association between NO_2 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

4. PAPER III METHODS MATTER: A COMPARATIVE REVIEW OF HEALTH RISK ASSESSMENTS FOR AMBIENT AIR POLLUTION IN SWITZERLAND [REVIEW].

Castro, A., Röösli, M., de Hoogh, K., Kappeler, R., **Kutlar Joss, M**., Vienneau, D., & Künzli, N. (2022).

Methods Matter: A Comparative Review of Health Risk Assessments for Ambient Air Pollution in Switzerland [Review]. *Public Health Reviews, 43*. https://doi.org/10.3389/phrs.2022.1604431

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Methods Matter: A Comparative Review of Health Risk Assessments for Ambient Air Pollution in Switzerland

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Objectives: Air pollution health risk assessments (AP-HRAs) provide a method to quantify health effects for entire populations. In Switzerland, AP-HRAs are included in Swiss assessments for Transport Externalities (STEs), ordered by public authorities since the 1990s. This study aimed to describe the differences among national and international AP-HRAs for Switzerland.

Methods: We compared input data, approaches and results across AP-HRAs over time. Results and input data for each AP-HRA were expressed as a ratio compared to the most recent STE (in most cases STE-2010).

Results: Substantial variation across AP-HRAs was found. For all-cause adult mortality attributed to particulate matter (the most frequent outcome-pollutant pair), the ratio in HRAs oscillated from 0.40 to 2.09 (times the STE-2010 value). Regarding input data, the ratio ranged from 0.69 to 1.26 for population exposure, from 0 to 1.81 for counterfactual scenario, from 0.96 to 1.13 for concentration-response function and from 1.03 to 1.13 for baseline health data.

Conclusion: This study demonstrates that methods matter for AP-HRAs. Transparent and possibly standardized reporting of key input data and assumptions should be promoted to facilitate comparison of AP-HRAs.

Keywords: Switzerland, air pollution, burden of disease, particulate matter, health risk assessment, health impact assessment, mortality

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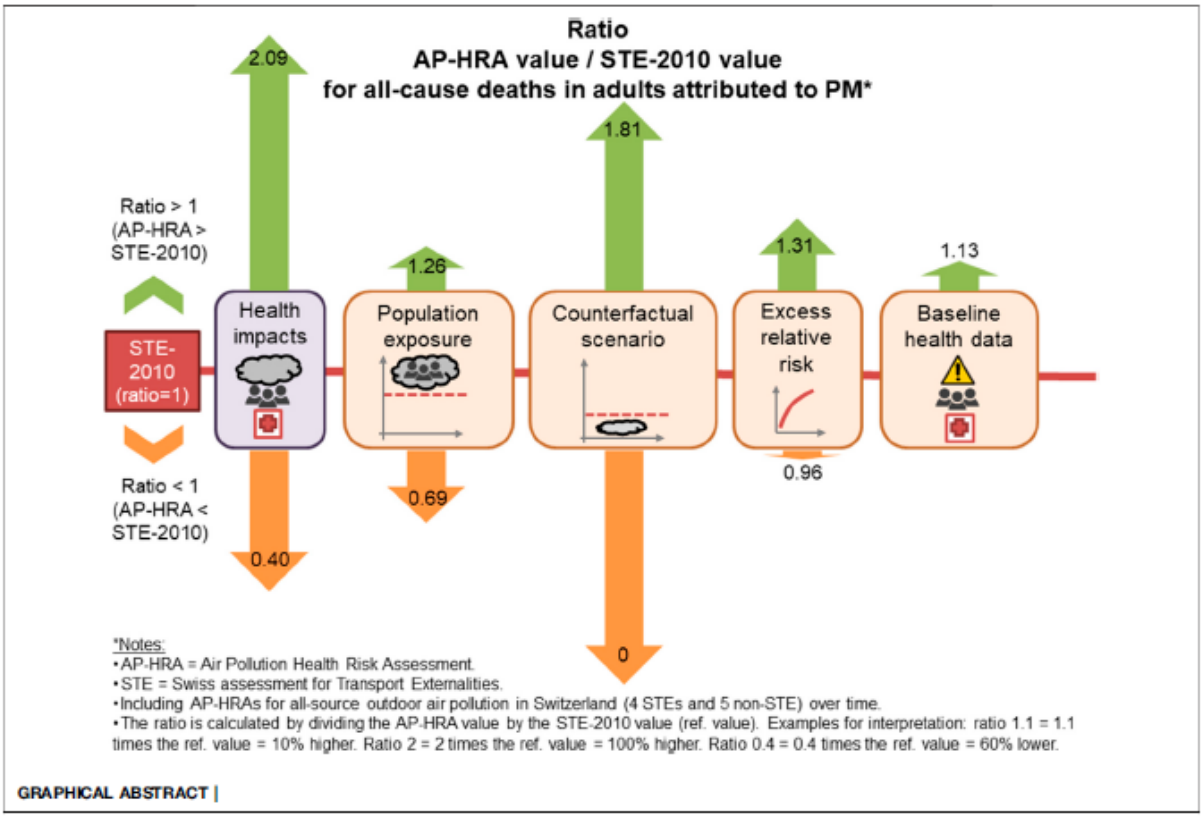
INTRODUCTION

Ambient (outdoor) air pollution causes health effects both in the short- and the long-term, as summarized in many reviews [1]. These health impacts in an entire population can be estimated using a health risk assessment (HRA), which has been defined as "the scientific evaluation of potential adverse health effects resulting from human exposure to a particular hazard" [2]. The concept of health impact assessment is different involving "a combination of procedures, methods and tools" and focusing on a specific "policy, program or project" [3, 5], but the term has also been used interchangeably to refer to HRAs [1]. Particulate matter (PM) up to 2.5 or 10 μm in diameter



GRAPHICAL ABSTRACT |

($PM_{2.5}$ or PM_{10}, respectively), ozone (O_3) and nitrogen dioxide (NO_2) are examples of harmful pollutants included in air pollution HRAs (AP-HRAs) [6].

The Swiss government was the first in the world to call for comprehensive assessment studies of environmental effects of heavy duty traffic to integrate the external costs of road transport into the road pricing policy [7], and thus at the interface between health impact assessment and HRA. These studies are abbreviated as STE (Swiss assessment for Transport Externalities). Given first findings of the Swiss SAPALDIA study on health effects of ambient air pollution [8], the Swiss government asked for the inclusion of traffic-related air pollution into STEs. Updates of the STEs were then carried out regularly. This initiative triggered the development of methods to derive the impact of short- and long-term ambient air pollution [9] and to estimate the health burden of traffic related air pollution in Switzerland [10]. Based on a further initiative of the Swiss Government, the first multi-country AP-HRA was conducted in collaboration with France and Austria [11]. This contributed to the inclusion of ambient air pollution into the GBD [12] and later to the development of international methodological standards for AP-HRAs through the project "Health Risks of Air Pollution in Europe" (HRAPIE) [13]. Further updates of the STEs were carried out for 2000 [14], 2005 [15], 2010 [16], 2015 [17] and 2017 [18] and 2018 [19]. In parallel to these Swiss national initiatives, a range of international AP-HRA studies, e.g., the Global Burden of Disease (GBD) [4, 20–22], have included specific estimations of health impacts attributed to air pollution in Switzerland.

Although AP-HRAs usually get high media attention, the ongoing development of AP-HRA methods are rarely addressed and comparison across AP-HRAs are scarce. The work of Malmqvist, Oudin [23] and Evangelopoulos, Perez-Velasco [24] are recent exceptions. As shown in these reviews, methodological approaches for quantifying health impacts and their input data may vary among AP-HRAs and strongly determine their results. The most relevant input data are the following: the population exposure; the counterfactual scenario (i.e., the minimum concentration considered in the AP-HRA to derive the overall impact); the concentration-response function (CRF, usually derived from a meta-analyses of epidemiological studies); and the baseline health data (i.e., prevalence or incidence of the disease data among the population at risk).

The ever-growing number of AP-HRAs for Switzerland proposing different health estimates poses a communication challenge for public authorities. Thus, this paper had as overall goal to identify differences between AP-HRAs of STEs and other AP-HRAs with specific results for Switzerland as well as the reasons behind these differences. To achieve this goal, the following two objectives were pursued: 1) to scrutinize all

TABLE 1 | Main features of the selected air pollution health risk assessments (Switzerland 2021).

Short name of the AP-HRA study	Year of analysis[a]	Swiss Area[b]	Types of outcomes	Pollutants[c]	Goal	Source
Studies designed for Switzerland						
STE	1993, 1996, 2000, 2005, 2010	National	• Mortality • Morbidity	PM_{10}	External cost of transport in Switzerland	STE reports for 1993 [7], 1996 [11, 47], 2000 [14], 2005 [15] and 2010 [16]
FCAH	2010	National	• Mortality	PM_{10}	Comparison of epidemiological and toxicological approaches	Study ordered by the Swiss Federal Commission for Air Hygiene (FCAH) [26]
International studies including results for Switzerland						
GBD	1990–2019	National	• Mortality • Morbidity • Mixed	$PM_{2.5}$, O_3	Burden of Disease calculation at global level (including air pollution among other risks)	Assessment of the GBD project in 2019, which includes multiple risk factors (being ambient particulate matter and ozone two of them). The results are stratified by risk factor, country, sex, disease and age. Data can be filtered and downloaded from an online tool [48]. The concentration and CRF data as well as the scientific paper explaining the methodology are published separately [4, 49, 50]
EEA	2009, 2011–2018	National	• Mortality	$PM_{2.5}$, O_3, NO_2 (in 2011 $PM_{2.5}$, O_3	Health impacts of air pollution in Europe	European Air Quality Reports of EEA [51-59]. The detailed description of the EEA methodology was published elsewhere [30, 59]
WHO	2012, 2016	National	• Mortality • Mixed	$PM_{2.5}$	Worldwide burden of disease calculation for ambient air pollution	WHO report for 2012, showing specific results by country [31]. An update for 2016 was available as online database [60]. The counterfactual scenario of WHO-2016 was published elsewhere [24]
CITIES	2015	10 largest cities	• Mortality	$PM_{2.5}$, NO_2	Health impacts of air pollution in European urban areas	AP-HRA ordered by the Spanish Ministry of Science and Innovation, which covers 1,000 urban areas in Europe for 2015 [39]

Abbreviations: AP-HRA, air pollution health risk assessment; STE, Swiss assessment for transport externalities; EEA, European Environment Agency; FCAH, Federal Commission for Air Hygiene; GBD, Global Burden of Disease; WHO, World Health Organization. CITIES = HIA for air pollution in around 1000 European urban areas. The short name was given by the authors of this paper.

[a]Single assessment for each year of analysis, except for GBD, which assessed in 2019 the whole time series 1990–2019, and EEA, which included the assessment of both 2009 and 2018 in the same report from 2020.

[b]CITIES covers the greater cities of Zurich, Geneva, Basel, Bern, Lausanne, Luzern and Lugano as well as the cities of Winterthur, St. Gallen and Biel/Bienne.

[c]Health impacts of NO_2 were estimated in STE-1993, but it was not shown in the final results (but in some kind of Appendix).

national and international AP-HRAs assessing health impacts of ambient air pollution for Switzerland, and 2) to compare them with the most recent STE in terms of assessed health impacts and their input data (namely the population exposure, counterfactual scenario, CRF and baseline health data).

METHODS

Out of all published STEs, we selected only those assessing health impacts for ambient air pollution from all sources, i.e., not exclusively for transport related air pollution. Exceptionally, we selected STE-1993, which only showed transport-related health impacts, because it stated that the transport-related exposure represented on average 40% of the total exposure. Therefore, we converted the transport-related health impacts into all source impacts by dividing by 0.4. This conversion implicitly assumed a zero counterfactual scenario to express the share of the total burden attributable to transport alone.

To find further AP-HRAs beyond the governmental STEs, we carried out a literature search with specific search terms using Google Search to capture not only scientific but also grey literature. These additional AP-HRAs had to meet the following inclusion criteria:

- Assessment of health impact from ambient air pollution from all sources of air pollution including burden of disease studies targeted to air pollution such as GBD
- Separate results for each pollutant and for each (present or past) year
- Specific results for Switzerland including the whole population or a large well defined subset of the country
- Original assessment (i.e., not only re-using results of other AP-HRAs)
- Most updated version, in case of multiple published AP-HRAs with the same authors, for the same region and with overlapping years of analysis.

TABLE 2 | Overview of absolute annual health impacts attributed to exposure to air pollution in Switzerland by pollutant (Switzerland 2021).

Mortality vs. Morbidity	Type of impact	Outcome disease	Population group[a]	Absolute number of cases per year[b]	AP-HRA—year of analysis[c]
PM_{10}/$PM_{2.5}$					
Mortality	Premature deaths	All causes	Adults	2,827	STE-2010
			Infants	13	STE-2010
			Workers	335	STE-2010
		Lung cancer	Adults	311	STE-2000
	Working YLLs	All causes	Adults	2,767	STE-2010
			Infants	346	STE-2010
	YLLs	All causes	Adults	28,138	STE-2010
			Infants	753	STE-2010
Morbidity	Attacks	Asthma	Adults	3,500,000	STE-1993
			Children	44,943	STE-2010
	Attacks (person-days)	Asthma	Adults	107,545	STE-2010
	Cases (incidence)	Acute bronchitis	Children	77,500	STE-1993
		Chronic bronchitis	Adults	3,078	STE-2010
	Cases (prevalence)	Acute bronchitis	Children	17,302	STE-2010
		Chronic bronchitis	Adults	55,000	STE-1993
	Hospital admissions	CVD	All	1,138	STE-2010
		RD	All	1,131	STE-2010
	Hospital days	CVD	All	10,940	STE-2010
		RD	All	9,420	STE-2010
	Invalidity cases	Chronic bronchitis	Adults	25	STE-1993
	Medication intake (person-days)	Asthma	Adults	3,750,000	STE-1993
	RADs	All causes	Adults	4,746,089	STE-2010
	Symptom days	RD	All	20,000,000	STE-1993
			Children	60,000	STE-1993
	Work loss days	All causes	Workers	1,138,140	STE-2010
	YLDs	All causes	All	7,196	GBD-2019
Mixed	DALYs	All causes	All	28,207	GBD-2019
O_3					
Mortality	Premature deaths	All causes	All	247	GBD-2019
	YLLs	All causes	All	3,255	GBD-2019
Mixed	DALYs	All causes	All	3,255	GBD-2019
NO_2					
Mortality	Premature deaths	All causes	Adults	270	EEA-2018
	YLLs	All causes	Adults	2,827	EEA-2018

Abbreviations: YLLs, years of life lost; DALYs, disability-adjusted life years; RADs, restricted activity person-days; YLDs, years lived with disability.
[a]Age ranges of the population groups differ across AP-HRAs. This table shows only aggregated GBD results, which are additionally available by age range, gender and disease.
[b]Some of the AP-HRAs provide 95% confidence intervals with a lower bound up to 70% lower and upper bounds up to 70% higher than the point estimates presented in this table.
[c]We estimated the health impacts of STE-1993 by dividing the transport-related impacts by 0.4 because STE-1993 only assessed transport externalities and pointed out that 40% of the total air pollution exposure account for transport.

Supplementary Material S1 reports information about the literature excluded from this comparison because of not meeting the inclusion criteria, the specific search terms, and the PRISMA flow chart.

Among the selected AP-HRAs, we compiled health impact estimates for all available years as well as the input data including population exposure, counterfactual scenarios, CRFs and baseline health data. For an overview of the most recent health impact estimations for Switzerland, we prioritized most recent STEs over other AP-HRAs; and if no STE was available, we used the most recent AP-HRAs. For the comparison between STEs and HRAs, we focused on the pollutant with the highest health impacts and selected the first and last year in case of AP-HRAs with time series (i.e., multiple years). We only considered health outcomes assessed by at least two AP-HRAs, being one of them a STE. To analyze the variability of health impacts and input data the following steps were applied. First, the AP-HRA results were normalized by calculating the impact per 100,000 persons (all ages) to remove the effect of population growth. $PM_{2.5}$ data were converted into PM_{10} with the assumption that $PM_{2.5}$ accounts for 73.5% of PM_{10} [26]. Next, we calculated the ratio of the AP-HRA value (numerator) to the reference STE (denominator) to quantify the heterogeneity. Thus, a ratio >1 indicates an AP-HRA with a larger value than the most recent STE and a ratio <1 a lower value. The ratios were used for comparisons across AP-HRAs and across input data (the latter building ranges defined by the minimum and maximal ratio).

We performed the data analysis and visualization in R 4.0.3 [27] using the package tidyverse 1.3.0 [28].

Further details on the methods of this paper, including population data for the normalization, equations for re-scaling

TABLE 3 | Annual mortality impacts attributed to particulate matter across air pollution health risk assessments, years and counterfactual scenarios expressed as per 100,000 inhabitants (all ages) and ratio in relation to the reference value, i.e., the most recent Swiss assessment for Transport Externalities. The ratio was calculated by dividing the value of the health risk assessment by the reference value (Switzerland 2021).

Type of Impact	Outcome disease	population Group[a]	STE 1993[b]	STE 1996	STE 2000	STE 2005	STE 2010	EEA 2009	EEA 2018	FCAH 2010 Low[c]	FCAH 2010 High[c]	GBD 1990	GBD 2019	WHO 2012	WHO 2016	CITIES 2015 Low[c]	CITIES 2015 High[c]
Mortality per 100,000 all-age persons																	
Premature deaths	All causes	Adults	76	47	52		**36**	64	41			53	16	19	26	44	14
		Infants			0.3		**0.2**					0.3	0.1	0.0			
	Lung cancer	Adults			**4**					5	3	7	3	5	3		
Working YLLs	All causes	Adults			74		**36**										
YLLs	All causes	Adults			569	624	**361**	721	459			922	237	327	379	540	177
		Infants			24	26	**10**					23	9	0.4	26		
Ratio in relation to reference value (last STE)[d]																	
Premature deaths	All causes	Adults	2.09	1.29	1.44		**1**	1.75	1.14			1.46	0.44	0.51	0.70	1.20	0.40
		Infants			1.50		**1**					1.50	0.50	0.00			
	Lung cancer	Adults			**1**					1.07	0.77	1.65	0.65	1.19	0.58		
Working YLLs	All causes	Adults			2.07		**1**										
YLLs	All causes	Adults			1.57	1.73	**1**	1.99	1.27			2.55	0.65	0.90	1.05	1.49	0.49
		Infants			2.44	2.68	**1**					2.35	0.90	0.04			

Abbreviations: YLLs, years of life lost. Bold values represent the reference values.

[a]Age ranges of the population groups differ across AP-HRAs.

[b]We estimated the health impacts of STE-1993 by dividing the transport-related impacts by 0.4 because STE-1993 only assessed transport externalities and pointed out that 40% of the total air pollution exposure account for transport.

[c]FCAH and CITIES, include two assessments—respectively called high and low–because they each use a lower and a higher counterfactual scenario.

[d]Examples for interpretation of the ratio: 1.1 = 1.1 times the ref. value = 10% higher. 2.0 = 2 times the ref. value = 100% higher. 0.4 = 0.4 times the ref. value = 60% lower.

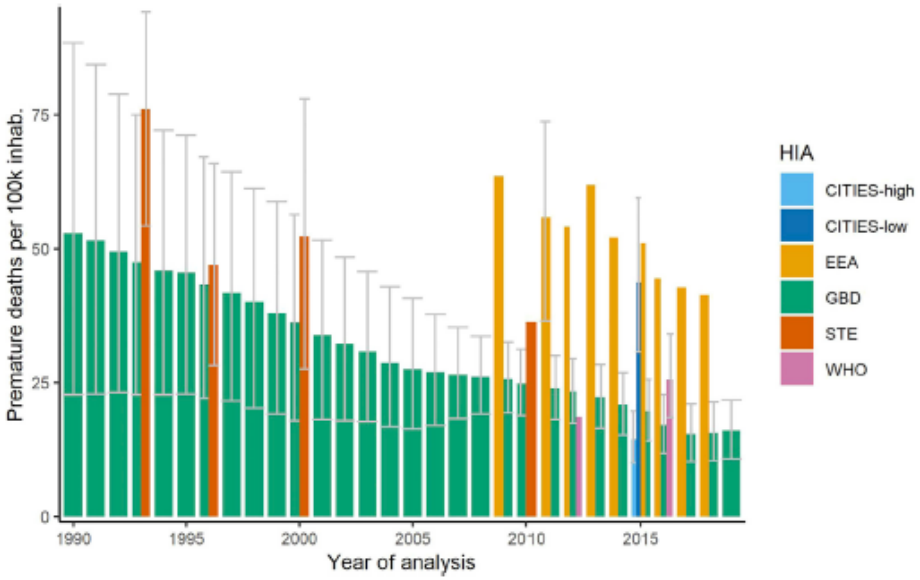


FIGURE 1 | Annual premature deaths per 100,000 persons in adults attributed to particulate matter with 95% confidence interval (if available) (Switzerland 2021).

TABLE 4 | Annual mean population exposure, counterfactual scenario and difference between both for particulate matter up to 10 µm in diameter across air pollution health risk assessments, years and counterfactual scenarios expressed as a concentration in µg/m^3 and as a ratio in relation to the reference value, i.e., the most recent Swiss assessment for Transport Externalities. The ratio was calculated by dividing the value of the health risk assessment by the reference value (Switzerland 2021).

Type of Concentration	STE 1993	STE 1996	STE 2000	STE 2005	STE 2010	EEA 2009	EEA 2018	FCAH 2010 Low[a]	FCAH 2010 High[a]	GBD 1990	GBD 2019	WHO 2012	WHO 2016	CITIES 2015 Low[a]	CITIES 2015 High[a]
Population-weighted annual mean in µg/m^3 PM_{10}															
Exposure	20.9	21.4	19.1	19.7	**19.4**	19.9	13.3	18	18	24.5	13.5		13.9	17.7	17.7
Counterfactual		7.5	7.5	7.5	**7.5**	0	0	3.3	7.5	5.6	5.6	9.9	5.6	5.0	13.6
Difference		13.9	11.6	12.2	**11.9**	19.9	13.3	14.7	10.5	18.8	7.8		8.2	12.7	4.1
Ratio in relation to reference value (last STE) [b]															
Exposure	1.08	1.10	0.98	1.02	**1**	1.03	0.69	0.93	0.93	1.26	0.70		0.72	0.91	0.91
Counterfactual		1.00	1.00	1.00	**1**	0	0	0.44	1.00	0.75	0.75	1.32	0.75	0.67	1.81
Difference		1.17	0.97	1.03	**1**	1.67	1.12	1.24	0.88	1.58	0.66		0.69	1.07	0.34

Notes: The PM concentrations were originally expressed as $PM_{2.5}$ instead of as PM_{10} in EEA, GBD and WHO. We re-scaled these concentrations to enable comparability across AP-HRAs. The original values are available in the ***Supplementary Material****. STE-1993 had no counterfactual scenario because it quantified the impact of transport related emissions. Bold values represent the reference values.*

[a]FCAH and CITIES, include two assessments—respectively called high and low–because they each use a lower and a higher counterfactual scenario.

[b]Examples for interpretation of the ratio: 1.1 = 1.1 times the ref. value = 10% higher. 2.0 = 2 times the ref. value = 100% higher. 0.4 = 0.4 times the ref. value = 60% lower.

as well as data preparation and assumptions for collected data, are available in the **Supplementary Material S1**.

RESULTS

Health Impacts

Table 1 presents the AP-HRAs that we selected for the comparison. **Table 2** shows an overview of the most recent health impacts attributed to PM (which refers to $PM_{2.5}$ and/or PM_{10}), O_3 and NO_2 in Switzerland from the STEs or, if not available, from other AP-HRAs. STE-2010 covered the majority of health endpoints ever assessed by STEs. STEs exclusively considered PM in the assessment, while some of the other AP-HRAs included O_3 and/or NO_2. All-cause mortality attributed to O_3 and NO_2 exposure was much lower than to PM in Switzerland. For instance the number of all-cause premature deaths in adults attributed to PM was 2,587 according to STE-2010, while it was 247 for all ages for O_3 according to GBD-2019, and 270 for NO_2 according to EEA-2018. We confirmed the large differences among pollutants in an additional analysis by analyzing all AP-HRAs covering multiple pollutants in the most recent

TABLE 5 | Mean excess relative risk of mortality impacts expressed as per 10 µg/m^3 particulate matter up to 10 µm in diameter, baseline health data across health impact assessments and years expressed as per 100,000 inhabitants (all ages) and as a ratio in relation to the reference value, i.e., the most recent Swiss assessment for Transport Externalities. The ratio was calculated by dividing the value of the health risk assessment by the reference value (Switzerland 2021).

Input Data	Outcome disease for mortality	Population group[a]	STE 1993	STE 1996	STE 2000	STE 2010	EEA 2009–2018	FCAH 2010	GBD 1990–2019	WHO 2012–2016	CITIES 2015
Concentration-response function expressed as excess relative risk						Mean per 10 µg/m^3 PM_{10}					
	All causes	Adults	0.044	0.043	0.059	**0.045**	0.045		Seven causes	Five causes	0.051
		Infants			0.056	**0.040**					
	Lung cancer	Adults			**0.106**			0.060	0.112		
						Ratio in relation to reference value (last STE)[b]					
	All causes	Adults	0.98	0.96	1.31	**1**	1				1.13
		Infants			1.40	**1**					
	Lung cancer	Adults			**1**			0.57	1.06		
Baseline health data						Value per 100,000 all-age persons					
	All causes	Adults	799	828	809	**735**	Not provided		Not provided	Not provided	759
		Infants			5	**4**					
	Lung cancer	Adults			**39**			55			
						Ratio in relation to reference value (last STE)[b]					
	All causes	Adults	1.09	1.13	1.10	**1**					1.03
		Infants			1.29	**1**					
	Lung cancer	Adults			**1**			1.40			

Note: STE-2005 used the CRFs of 2000 and did not provided baseline health data. Bold values represent the reference values.

[a]*Age ranges of the population groups differ across AP-HRAs.*

[b]*Examples for interpretation of the ratio: 1.1 = 1.1 times the ref. value = 10% higher. 2.0 = 2 times the ref. value = 100% higher. 0.4 = 0.4 times the ref. value = 60% lower.*

overlapping year (2015) and by normalizing by population (see **Supplementary Material S2**). Since STEs exclusively assessed health impacts attributed to PM and the health impacts attributed to O_3 and NO_2 were considerably lower, further comparisons of this paper focus on PM only.

As shown in **Table 3**, all population-normalized mortality impacts were lower in STE-2010 than in previous STEs, EEA-2019 and EEA-2009. In contrast, the STE-2010 values were higher than in GBD-2019, WHO-2012 and WHO-2016. Two AP-HRAs, the FCAH and CITIES, include two assessments because they each used two counterfactual scenarios, respectively called high and low. Premature deaths and YLLs, both in adults, were the most assessed health impact across AP-HRAs. The number of premature deaths in adults per 100,000 inhabitants differed from the STE-2010 by a factor of 0.4–2.09, while for YLLs in adults per 100,000 inhabitants this ratio varied from 0.49 to 2.55.

Figure 1 shows that, as assumed, the first and last year of time series captured the whole heterogeneity of the population-normalized premature deaths in adults over time, when considering the entire GBD and EEA time series (see values in **Supplementary Material S2**). Only the GBD values for 2017 and 2018 were slightly lower than the value for 2019 (the last year of the time series). Furthermore, population-normalized premature deaths were considerably higher for EEA than for GBD in overlapping years. Regarding YLLs, the differences between EEA and GBD were smaller (see **Supplementary Material S2**).

The morbidity outcomes of STEs were not assessed in other AP-HRAs, which focus on indicators such as Years Lived with Disabilities (YLDs) and Disability-Adjusted Life Years (DALYs). Comparisons of health impacts, CRFs and baseline health data for morbidity across STEs are available in the **Supplementary Material S2**.

Population Exposure

Population exposure refers to the (measured or modeled) air pollution concentration that is assumed to cause health impacts. The population-weighted annual mean exposures estimated in AP-HRAs spanned from 0.69 to 1.26 times the STE-2010 reference value (**Table 4**).

The population-weighted exposure used in STE-2010 was 19.4 µg/m^3 PM_{10}, while it was 13.3 and 13.5 for GBD-2019 and EEA-2018, respectively (the AP-HRAs with the largest differences). The population-weighted mean exposure estimated in AP-HRAs for Switzerland has decreased (with few exceptions) over time and the values slightly differed in overlapping years across AP-HRAs, as an additional analysis including the entire EEA and GBD time series showed (see **Supplementary Material S2**).

Population exposure data, including conversion from $PM_{2.5}$ to PM_{10}, are available in the **Supplementary Material**.

Counterfactual Scenario

The counterfactual scenario refers to the lowest concentration used for comparison with the respective population-weighted annual mean exposure. Health impacts below this cut-off are excluded from the assessment either because they are considered to have insufficient scientific evidence or deemed not relevant for the AP-HRA (e.g., to exclude natural air pollution sources). The STEs used the term "reference concentration" for the "counterfactual scenario".

STE-2010, as previous STEs, chose 7.5 $\mu g/m^3$ PM_{10} as counterfactual scenario, while other AP-HRAs used values from 0 to 81% higher, i.e., ratio 0 to 1.81 (**Table 4**). STE-1993 had no counterfactual scenario because it quantified the impact of all transport related emissions. The other STEs chose 7.5 $\mu g/m^3$ PM_{10} arguing that, although there was no evidence of a threshold, the existing literature included only populations with at least 5–10 $\mu g/m^3$ annual mean concentrations. Thus, the average was used as counterfactual scenario. The FCAH considered a "high" counterfactual scenario assuming 7.5 $\mu g/m^3$ PM_{10} for comparability with STEs and a "low" scenario assuming 3.3 $\mu g/m^3$ PM_{10} based on a recent publication which derived a CRF down to this level [29]. CITIES also used two scenarios. The high scenario corresponded to the WHO Air Quality Guideline value (10 $\mu g/m^3$ $PM_{2.5}$, i.e., 13.6 $\mu g/m^3$ PM_{10}) and the low scenario corresponded to the lowest measured exposure in the considered European cities (3.7 $\mu g/m^3$ $PM_{2.5}$, i.e., 5 $\mu g/m^3$ PM_{10}). EEA assumed zero exposure as counterfactual scenario arguing that the HRAPIE report recommends "the quantification of health impacts at all concentrations" [30]. WHO and GBD counterfactual scenarios were expressed as a uniform distribution from 2.4 to 5.9 $\mu g/m^3$ $PM_{2.5}$ for GBD and WHO-2016 as well as from 5.9 to 8.7 $\mu g/m^3$ $PM_{2.5}$ for WHO-2012. These bounds referred to the minimum and 5th percentiles of air pollution concentrations observed in relevant cohort studies [31], which provided "the uncertainty regarding the level at which the scientific evidence was consistent with adverse effects of exposure" [4]. We calculated the average of these bounds (and re-scaled from $PM_{2.5}$ to PM_{10}), to enable comparisons with the other AP-HRAs, resulting in 5.6 $\mu g/m^3$ PM_{10} for GBD and WHO-2016 and 9.9 $\mu g/m^3$ PM_{10} for WHO-2012.

In AP-HRAs, health impacts are derived on the basis of the difference between the population-weighted mean exposure and the counterfactual scenario. This difference in the selected AP-HRAs was 0.34–1.67 times the STE-2010 value (**Table 4**). More specifically, this difference was lower for STE-2000, GBD-2019, WHO-2016 as well as in the high scenario of FCAH-2010 and CITIES-2015 than for STE-2010.

Concentration-Response Functions

Table 5 shows the CRFs for mortality outcomes in form of mean excess relative risk (relative risk minus one) per 10 $\mu g/m^3$ PM_{10} and the ratios in relation to the reference value, i.e., the most recent STE. The ratio for all-cause mortality in adults (the most assessed health impact) ranged from 0.96 to 1.31.

Regarding all-cause mortality in adults, EEA used the same CRF as STE-2010, from the HRAPIE recommendations [13], while CITIES used a higher CRF based on a more recent WHO meeting report [32] and STE-2000 a lower CRF based on an own meta-analysis of three studies [33–35]. For lung cancer mortality, STE-2000 carried out a purpose-designed meta-analysis among the same three studies as for all-cause mortality, while FCAH used a meta-analysis by Huang, Pan [36] after considering eight alternatives. CRFs in form of relative risk, before and after re-scaling from $PM_{2.5}$ to PM_{10}, as well as the excess relative risk and the ratios of morbidity outcomes are available in the **Supplementary Material**.

Regarding the methodological approaches used for health impact quantification, we found differences across AP-HRAs, as described below, in terms of definition of mortality in the CRFs (all-cause vs. cause-specific mortality), shape of CRFs, Population Attributable Fractions (PAF) and quantification of mortality estimates.

Both the GBD and WHO did not use a single all-cause CRF (as in the other AP-HRAs); rather multiple cause-specific estimates were used and the impacts aggregated to obtain the all-cause mortality estimates. WHO considered five causes of deaths (lower respiratory disease, chronic obstructive pulmonary disease, ischemic heart disease, lung cancer and stroke), and the GBD seven (additionally considering diabetes and adverse birth outcomes). Moreover, STE-2010, EEA, GBD and WHO obtained health impacts stratified by sex and age, while CITIES stratified by age. In a later step, stratified impacts were aggregated to obtain all-cause impacts.

STE-1996 and STE-2000 assumed a linear CRF, while the others used a log-linear function. In 2010 the GBD developed the so-called "integrated exposure-response risk functions" based on computer simulations [4, 37]. These functions have been updated over time. WHO-2012 used the 2013 version and WHO-2016 the one from 2015, which were superseded by the most recent update of GBD 2019 (included in our comparison).

Depending on the AP-HRA, the PAF can be calculated assuming a single population-weighted exposure level for the whole country or by smaller spatial units of analysis such as regions. GBD, WHO and CITIES applied the second approach, calculating the exposure for all ages combined. While the STE-2010 applied the first approach, the population-weighted PM exposures were specifically calculated by population group (children, adults or all).

Instead of the general approaches described above, STE-2010 used life tables (i.e., demographic data containing the probability of death for each age group) to quantify both premature deaths and YLLs. EEA and CITIES only used them for YLLs.

Equations used in the selected AP-HRAs for their approaches are available in the **Supplementary Material S2**.

Baseline Health Data

Table 5 shows the mortality baseline health data per 100,000 inhabitants and their ratios calculated as the AP-HRA value divided by the reference value (from most recent STE). The

ratio for all-cause mortality in adults (the most assessed outcome) ranged from 1.03 to 1.13.

Looking at differences between specific AP-HRAs, CITIES used a higher baseline all-cause mortality than STE-2010, and FCAH a higher one than STE-2000 for cancer mortality. Baseline health data were not reported in GBD, WHO and EEA studies.

Differences in age ranges in population at risk (based on the age defined in CRFs), together with differences in definition of outcomes and methodologies of data sources, lead to differences in baseline health data. Thus, most AP-HRAs assume age of less than 1 year for infant mortality, while WHO included ages below 5. For adults, most AP-HRAs assume ages of 30 and above, while WHO derived the burden for those above 25 and CITIES above 20 years old.

DISCUSSION

Main Findings

The aim of this study was to explore differences between the STEs, especially STE-2010, and other AP-HRAs for Switzerland. Our results indicate that the variation of health impacts obtained across AP-HRAs, and over time can be wide. Indeed, the most frequently assessed outcome-pollutant pair, i.e., the number of premature deaths in adults per 100,000 inhabitants attributed to ambient PM exposure, ranged from 14 to 76 (with STE-2010 reporting 36). Thus, the ratios ranged from 0.4 to 2.09 times the STE-2010 value, which was used as reference.

The divergences in approaches and input data used in the AP-HRAs played a role. Overall, for the above mentioned outcome-pollutant pair, the choice of the counterfactual scenario showed the highest heterogeneity among the input data (ratio from 0 to 1.81) followed by the population exposure (0.69–1.26), the CRF (0.96–1.31) and baseline health data (1.03–1.13).

The values of the counterfactual scenario and the CRF relied on choices of authors of AP-HRAs and available evidence. The choice of the counterfactual scenario was based on the specific assumption related to the goal of the AP-HRAs and supported by literature, while the CRF was chosen among available (or purpose-designed) meta-analyses of multiple epidemiological studies. Sometimes published meta-analyses provided multiple CRFs to select from. For instance, FCAH chose a CRF among nine available CRFs, which differed in terms of source (three were considered), type of PM ($PM_{2.5}$ vs. PM_{10}), health endpoint (cases vs. deaths) and geographical scope (worldwide vs. Europe) [26].

Differences in population-weighted exposure appeared not only when comparing different years, but also in the same year across different AP-HRAs. An obvious reason behind these divergences was the different level of resolution of the underlying air pollution exposure models and subsequent aggregation to the population weighted mean exposure. The grid size of these models for PM was 200 m × 200 m for STE-2000, 2005 and 2010 [14–16, 38], 250 m × 250 m for CITIES [39], 1 km × 1 km for EEA [30] and STE-1996 [11], and 0.1° × 0.1° for GBD [4] and WHO [31] which is equivalent to 11 km × 7 km in Europe [23]. Larger grid sizes would smooth the variation in concentrations, minimizing the exposure contrasts. This naturally influences the subsequent population-weighted mean [40], and can be more of an issue for pollutants like NO_2 that vary over small spatial scales (e.g., decay to background levels within hundreds of meters from roads). Furthermore, modifiable areal unit problems and rounding issues explain further differences in health impacts. The former affect aggregations of point or small scale based measures into larger geographic scales and has no solution [41], while the latter can be minimized by applying a generous and consistent rounding in final results which avoids a claim for pseudo-precision. We identified differences in terms of age ranges considered as population at risk, partly due to age differences in the population used for the derivation of CRFs. The broader the age range, the larger the number of people included in the baseline health data and, consequently, the larger the health impacts. However, the final weight of this issue was limited. For instance, according to the assessment of GBD-2019, the number of all-cause premature deaths in the total population was only 0.62% higher than in the population 20 years and older (as in CITIES) or 25 years and older (as in WHO) and 0.67% higher than for ages of 30 and older (as in EEA and STEs).

EEA mortality impacts were considerably higher than STE-2010 impacts, even in closer years of analysis. For instance, premature deaths in adults were 1.75 times higher for EEA-2009 than for STE-2010. The main reason for such divergence was the choice of the counterfactual scenario (0 instead of 7.5 $\mu g/m^3$ PM_{10}). EEA uses the same CRF as in STE-2010 and a similar reference concentration (we did not find EEA baseline health data). STE-2010 applies a different method for quantification of premature deaths (life table approach). However, it may not lead to large differences because when using both the life table approach, for YLLs, the differences in results were even larger.

CITIES mortality impacts relative to the STE-2010 impacts depended on the scenario. Regarding the low scenario, the difference between population exposure and counterfactual scenario was 7% higher in CITIES-2015 than in STE-2010 and the CRF 13% higher (baseline health data were very similar in both). This partly explains the up to 50% higher mortality impacts. Regarding the high scenario, the difference between population exposure and counterfactual scenario in CITIES-2015 was only around one third of the value for STE-2010, which counteracted the effect of the 13% higher CRF and partly explained the lower health impacts. It is worth mentioning that in the comparison CITIES-2015 vs. STE-2010, two opposite effects interplayed. Since CITIES-2015 only cover urban (and therefore more polluted) areas, a higher impact per inhabitant could be expected. On the other hand, since CITIES-2015 assesses the impacts 5 years later, a lower impact could be expected (following the decreasing pollution levels in Switzerland).

Whereas, WHO and GBD mortality (especially in terms of YLLs in adults) were rather similar to STE impacts. This similarity between WHO and GBD was expected because the former was partly based on the methodology of the latter (WHO-2012 on GBD update for 2013 and WHO-2016 on GBD update for 2015). The difference between WHO and GBD in this study was somewhat larger than the one reported in a previous international comparison of AP-HRAs [24]. This was because

we compared WHO-2012 and WHO-2016 with the GBD update for 2019 instead of with the GBD update for 2013 and 2015.

Limitations

Our study is a unique comparison of national and international AP-HRAs for a specific country, which includes rarely available quantitative comparisons of health impacts and the related input data. However, we have to acknowledge that comparability across the selected AP-HRAs was limited in some regards. Firstly, the year of analysis of the selected AP-HRAs rarely overlap. We partly corrected for this by normalizing for population, although this correction did not cover influences of other demographic changes such as in life expectancy or in age distribution. Secondly, CITIES covered the ten largest urban areas in Switzerland, which represent 27% of the Swiss population. Therefore, input data and results may be biased towards rather urban and more polluted areas. Thirdly, we converted the transport-related health impacts of STE-1993 into all-source health impacts by dividing by 0.4 because it states that on average 40% of the total air pollution exposure were caused by transport. However, 40% was just the average, while this value can reach up to 60% in some areas. Fourthly, the CRFs of GBD and WHO are based on multiple causes of death instead on a single CRF, which does not enable a direct comparison. Fifthly, we acknowledge that the literature search for the selection of AP-HRAs was limited. Due to the commercially driven algorithm of Google Search and the small number of results [50] retrieved and screened for eligibility; some AP-HRA might be unintentionally left out of the selection. Finally, baseline health data were not reported in some of the selected AP-HRAs. However, these AP-HRAs used international data sets that rely on national data collections (as the ones used in STEs). Therefore, no large differences are expected among them.

Implications for Existing and Forthcoming Research

The result of this study was consistent with existing literature. Two previous reviews [23, 24] found that the mortality attributed to ambient air pollution was substantially different across international AP-HRAs. The review of Evangelopoulos, Perez-Velasco [24], comparing international AP-HRAs, the highest number of premature deaths was around 3 times higher than the lowest one, whereas we report a 5-fold range across AP-HRAs for Switzerland (76 vs. 14 deaths in adults per 100,000 inhabitants). Both above-mentioned reviews found similar differences in terms of methodological approaches and input data across AP-HRAs, which may explain the different results, with the exception of the counterfactual scenario in the work of Evangelopoulos, Perez-Velasco [24], with a range rather smaller than in our study.

Given such differences across AP-HRAs, it would be desirable that forthcoming AP-HRAs redouble efforts showing transparently the methodological approach and the input data to enable comparisons. Moreover, a lack of agreement concerning terminology and the corresponding equations have been already documented, e.g., for PAF [42, 43]. A full consistency across AP-HRAs is probably unpractical. However, some agreement in basic assumptions and transparent reporting would increase the comparability across AP-HRAs. International agreements on AP-HRAs, e.g., regarding general guiding principles [44], air quality guidelines (e.g., 45) or updated HRAPIE recommendations [46] would no doubt help to unify criteria.

Conclusion

Even for low population exposure, health impacts are considerable. AP-HRAs for Switzerland use different methodological approaches and input data, which result in different estimated health impacts for all-cause mortality in adults related to PM ranging from 0.4 to 2.09 times the STE-2010 estimate. The largest differences among input data were found in terms of assumptions for counterfactual scenarios, which was owed to different motivations and goals to conduct a specific AP-HRA (e.g., impact of regulation vs. impact of total air pollution). International cooperation based on consensus decisions, for example under the umbrella of the WHO, and further research is required to develop updated guidelines for the application of AP-HRAs regarding methodology, the choice of input data, and the derivation of counterfactual scenarios. Such international agreement may increase consistency across future AP-HRAs and reduce challenges in terms of communication of results.

AUTHOR CONTRIBUTIONS

AC: editing, data analysis, and study design. MR and NK: editing, funding, and study design. KdH, RK, MK, and DV: editing.

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CONFLICT OF INTEREST

The authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

SUPPLEMENTARY MATERIAL

The Supplementary Material for this article can be found online at: https://www.ssph-journal.org/articles/10.3389/phrs.2022.1604431/full#supplementary-material

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4.1 Paper III – Publication Appendix

SUPPLEMENTARY MATERIAL 1: METHODS

Literature review

We carried out a literature search in January 2021 to identify publications with health impact assessments of exposure to outdoor air pollution in Switzerland beyond the STEs. For this task, we used Google Search instead of research-specific searchers to find not only academic but also “grey” literature. Iteratively the following search terms was used: 1) Switzerland "air pollution" health burden assessment, 2) Switzerland "air pollution" deaths "years of life lost" mortality, 3) Switzerland "air pollution" "health impacts", 4) Switzerland "air pollution" "mortality". We examined the first 50 search results of each iteration.

Additionally, we carried out a specific search for studies using the three majoritarian Swiss local languages: German, French and Italian. Thus, we searched the following two word combinations: 1) Switzerland "air pollution” health and 2) Switzerland "air pollution” health city (i.e. same search terms just adding the word “city”). Translated into German, French and Italian: Schweiz Luftverschmutzung Gesundheit (Stadt), Suisse "pollution de l'air" santé (ville), Svizzera "inquinamento dell'aria" salute (città). We examined the first 20 search results of each search in local language.

Finally, we consulted the Swiss Literature Database on Air Pollution and Health (LUDOK in German) to confirm that we did not overlook a relevant air pollution health risk assessment (AP-HRA) (1).

Beyond the selected AP-HRAs, we excluded the following literature based on the inclusion criteria described. Out of the published STEs, we excluded the STE-2015 (2) and 2017 (3) because they only show transport-related external costs. Beyond the STEs, from the reviewed literature reviewed, we excluded some publications because they used results from other AP-HRAs such as the GBD (e.g. 4, 5) or made only future projections (e.g. 6). Some Swiss-designed projects were excluded because they assess transport-related (instead of all-source) emissions (e.g. 7, 8) or focused on some methodological aspects, .such as exposure-response models (e.g. 9, 10). Furthermore, although the EEA reports were selected for this study, we excluded those for 2009 and 2010 because they re-use GBD results. The above mentioned results for 2009 were compiled from the EEA report for 2018, which exceptionally included this new assessment of a past year (11).

In the literature review we additionally identified some local AP-HRAs at regional level, namely for the canton of Zurich (12, 13), the canton of Basel (14) and the agglomeration of Lausanne-Morges (15) (Table A 1). We excluded them because their small geographic scale does not enable a comparison with national scale AP-HRAs. Additionally, some of them re-use STE results (AP-HRAs in Zurich) or focus on comparing two years without specific result for each year (AP-HRA in Lausanne-Morges).

Table A 1 Regional AP-HRAs not selected for the comparison (Switzerland 2021).

AP-HRA [1]	Year	Swiss area	Mortality outcomes	Morbidity outcomes	Pollutants
BASEL	1996	Canton of Basel	• Lung cancer deaths		PM_{10}
LAUSANNE	2015	Agglomeration Lausanne-Morges	• Deaths	• Asthma attacks • Bronchitis cases • Hospital admissions • Invalidity cases • Restricted activity person-days • Symptom days • Work loss days	$PM_{2.5}$, NO_2
ZURICH	2005, 2010, 2015	Canton of Zurich	• Deaths	• Hospital admissions • Bronchitis cases • Restricted activity person-days • Symptom days	PM_{10}, NO_2

[1] Sources: BASEL: Röösli, Künzli (14); LAUSANNE: Castro, Künzli (15); ZURICH: ECONCEPT (13).

Finally, we selected five AP-HRAs, which met the inclusion criteria and that were compared to the STEs (Figure A 1).

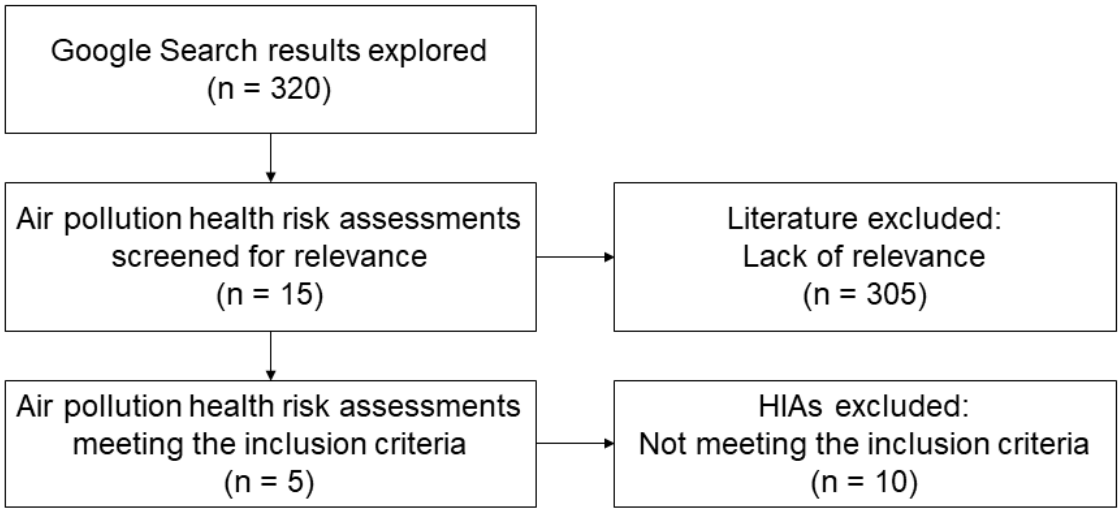

Figure A 1 Prisma flow chart of the literature review (Switzerland 2021).

Data processing

Data filtering

We collected results and input data from all selected AP-HRAs, including all chosen pollutants, all years of analysis (whole time series), and the counterfactual scenarios. To show an overview of the assessed health impacts and the data heterogeneity, we limited the number of variables (pollutants, years of analysis, and outcomes), enabling a more targeted analysis, as follows.

For the overview of health impacts, we selected only one AP-HRA and year of analysis. We prioritized data from the last available STE over other AP-HRAs assuming that STEs have a better knowledge of local circumstances. If no STE data were available, we selected data from other AP-HRA prioritizing the most recent ones.

For the heterogeneity of health impacts, we carried out a three-step filtering process. Firstly, we identified the pollutant with the highest attributed impacts pollutants by comparing AP-HRAs with more than one pollutant in their most recent overlapping year. In further steps, we focused on this pollutant. Secondly, we focused on the most relevant years of analysis. We included all STEs years, but in case of other AP-HRAs with time series, we selected only the first and the last year. We assumed that the first and last year capture the largest heterogeneity of data, given that air pollution concentration has decreased in Switzerland over the last decades (16). Thirdly, we removed the health outcomes that were assessed by only one AP-HRA or not assessed by a STE, since they do not allow comparability with STEs.

Normalization and re-scale

We normalized the absolute health impact from AP-HRAs by dividing by all-age population (per 100,000 persons). The normalization mitigates the effect of yearly variation due to changes in population and increases comparability across AP-HRAs. For population at national level, we used data from the Swiss Federal Office for Statistics (17), while for cities and agglomerations we used data from the AP-HRA to avoid discrepancies in the definition of the agglomeration boundaries. Table **A 2** and

Table A 3 show the population data used for normalizing health impacts of the selected AP-HRAs. The national values are from Swiss Federal Office for Statistics (17), while the population for CITIES (ten largest urban areas) are from this AP-HRA. CITIES considered both cities and when available “greater cities”, which include the whole agglomeration beyond the city boundaries.

Table A 2 Population in Switzerland on January 1 (17) (Switzerland 2021).

Year	Population
1990	6,673,850
1991	6,757,188
1992	6,842,768
1993	6,907,959
1994	6,968,570
1995	7,019,019
1996	7,062,354
1997	7,081,346
1998	7,096,465
1999	7,123,537
2000	7,164,444
2001	7,197,638
2002	7,255,653
2003	7,313,853
2004	7,364,148
2005	7,415,102
2006	7,459,128
2007	7,508,739
2008	7,593,494
2009	7,701,856
2010	7,785,806
2011	7,870,134
2012	7,954,662
2013	8,039,060
2014	8,139,631
2015	8,237,666
2016	8,327,126
2017	8,419,550
2018	8,484,130
2019	8,544,527

Table A 3 Total (all-age) population in the ten largest Swiss urban areas in 2015 according to CITIES (18) (Switzerland 2021).

Category of the urban area	Name of the urban area	Population
Greater City	Zurich	618,300
Greater City	Geneva	368,188
Greater City	Basel	308,348
Greater City	Bern	215,216
Greater City	Lausanne	228,687
City	Winterthur	106,230
City	St. Gallen	74,024
Greater City	Luzern	152,531
Greater City	Lugano	81,929
City	Biel/Bienne	59,255
Sum	10 Swiss urban areas	2,212,708

Regarding the input data, conversions were required to make values comparable. Thus, we re-scaled concentration values from $PM_{2.5}$ into PM_{10} values assuming that $PM_{2.5}$ accounts for 73.5% of $PM_{10,}$ i.e. by dividing $PM_{2.5}$ concentrations by a conversion factor of 0.735 (19). Additionally, we used this conversion factor to re-scale the CRF of the selected AP-HRAs. We converted the CRF expressed in terms of $PM_{2.5}$ into PM_{10} exposure by applying a logarithmic transformation. Furthermore, most AP-HRAs express the counterfactual scenario as a single value, while some of them express it as a bound. We calculated the average of the lower and upper limits of these uniform distributions to make the values comparable with the others.

To compare PM_{10} with $PM_{2.5}$ values, we re-scaled $PM_{2.5}$ concentrations into a PM_{10} form using Equation A 1.

Equation A 1 Re-scale of $PM_{2.5}$ into PM_{10} concentration.

$$C_{PM10} = \frac{C_{PM2.5}}{CF}$$

C_{PM10} = PM_{10} concentration.
$C_{PM2.5}$ = $PM_{2.5}$ concentration.
CF = Conversion factor, i.e. proportion of $PM_{2.5}$ in $PM_{10,}$ i.e. 73.5% (19, 20)

We compiled these data from the corresponding AP-HRAs. We re-scaled the relative risk coefficients of the selected studies expressed in terms of $PM_{2.5}$ exposure into PM_{10} exposure by applying Equation A 2. Thus, EEA used the following $PM_{2.5}$ relative risk for premature deaths in adults: 1.062 (95%-CI: 1.04; 1.083). After re-scaling, the PM_{10} relative risk is 1.0452 (95%-CI: 1.0292; 1.0604).

Equation A 2 Re-scale of relative risks from $PM_{2.5}$ to PM_{10}.

$$RR_{PM10} = e^{\ln(RR_{PM2.5})*CF}$$

RR_{PM10} = Relative risk for PM_{10} exposure
$RR_{PM2.5}$ = Relative risk for $PM_{2.5}$ exposure
CF = Conversion factor (proportion of $PM_{2.5}$ in PM_{10})

Ratio and reference value

To measure the heterogeneity of quantitative data (health impacts and input data) across AP-HRAs, we expressed the values of the AP-HRA as ratios in relation to a reference value. We assigned the reference value to the most recent STE of the selected AP-HRAs. If a certain health impact was not assessed in the most recent STE, the value of a previous STE was selected as reference value.

We calculated the ratios by dividing the value of the AP-HRA by the reference value. Thus, ratios less than 1 show that the AP-HRA value is lower than the reference value, while ratios higher than 1 show AP-HRA values higher than reference value. Exceptionally, for CRF, we subtracted one from both the numerator and denominator before dividing, i.e. we calculated the ratio of the excess relative risk.

Data preparation and assumptions

Collected data required minor edits as follows. For STE-2000 and STE-2005, we calculated the YLLs in adults and infants based on the total number of YLLs as follows. The AP-HRAs states that 96% of the total number refers to adults and 4% to infants. For AP-HRAs with results at city level, we summed up the health impacts of the cities. For STE-2005, we calculated the reference value by multiplying the value in 2000 by 1.0289 because STE-2005 only indicates that the value is 2.89% higher than in STE-2000. For WHO-2012, we assigned the mortality to infants and the sum of the rest of disease-specific health impacts to adults, as described in the report.

Furthermore, in case of unclear information, we had to make assumptions as follows. Given that the GBD dataset categorizes lung cancer as “tracheal, bronchus, and lung cancer”, we assumed that the value is comparable with lung cancer values provided in other AP-HRAs. Concerning the age ranges that correspond to the population groups (adults vs. children vs. infants) we made multiple assumptions. STE-2005 (short update of STE-2000) does not provide the age of the YLLs; thus, we assumed the age of STE 2000. STE-1993 only provided the population group for premature deaths, acute bronchitis in children and symptom days as well as the age for acute bronchitis in children; we deduced the missing information based on later STE studies (if available). Otherwise, we made further assumptions. Thus, we deduced the age of incidence of chronic bronchitis and invalidity cases in adults for prevalence. We deduced the age of bronchitis in children for symptom days and the age of asthma attacks for days of medication intake of this disease. Additionally, we deduced that cases of acute bronchitis in children refer to prevalence instead of incidence based on next STE.

WHO-2016 presents specific DALYs for lower respiratory infections in children younger than 5 years old, while this value was not available for premature deaths and YLLs. Therefore, we assumed that it this value was zero, i.e. the whole number of premature deaths and YLLs refer to people at the age of 25 years or older.

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SUPPLEMENTARY MATERIAL 2: RESULTS

Selected studies

Table A 4 summarizes the health outcomes assessed in the selected air pollution health risk assessments (AP-HRAs). All selected AP-HRAs assess mortality impacts, while only STEs, GBD as well as WHO assess both mortality and morbidity impacts. The variety of outcomes for morbidity is higher than for mortality (see Supplementary Material). Regarding mortality, most studies assess deaths and years of life lost (YLLs). Regarding morbidity, the STEs assess multiple health outcomes, while the GBD combines the effects on multiple health outcomes into one overall indicator, namely years lived with disability (YLDs). GBD and WHO additionally used disability-adjusted life years (DALYs) as a combined mortality-morbidity indicator, which condensates the meaning of both YLLs and YLDs (1). The GBD and WHO show cause-specific health impacts (including lung cancer).

Table A 4 Summary of outcomes assessed in the selected AP-HRAS

Short name	Year of analysis [1]	Summary of outcomes[2][3]		
		Mortality	Morbidity	Mixed
STE	1993, 1996, 2000, 2005, 2010	• Deaths (except analysis 2005) • Lung cancer deaths (only analysis 2000) • YLLs (only analysis 2000, 2005 & 2010) • Working YLLs (only analysis 2000&2010)	• Asthma attacks (all years of analysis) • Bronchitis cases (all years of analysis) • Days of medication (only analysis 1993) • Hospital admissions (only analysis 1996 & 2010) • Hospital days (except analysis 1996) • Invalidity cases (only analysis 1993) • RADs (all years of analysis) • Symptom days (only analysis 1993) • Work loss days (only analysis 1993 & 2010)	
FCAH	2010	• Lung cancer deaths		
GBD	1990-2019	• Deaths • YYLs	• YLDs (by cause)	• DALYs
EEA	2009, 2011-2018	• Deaths • YLLs (except 2011)		
WHO	2012, 2016	• Deaths • YLLs		• DALYs
CITIES	2015	• Deaths • YLLs		

Abbreviations: STE = Swiss assessment for Transport Externalities. EEA = European Environment Agency. FCAH = Federal Commission for Air Hygiene. GBD = Global Burden of Disease. WHO = World Health Organization. CITIES = AP-HRA for air pollution in around 1,000 European urban areas. YLLs = Years of life lost. DALYs = Disability-adjusted life years. RADs = Restricted activity person-days. YLDs = Years lived with disability.

[1] Single assessment for each year of analysis, except for GBD, which assessed in 2019 the whole time series 1990-2019, and EEA, which included the assessment of both 2009 and 2018 in the same report from 2020.

[2] GBD and WHO health impacts are stratified by cause and include lung cancer specific results.

[3] The health outcomes assessed by STEs depend from the year of analysis.

Health impacts

Table A 5 shows the all-cause mortality in adults per 100,000 all-age persons attributed to exposure to PM, O_3 and NO_2 in the most recent overlapping year of analysis of CITIES, EEA and GBD (i.e. 2015). Premature deaths per 100,000 inhabitants (all ages) attributed to O_3 in 2015 were 7% to 14% of those attributed to PM (3.6 vs. 51 for EEA and 2.8 vs. 19.7 for GBD, respectively). Regarding NO_2, the estimates were 1% to 70% of those attributed to PM, according to CITIES (0.2 vs. 14.4 for high and 30.6 vs. 43.7 for low scenario, respectively) and 25% according to EEA (12.1 vs. 51). Similar proportions can be found for years of life lost (YLLs, see Supplementary Materials).

Table A 5 Annual all-cause mortality per 100,000 all-age persons attributed to PM, O_3 and NO_2 and ratio in relation to PM (O_3 and NO_2 mortality divided by PM mortality) (Switzerland 2021).

Type of impact [1]	Study	Mortality per 100,000 persons-year		
		PM	O_3	NO_2
Premature deaths	CITIES-2015-high	14.4		0.2
	CITIES-2015-low	43.7		30.6
	EEA-2015	51.0	3.6	12.1
	GBD-2015	19.7	2.8	
YLLs	CITIES-2015-high	177.0		2.3
	CITIES-2015-low	539.8		377.5
	EEA-2015	519.6	40.1	127.5
	GBD-2015	294.9	37.7	

Abbreviations: YLLs = Years of life lost.
[1] PM and NO_2 for adults, i.e. ages of 30 or older for EEA and GBD and 20 or older for CITIES. O_3 for all ages.

Table A 6 and Table A 7 show the absolute annual mortality and morbidity (respectively) attributed to PM. The choice of health outcomes to be assessed has not been consistent among STEs. Thus, only one out of 25 health outcomes ever assessed by STEs (4%) are available in all five STEs (1993, 1996, 2000, 2005 and 2010), six outcomes (24%) are available in four STEs and two outcomes (8%) in three STEs. Therefore, around two thirds of the health outcomes ever assessed by STEs were available only in one or two STEs (out the five STEs reviewed). Although new evidences of health effects may arise in the future and although the capacity to make assessments for past years might be limited due to lack of data, a higher consistency in the selection of outcomes in STEs (especially regarding morbidity e.g. including broadly used outcomes such as DALYs and YLDs) would be desirable to increase comparability.

Table A 6 Annual absolute mortality attributed to PM across AP-HRAs, years and counterfactual scenarios (including all outcomes, also those that are removed in a further step because of lack of comparability with a STE) (Switzerland 2021).

Type of impact	Outcome disease [1]	Population group [1]	STE	STE	STE	STE	STE	EEA	EEA	FCAH	FCAH	GBD	GBD	WHO	WHO	CITIES	CITIES
			1993	1996	2000	2005	2010	2009	2018	2010	2010	1990	2019	2012	2016	2015	2015
										Low [2]	High [2]					Low [2]	High [2]
Premature deaths	All causes	Adults	5,250	3,314	3,746		2,827	4,900	3,500			3,531	1,364	1,481	2,121	968	318
		Infants			23		13					17	8	0			
		Workers					335										
	Lung cancer	Adults			311					357	255	472	240	408	206		
Working YLLs	All causes	Adults			5,267		2,767										
		Infants					346										
YLLs	All causes	Adults			40,751	46,232	28,138	55,500	38,900			61,538	20,213	25,995	31,528	11,944	3,918
		Infants			1,698	1,926	753					1,523	741	33			

Abbreviations: YLLs = Years of life lost.

[1]Age ranges of the population groups differ across AP-HRAs.

[2] FCAH and CITIES, include two assessments – respectively called high and low - because they each use a lower and a higher counterfactual scenario..

Table A 7 Annual absolute morbidity attributed to PM across AP-HRAs, years and counterfactual scenarios (including all outcomes, also those that are removed in a further step because of lack of comparability with a STE) (Switzerland 2021).

Type of impact	Outcome disease	Population group [1]	STE	STE	STE	STE	STE	GBD	GBD	WHO	WHO
			1993	1996	2000	2005	2010	1990	2019	2012	2012
Attacks	Asthma	Adults	3,500,000								
		Children		23,637	41,073	44,477	44,943				
Attacks (person-days)	Asthma	Adults		62,593			107,545				
Cases (incidence)	Acute bronchitis	Children	77,500								
	Chronic bronchitis	Adults		4,238	999	1,081	3,078				
Cases (prevalence)	Acute bronchitis	Children		45,446	39,049	41,813	17,302				
	Chronic bronchitis	Adults	55,000								
DALYs	All causes	Adults						69,589	27,332	28,116	34,747
		Infants						1,529	745	41	43
Hospital admissions	CVD	All		2,979			1,138				
	RD	All		1,308			1,131				
Hospital days	CVD	All	14,250		9,780	9,631	10,940				
	RD	All	16,250		5,858	5,873	9,420				
Invalidity cases	Chronic bronchitis	Adults	25								
Medication intake (person-days)	Asthma	Adults	3,750,000								
RADs	All causes	Adults	6,250,000	2,762,682	1,773,821	1,914,797	4,746,089				
Symptom days	RD	All	20,000,000								
		Children	60,000								
Work loss days	All causes	Workers	1,065,000				1,138,140				
YLDs	All causes	All						8,175	7,196		

Abbreviations: DALYs = Disability-adjusted life years. CVD = Cardio-vascular diseases. RD = Respiratory diseases. RADs = Restricted activity person-days. YLDs = Years lived with disability.
[1] Age ranges of the population groups differ across AP-HRAs.

Figure A 2 shows the annual premature deaths, Figure A 3 the YLLs attributed to PM in adults and Figure A 4 these YLLs per all-age 100,000 persons in Switzerland across AP-HRAs. Of particular interest is the case of CITIES. The absolute health impacts are lower than for STE-2010 since the assessment only covers the ten largest urban areas (instead of the whole country), but when looking at population-normalized impacts the values are higher or lower depending on the scenario.

Table A 8 and Table A 9 show the values used for the above mentioned figures.

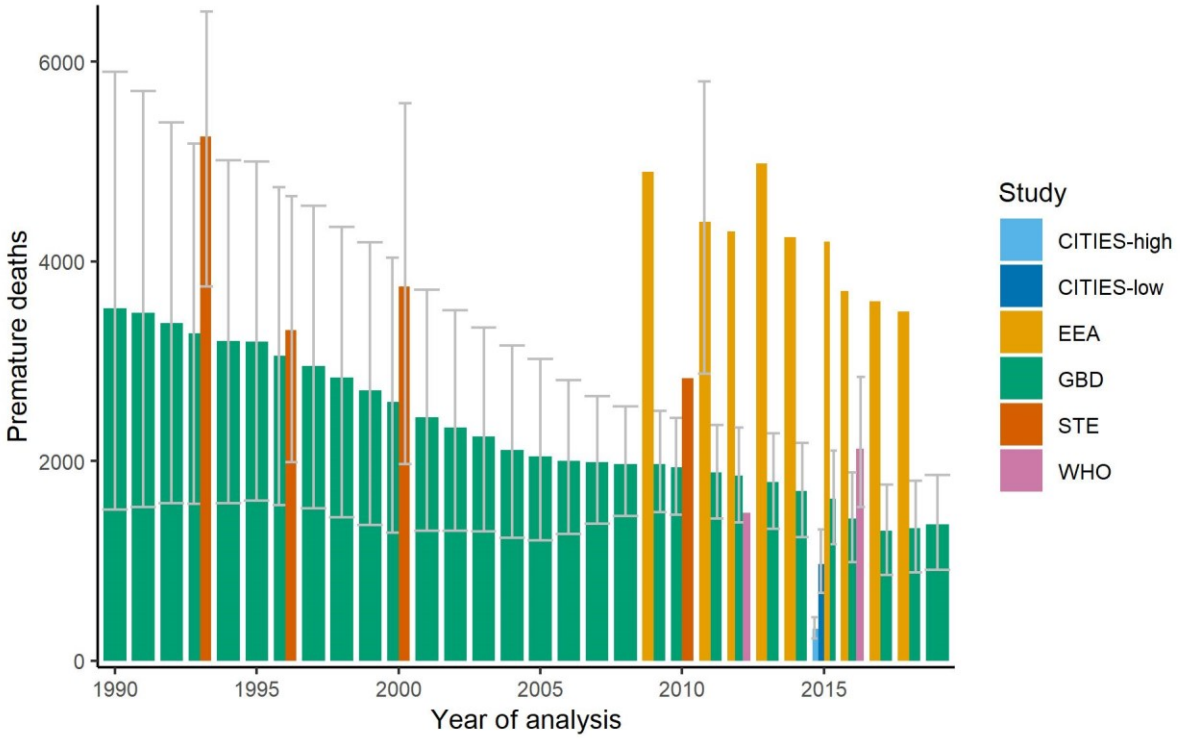

Figure A 2 Annual premature deaths in adults (≥20 years old for CITIES, ≥25 for WHO, ≥30 in the rest) attributed to PM with 95% confidence interval (if available) (Switzerland 2021).

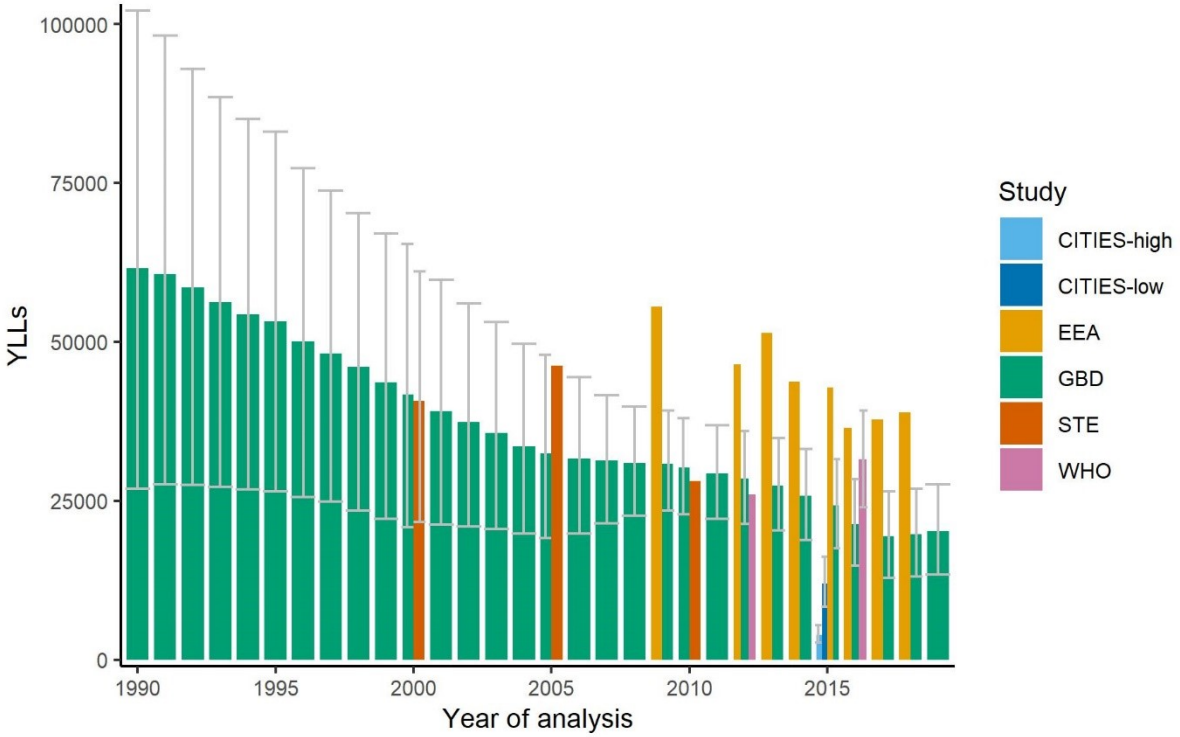

Figure A 3 Annual years of life lost due to all causes in adults (≥20 years old for CITIES, ≥25 for WHO, ≥30 in the rest) attributed to ambient PM exposure with 95% confidence interval (if available) (Switzerland 2021).

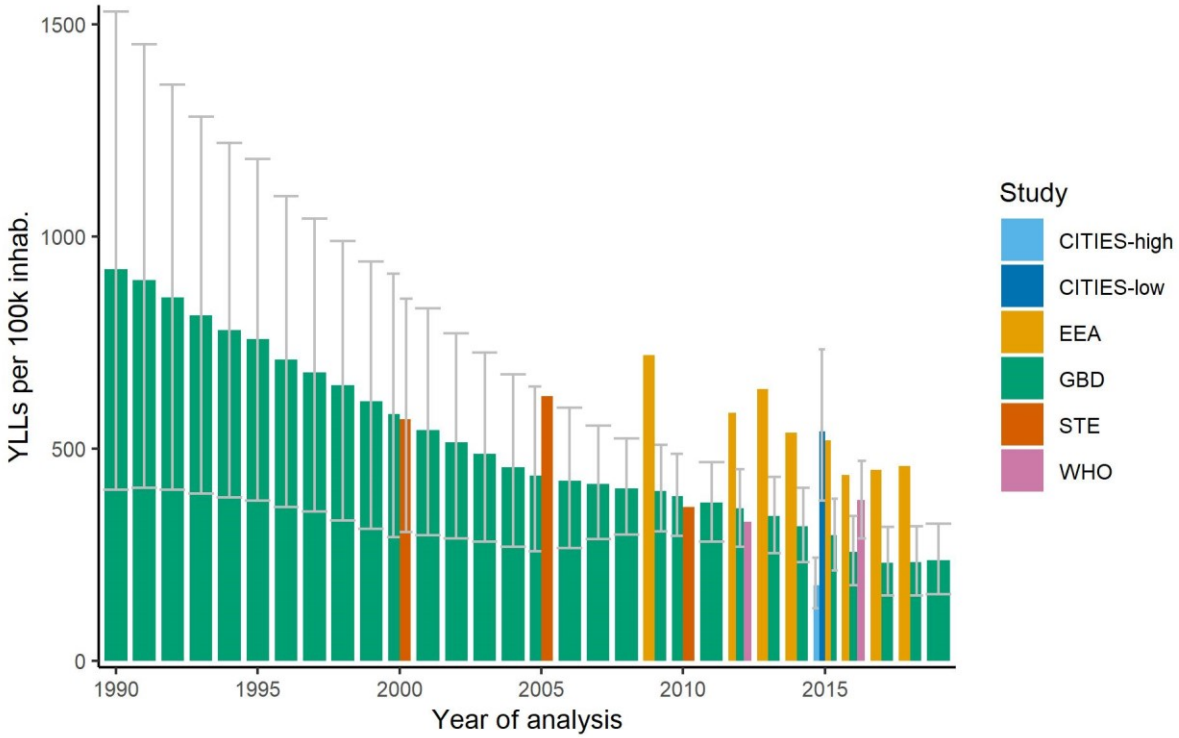

Figure A 4 Annual years of life lost per 100,000 persons in adults (≥20 years old for CITIES, ≥25 for WHO, ≥30 in the rest) attributed to PM with 95% confidence interval (if available) (Switzerland 2021).

Table A 8 Annual absolute premature deaths and per 100,000 persons attributed to PM in adults (age ≥20 for CITIES, ≥25 for WHO and ≥30 for the rest, 95% confidence interval when available) (Switzerland 2021).

Author - year of analysis	Annual deaths	Annual deaths per 100,000 persons
CITIES-2015-high	318 [221; 435]	14.4 [10; 19.7]
CITIES-2015-low	968 [677; 1316]	43.7 [30.6; 59.5]
EEA-2009	4900	63.6
EEA-2011	4394 [2876; 5803]	55.8 [36.5; 73.7]
EEA-2012	4300	54.1
EEA-2013	4980	61.9
EEA-2014	4240	52.1
EEA-2015	4200	51
EEA-2016	3700	44.4
EEA-2017	3600	42.8
EEA-2018	3500	41.3
GBD-1990	3531 [1512; 5901]	52.9 [22.7; 88.4]
GBD-1991	3482 [1538; 5705]	51.5 [22.8; 84.4]
GBD-1992	3382 [1577; 5395]	49.4 [23.1; 78.8]
GBD-1993	3282 [1568; 5183]	47.5 [22.7; 75]
GBD-1994	3200 [1580; 5015]	45.9 [22.7; 72]
GBD-1995	3194 [1600; 4997]	45.5 [22.8; 71.2]
GBD-1996	3056 [1560; 4742]	43.3 [22.1; 67.1]
GBD-1997	2951 [1524; 4555]	41.7 [21.5; 64.3]
GBD-1998	2835 [1434; 4343]	40 [20.2; 61.2]
GBD-1999	2708 [1358; 4192]	38 [19.1; 58.8]
GBD-2000	2593 [1284; 4038]	36.2 [17.9; 56.4]
GBD-2001	2440 [1300; 3715]	33.9 [18.1; 51.6]
GBD-2002	2338 [1299; 3510]	32.2 [17.9; 48.4]
GBD-2003	2245 [1297; 3339]	30.7 [17.7; 45.7]
GBD-2004	2108 [1233; 3159]	28.6 [16.7; 42.9]
GBD-2005	2043 [1206; 3022]	27.5 [16.3; 40.8]
GBD-2006	2004 [1266; 2810]	26.9 [17; 37.7]
GBD-2007	1988 [1373; 2648]	26.5 [18.3; 35.3]
GBD-2008	1972 [1450; 2549]	26 [19.1; 33.6]
GBD-2009	1972 [1488; 2500]	25.6 [19.3; 32.5]
GBD-2010	1934 [1463; 2433]	24.8 [18.8; 31.2]
GBD-2011	1884 [1421; 2359]	23.9 [18.1; 30]
GBD-2012	1851 [1384; 2337]	23.3 [17.4; 29.4]
GBD-2013	1791 [1322; 2277]	22.3 [16.4; 28.3]
GBD-2014	1699 [1237; 2180]	20.9 [15.2; 26.8]
GBD-2015	1624 [1164; 2102]	19.7 [14.1; 25.5]
GBD-2016	1426 [985; 1887]	17.1 [11.8; 22.7]
GBD-2017	1301 [860; 1765]	15.4 [10.2; 21]
GBD-2018	1328 [882; 1804]	15.6 [10.4; 21.3]
GBD-2019	1364 [911; 1857]	16 [10.7; 21.7]
STE-1993	5250 [3750; 6500]	76 [54.3; 94.1]
STE-1996	3314 [1986; 4651]	46.9 [28.1; 65.9]
STE-2000	3746 [1968; 5587]	52.3 [27.5; 78]
STE-2010	2827	36.3
WHO-2012	1481	18.6
WHO-2016	2121 [1541; 2843]	25.5 [18.5; 34.1]

Table A 9 Annual absolute YLLs and per 100,000 persons attributed to PM in adults (age ≥20 for CITIES, ≥25 for WHO and ≥30 for the rest, 95% confidence interval when available) (Switzerland 2021).

Author - year of analysis	YLLs	Annual YLLs per 100,000 persons
CITIES-2015-high	3918 [2723; 5365]	177 [123.1; 242.4]
CITIES-2015-low	11944 [8361; 16242]	539.8 [377.9; 734]
EEA-2009	55500	720.6
EEA-2012	46500	584.6
EEA-2013	51400	639.4
EEA-2014	43700	536.9
EEA-2015	42800	519.6
EEA-2016	36500	438.3
EEA-2017	37800	449
EEA-2018	38900	458.5
GBD-1990	61538 [26839; 102077]	922.1 [402.1; 1529.5]
GBD-1991	60630 [27548; 98151]	897.3 [407.7; 1452.5]
GBD-1992	58553 [27520; 92899]	855.7 [402.2; 1357.6]
GBD-1993	56209 [27200; 88539]	813.7 [393.8; 1281.7]
GBD-1994	54322 [26796; 85059]	779.5 [384.5; 1220.6]
GBD-1995	53191 [26474; 83035]	757.8 [377.2; 1183]
GBD-1996	50118 [25595; 77306]	709.6 [362.4; 1094.6]
GBD-1997	48153 [24913; 73824]	680 [351.8; 1042.5]
GBD-1998	46028 [23492; 70227]	648.6 [331; 989.6]
GBD-1999	43607 [22112; 67046]	612.1 [310.4; 941.2]
GBD-2000	41685 [20848; 65396]	581.8 [291; 912.8]
GBD-2001	39137 [21253; 59763]	543.7 [295.3; 830.3]
GBD-2002	37332 [20919; 56005]	514.5 [288.3; 771.9]
GBD-2003	35683 [20497; 53133]	487.9 [280.2; 726.5]
GBD-2004	33531 [19784; 49667]	455.3 [268.6; 674.4]
GBD-2005	32390 [19096; 47941]	436.8 [257.5; 646.5]
GBD-2006	31641 [19807; 44436]	424.2 [265.5; 595.7]
GBD-2007	31275 [21459; 41613]	416.5 [285.8; 554.2]
GBD-2008	30870 [22608; 39792]	406.5 [297.7; 524]
GBD-2009	30845 [23414; 39188]	400.5 [304; 508.8]
GBD-2010	30195 [22845; 37963]	387.8 [293.4; 487.6]
GBD-2011	29275 [22134; 36827]	372 [281.2; 467.9]
GBD-2012	28522 [21361; 35945]	358.6 [268.5; 451.9]
GBD-2013	27428 [20321; 34851]	341.2 [252.8; 433.5]
GBD-2014	25802 [18857; 33118]	317 [231.7; 406.9]
GBD-2015	24295 [17473; 31479]	294.9 [212.1; 382.1]
GBD-2016	21321 [14746; 28366]	256 [177.1; 340.7]
GBD-2017	19466 [12887; 26524]	231.2 [153.1; 315]
GBD-2018	19748 [13053; 26930]	232.8 [153.9; 317.4]
GBD-2019	20213 [13406; 27577]	236.6 [156.9; 322.7]
STE-2000	40751 [21662; 61087]	568.8 [302.4; 852.6]
STE-2005	46232	623.5
STE-2010	28138	361.4
WHO-2012	25995	326.8
WHO-2016	31528 [23956; 39220]	378.6 [287.7; 471]

Table A 10 shows the annual morbidity impacts per 100,000 all-age persons attributed to PM in Switzerland and the ratios of these values in relation to the reference value of the last available STE. Morbidity outcomes of STEs were not assessed in other AP-HRAs. The ratios STE morbidity impacts in relation to STE-2010 range from 0.35 to 2.9. The values in STE-1993 are higher than in STE-2010, while most impacts in STE-2000 and STE-2005 are lower.

Table A 10 Annual morbidity impacts attributed to PM across AP-HRAs and years expressed as per 100,000 all-age persons and as a ratio in relation to the reference value (most recent STE, in bold). The ratio is calculated by dividing the AP-HRA value by the reference value (Switzerland 2021).

Type of impact	Outcome disease	Population group [1]	STE 1993	STE 1996	STE 2000	STE 2005	STE 2010
Morbidity **per 100,000 persons**							
Attacks	Asthma	Adults		335	573	600	577
		Children		886			1,381
Cases (incidence)	Chronic bronchitis	Adults		60	14	15	40
	Acute bronchitis	Children		644	545	564	222
Hospital admissions	CVD	All		42			15
	RD	All		19			15
Hospital days	CVD	All	206		137	130	141
	RD	All	235		82	79	121
RADs	All causes	Adults	90,475	39,118	24,759	25,823	60,958
Work loss days	All causes	Workers	15,417				14,618
Ratio in relation to reference value (last STE) [2]							
Attacks	Asthma	Adults		0.58	0.99	1.04	1
		Children		0.64			1
Cases (incidence)	Chronic bronchitis	Adults		1.52	0.35	0.37	1
	Acute bronchitis	Children		2.90	2.45	2.54	1
Hospital admissions	CVD	All		2.89			1
	RD	All		1.28			1
Hospital days	CVD	All	1.47		0.97	0.92	1
	RD	All	1.94		0.68	0.65	1
RADs	All causes	Adults	1.48	0.64	0.41	0.42	1
Work loss days	All causes	Workers	1.05				1

Abbreviations: CVD = Cardio-vascular diseases. RD = Respiratory diseases. RADs = Restricted activity person-days.

[1] Age ranges of the population groups differ across AP-HRAs.

[2] Examples for interpretation of the ratio: 1.1 = 1.1 times the ref. value = 10% higher. 2.0 = 2 times the ref. value = 100% higher. 0.4 = 0.4 times the ref. value = 60% lower.

Population exposure and counterfactual scenario

As Table A 6 shows, the population exposure has decreased over time in Switzerland. Regarding differences across specific AP-HRAS in overlapping years, the STE population exposure is higher than the GBD concentration in 2010 and 2005, while it is lower in 2000. The STE population exposure is higher to the FCAH value in 2010. WHO, EEA and CITIES have no overlapping year with STEs, but they can be compared with GBD. Thus, the population exposure for WHO is lower than for GBD in 2016 and lower for CITIES in 2015. EEA values are rather similar to GBD values, being higher or lower depending on the year. WHO-2012 did not publish the annual population-weighted mean used in the assessment for Switzerland, but only the median for a different year. Therefore, WHO-2012 has not been included in the comparison of population exposures.

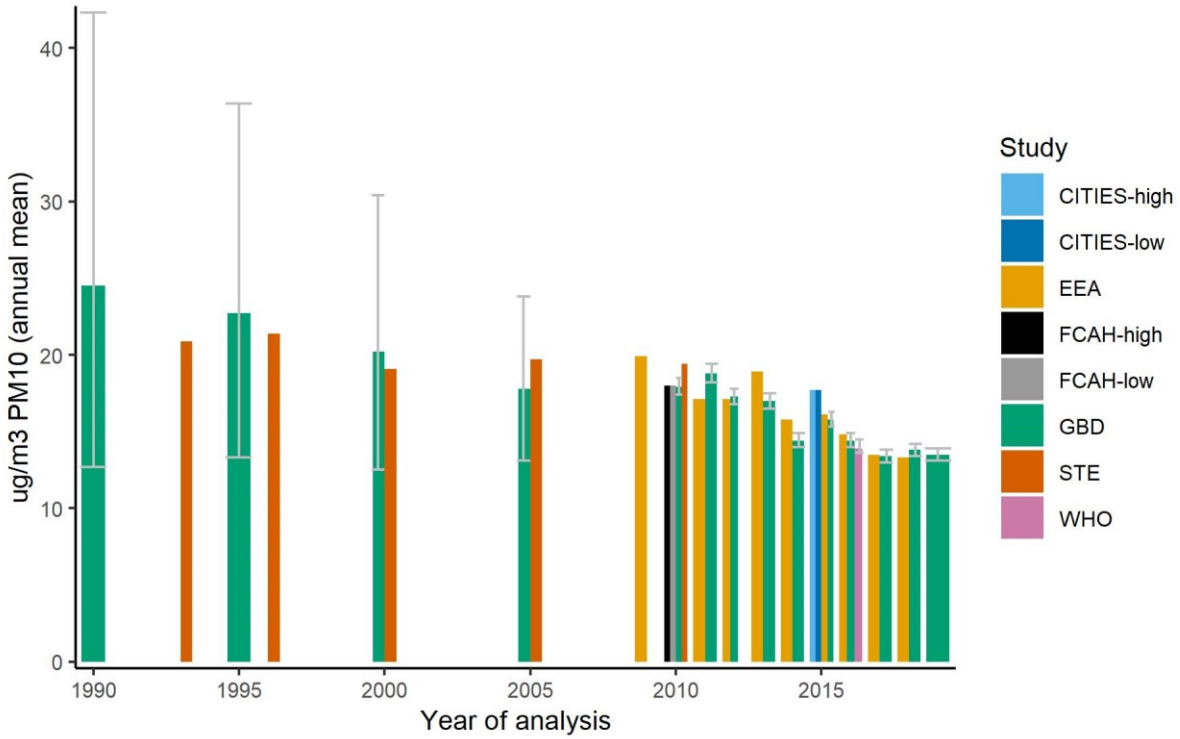

Figure A 5 Annual population-weighted mean PM_{10} concentration over time in the selected studies with 95% confidence interval (if available) (Switzerland 2021).

Table A 11, Table A 12, Table A 13 and Table A 14 show the population exposure and counterfactual scenario for PM_{10}, $PM_{2.5}$, O_3, NO_2, respectively.

As metric for O_3 concentrations, the GBD uses the daily 8-hour maximum (MDA8) in parts per billion (ppb) during the warm season, defined as the six months with the highest average O_3 levels (2), while the EEA reports use the yearly accumulated MDA8 in µg/m^3 exceeding 35 ppb (SOMO35). Since 1 ppb is equivalent to 2.00 µg/m^3 in the case of O_3 , the 35 ppb are equal to 70 µg/m^3 (3).

The difference between population exposure and counterfactual scenarios of NO_2 in EEA assessments for 2016, 2017 and 2018 are negative. Therefore, we did not use these values for normalizing absolute health impacts. EEA aggregated effects of grids inside countries (4). Thus, the negative value of the exposure difference implies that population exposure is lower or higher than the counterfactual scenario depending on the grid.

Table A 11 PM_{10} concentrations (population-weighted annual mean) in Switzerland (2021).

Author-year of analysis	Age group	Concentration (µg/m³ PM_{10})		
		Population exposure	Counterfactual scenario	Difference
FCAH-2010-high	All	18	7.5	10.5
FCAH-2010-low	All	18	3.3	14.7
STE-1993	All	20.9		
STE-1996	All	21.4	7.5	13.9
STE-2000	<15	18.7	7.5	11.2
STE-2000	≥30	19.2	7.5	11.7
STE-2000	All	19.1	7.5	11.6
STE-2005	<15	19.2	7.5	11.7
STE-2005	≥30	19.8	7.5	12.3
STE-2005	All	19.7	7.5	12.2
STE-2010	<15	19.4	7.5	11.9
STE-2010	≥30	19.5	7.5	12
STE-2010	All	19.4	7.5	11.9

Table A 12 $PM_{2.5}$ concentration (population-weighted annual mean, all ages) in Switzerland (2021).

Author-year of analysis	Original concentration (µg/m³ $PM_{2.5}$)		Re-scaled concentration (µg/m³ PM_{10})		
	Population exposure [1]	Counterfactual scenario [1]	Population exposure	Counterfactual scenario	Difference
CITIES-2015-high	13	10	17.7	13.6	4.1
CITIES-2015-low	13	3.7	17.7	5	12.7
EEA-2009	14.6	0	19.9	0	19.9
EEA-2011	12.6	0	17.1	0	17.1
EEA-2012	12.6	0	17.1	0	17.1
EEA-2013	13.9	0	18.9	0	18.9
EEA-2014	11.6	0	15.8	0	15.8
EEA-2015	11.8	0	16.1	0	16.1
EEA-2016	10.9	0	14.8	0	14.8
EEA-2016	9.9	0	13.5	0	13.5
EEA-2018	9.8	0	13.3	0	13.3
GBD-1990	18 [9.3; 31.1]	4.2 [2.4; 5.9]	24.5 [12.7; 42.3]	5.6 [3.3; 8]	18.8 [9.4; 34.2]
GBD-1995	16.7 [9.8; 26.7]	4.2 [2.4; 5.9]	22.7 [13.3; 36.4]	5.6 [3.3; 8]	17.1 [10; 28.3]
GBD-2000	14.9 [9.2; 22.3]	4.2 [2.4; 5.9]	20.2 [12.5; 30.4]	5.6 [3.3; 8]	14.6 [9.3; 22.4]
GBD-2005	13.1 [9.6; 17.5]	4.2 [2.4; 5.9]	17.8 [13.1; 23.8]	5.6 [3.3; 8]	12.1 [9.8; 15.7]
GBD-2010	13.2 [12.8; 13.6]	4.2 [2.4; 5.9]	17.9 [17.4; 18.5]	5.6 [3.3; 8]	12.2 [14.1; 10.4]
GBD-2011	13.8 [13.4; 14.3]	4.2 [2.4; 5.9]	18.8 [18.2; 19.4]	5.6 [3.3; 8]	13.2 [15; 11.4]
GBD-2012	12.7 [12.3; 13.1]	4.2 [2.4; 5.9]	17.3 [16.8; 17.8]	5.6 [3.3; 8]	11.6 [13.5; 9.8]
GBD-2013	12.5 [12.1; 12.9]	4.2 [2.4; 5.9]	17 [16.5; 17.5]	5.6 [3.3; 8]	11.3 [13.2; 9.5]
GBD-2014	10.6 [10.3; 10.9]	4.2 [2.4; 5.9]	14.4 [14; 14.9]	5.6 [3.3; 8]	8.8 [10.8; 6.8]
GBD-2015	11.6 [11.2; 11.9]	4.2 [2.4; 5.9]	15.8 [15.3; 16.3]	5.6 [3.3; 8]	10.1 [12; 8.2]
GBD-2016	10.6 [10.3; 10.9]	4.2 [2.4; 5.9]	14.4 [14; 14.9]	5.6 [3.3; 8]	8.8 [10.7; 6.8]
GBD-2017	9.9 [9.6; 10.2]	4.2 [2.4; 5.9]	13.4 [13; 13.8]	5.6 [3.3; 8]	7.8 [9.7; 5.8]
GBD-2018	10.2 [9.9; 10.5]	4.2 [2.4; 5.9]	13.8 [13.4; 14.2]	5.6 [3.3; 8]	8.2 [10.1; 6.2]
GBD-2019	9.9 [9.6; 10.2]	4.2 [2.4; 5.9]	13.5 [13.1; 13.9]	5.6 [3.3; 8]	7.8 [9.8; 5.9]
WHO-2012		7.3 [5.9; 8.7]		9.9 [8; 11.8]	
WHO-2016	10.2 [10; 10.6]	4.2 [2.4; 5.9]	13.9 [13.6; 14.5]	5.6 [3.3; 8]	8.2 [10.3; 6.4]

[1] Average of the uniform distribution with lower and upper limits of 5.9 and 8.7 µg/m3 PM2.5 for WHO-2012 and between 2.4 and 5.9 for GBD and WHO-2016.

Table A 13 Population-weighted O_3 concentrations in Switzerland (all ages) (Switzerland 2021).

Author-year of analysis	Concentration		
	Population exposure	Counterfactual scenario	Metric & unit
EEA-2009	5119		SOMO35 (µg/m^3*day)
EEA-2011	5435		SOMO35 (µg/m^3*day)
EEA-2012	4990		SOMO35 (µg/m^3*day)
EEA-2013	4919		SOMO35 (µg/m^3*day)
EEA-2014	4417		SOMO35 (µg/m^3*day)
EEA-2015	6170		SOMO35 (µg/m^3*day)
EEA-2016	4842		SOMO35 (µg/m^3*day)
EEA-2017	5281		SOMO35 (µg/m^3*day)
EEA-2018	7214		SOMO35 (µg/m^3*day)
GBD-1990	49.2 [48.5; 49.9]	32.4 [29.1; 35.7]	DMA8 (ppb)
GBD-1991	48 [47.2; 48.8]	32.4 [29.1; 35.7]	DMA8 (ppb)
GBD-1992	46.9 [46.2; 47.6]	32.4 [29.1; 35.7]	DMA8 (ppb)
GBD-1993	45.5 [44.8; 46.1]	32.4 [29.1; 35.7]	DMA8 (ppb)
GBD-1994	46.3 [45.5; 46.9]	32.4 [29.1; 35.7]	DMA8 (ppb)
GBD-1995	47.5 [46.8; 48.1]	32.4 [29.1; 35.7]	DMA8 (ppb)
GBD-1996	47.9 [47.2; 48.6]	32.4 [29.1; 35.7]	DMA8 (ppb)
GBD-1997	48.7 [48; 49.4]	32.4 [29.1; 35.7]	DMA8 (ppb)
GBD-1998	48.5 [47.8; 49.2]	32.4 [29.1; 35.7]	DMA8 (ppb)
GBD-1999	48.3 [47.6; 48.9]	32.4 [29.1; 35.7]	DMA8 (ppb)
GBD-2000	47.3 [46.6; 48]	32.4 [29.1; 35.7]	DMA8 (ppb)
GBD-2001	47.3 [46.6; 48]	32.4 [29.1; 35.7]	DMA8 (ppb)
GBD-2002	50.8 [50.1; 51.5]	32.4 [29.1; 35.7]	DMA8 (ppb)
GBD-2003	51.2 [50.5; 51.9]	32.4 [29.1; 35.7]	DMA8 (ppb)
GBD-2004	51.4 [50.7; 52.1]	32.4 [29.1; 35.7]	DMA8 (ppb)
GBD-2005	49 [48.3; 49.7]	32.4 [29.1; 35.7]	DMA8 (ppb)
GBD-2006	48.2 [47.5; 48.9]	32.4 [29.1; 35.7]	DMA8 (ppb)
GBD-2007	47.6 [47; 48.3]	32.4 [29.1; 35.7]	DMA8 (ppb)
GBD-2008	46.8 [46; 47.4]	32.4 [29.1; 35.7]	DMA8 (ppb)
GBD-2009	47.1 [46.3; 47.8]	32.4 [29.1; 35.7]	DMA8 (ppb)
GBD-2010	47.7 [46.9; 48.4]	32.4 [29.1; 35.7]	DMA8 (ppb)
GBD-2011	47.4 [46.7; 48.1]	32.4 [29.1; 35.7]	DMA8 (ppb)
GBD-2012	48 [47.3; 48.8]	32.4 [29.1; 35.7]	DMA8 (ppb)
GBD-2013	48.2 [47.4; 49]	32.4 [29.1; 35.7]	DMA8 (ppb)
GBD-2014	49.4 [48.6; 50.1]	32.4 [29.1; 35.7]	DMA8 (ppb)
GBD-2015	48.3 [47.5; 49.1]	32.4 [29.1; 35.7]	DMA8 (ppb)
GBD-2016	47.8 [47.1; 48.6]	32.4 [29.1; 35.7]	DMA8 (ppb)
GBD-2017	46.7 [46.2; 47.2]	32.4 [29.1; 35.7]	DMA8 (ppb)
GBD-2018	48.3 [47.5; 49]	32.4 [29.1; 35.7]	DMA8 (ppb)
GBD-2019	48.3 [47.5; 49.1]	32.4 [29.1; 35.7]	DMA8 (ppb)

Table A 14 NO_2 concentration in Switzerland (population-weighted annual mean, all-ages) (Switzerland 2021).

Author-year of analysis	Population exposure (µg/m^3)	Counterfactual scenario (µg/m^3)
CITIES-2015-high	27.3	40
CITIES-2015-low	27.3	3.5
EEA-2009	23.1	20
EEA-2012	21.6	20
EEA-2013	22.4	20
EEA-2014	20.9	20
EEA-2015	21.4	20
EEA-2016	19.7	20
EEA-2017	18.8	20
EEA-2018	17.6	20

Figure A 6 and Figure A 7 show the annual number of premature deaths and YLLs, respectively, in adults attributed to PM normalized by both population and difference between population exposure and counterfactual scenario. Differences of these double-normalized mortality impacts across AP-HRAs (and over time) become smaller than of absolute values or single normalized values by population. It implies that the difference between population exposure and counterfactual scenario largely explains the heterogeneity of health impacts.

Looking at the specific comparisons across AP-HRAs, the double-normalized mortality impacts are higher for STE than for GBD, although the difference is smaller for YLLs than for premature deaths. There are no overlapping years for STEs and other AP-HRAs such as EEA, WHO or CITIES. Nevertheless, in close years to STE-2010, WHO and CITIES values seem to be higher in terms of YLLs and similar in terms of premature deaths. Both impacts are rather similar when comparing STE-2010 with EEA, while EEA values are rather similar. Double normalized premature deaths are similar across these AP-HRAs. Anyway, the confidence intervals (when available) are rather wide. Therefore, differences across AP-HRAs might not be statistically different.

We normalized the health impacts per 100,000 (all-age) persons by dividing by 10 units of difference in concentration between population exposure and counterfactual scenario, assuming a linear relationship. We used concentration data from the selected AP-HRAs. Some of these concentration data were expressed with CI. However, the CI of the normalized health impacts (when available) only refer to the lower and upper bound of the impacts and not to the concentration data (we only use mean values of concentration data for normalizing.

Table A 15 and Table A 16 show the values used for the estimation of premature normality normalized per population and PM concentration. Table A 17 and Table A 18 show all health outcomes across normalized by population and PM concentration.

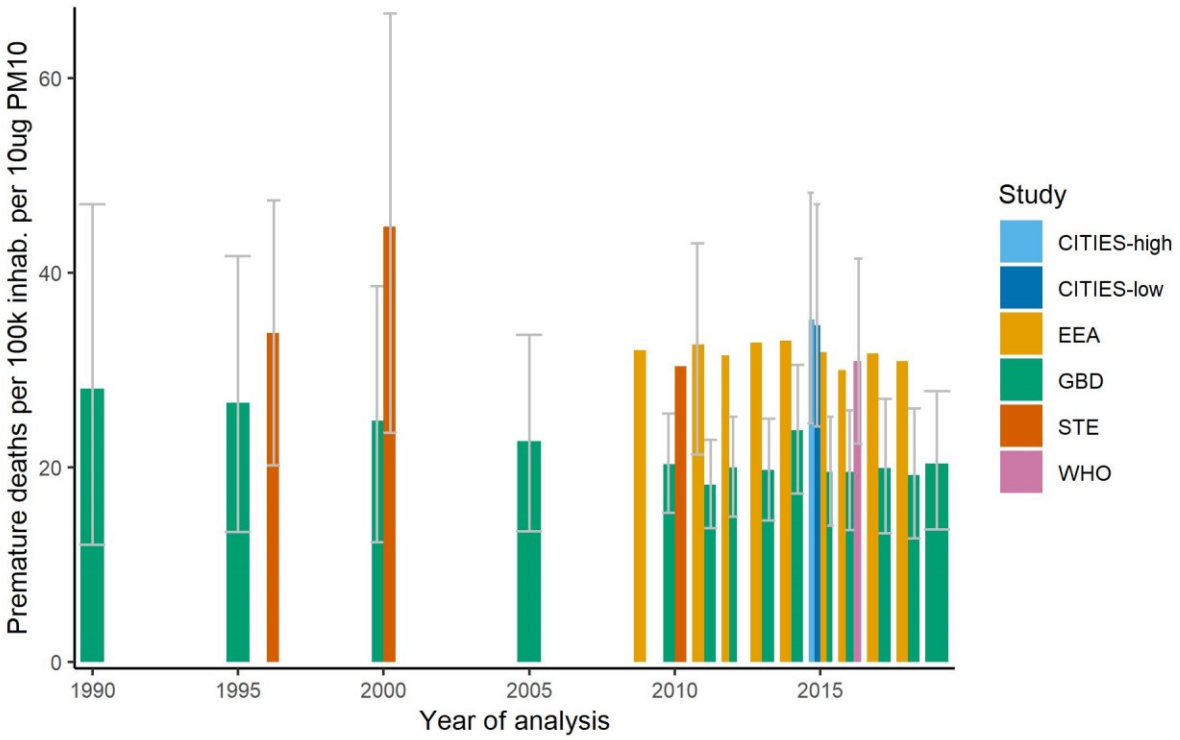

Figure A 6 Annual premature deaths per 100,000 persons and per 10 µg/m^3 PM_{10} in adults (≥20 years old for CITIES, ≥25 for WHO, ≥30 in the rest) attributed to PM with 95% confidence interval (if available) (Switzerland 2021).

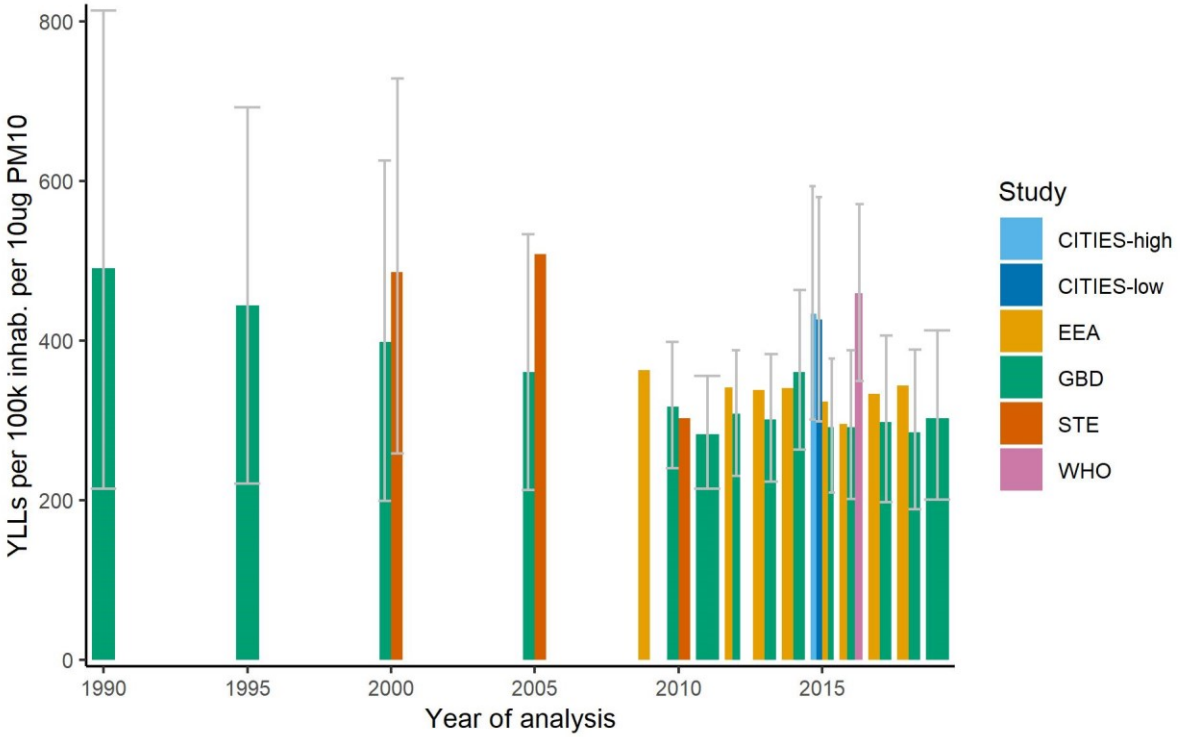

Figure A 7 Annual years of life lost per 100,000 persons and per 10 µg/m3 PM10 in adults (≥20 years old for CITIES, ≥25 for WHO, ≥30 in the rest) attributed to PM with 95% confidence interval (if available) (Switzerland 2021).

Table A 15 Annual premature deaths per 100,000 persons and 10 µg/m^3 PM_{10} attributed to PM in adults (age ≥20 for CITIES, ≥25 for WHO and ≥30 for the rest, 95% confidence interval when available) (Switzerland 2021).

Author - year of analysis	Annual deaths per 100,000 persons and 10 µg/m^3 PM_{10}
CITIES-2015-high	35.2 [24.5; 48.2]
CITIES-2015-low	34.6 [24.2; 47]
EEA-2009	32
EEA-2012	32.6 [21.3; 43]
EEA-2013	31.5
EEA-2014	32.8
EEA-2015	33
EEA-2016	31.8
EEA-2017	30
EEA-2018	31.7
GBD-1990	30.9
GBD-1991	28.1 [12; 47]
GBD-1992	
GBD-1993	
GBD-1994	
GBD-1995	
GBD-1996	26.6 [13.3; 41.7]
GBD-1997	
GBD-1998	
GBD-1999	
GBD-2000	
GBD-2001	24.8 [12.3; 38.6]
GBD-2002	
GBD-2003	
GBD-2004	
GBD-2005	
GBD-2006	22.7 [13.4; 33.6]
GBD-2007	
GBD-2008	
GBD-2009	
GBD-2010	
GBD-2011	20.3 [15.3; 25.5]
GBD-2012	18.2 [13.7; 22.8]
GBD-2013	20 [14.9; 25.2]
GBD-2014	19.7 [14.5; 25]
GBD-2015	23.8 [17.3; 30.5]
GBD-2016	19.5 [14; 25.2]
GBD-2017	19.5 [13.5; 25.8]
GBD-2018	19.9 [13.2; 27]
GBD-2019	19.2 [12.7; 26]
STE-2000	20.4 [13.6; 27.8]
STE-2005	47.8 [34.2; 59.2]
STE-2010	33.8 [20.2; 47.4]
WHO-2016	30.9 [22.4; 41.4]

Table A 16 Annual YLLs per 100,000 persons and 10 µg/m^3 PM_{10} attributed to PM in adults (age ≥20 for CITIES, ≥25 for WHO and ≥30 for the rest, 95% confidence interval when available) (Switzerland 2021).

Author - year of analysis	Annual YLLs per 100,000 persons and 10 µg/m^3 PM_{10}
CITIES-2015-high	433.7 [301.5; 593.9]
CITIES-2015-low	426.6 [298.6; 580.1]
EEA-2009	362.8
EEA-2012	341
EEA-2013	338.1
EEA-2014	340.2
EEA-2015	323.6
EEA-2016	295.6
EEA-2017	333.3
EEA-2018	343.9
GBD-1990	490.3 [213.8; 813.2]
GBD-1991	
GBD-1992	
GBD-1993	
GBD-1994	
GBD-1995	443.6 [220.8; 692.4]
GBD-1996	
GBD-1997	
GBD-1998	
GBD-1999	
GBD-2000	398.5 [199.3; 625.2]
GBD-2001	
GBD-2002	
GBD-2003	
GBD-2004	
GBD-2005	360.1 [212.3; 533]
GBD-2006	
GBD-2007	
GBD-2008	
GBD-2009	
GBD-2010	316.7 [239.6; 398.1]
GBD-2011	282.8 [213.8; 355.7]
GBD-2012	307.8 [230.5; 387.9]
GBD-2013	301.3 [223.3; 382.9]
GBD-2014	360.7 [263.6; 463]
GBD-2015	291.3 [209.5; 377.5]
GBD-2016	291.6 [201.7; 388]
GBD-2017	297.9 [197.2; 405.9]
GBD-2018	285.1 [188.5; 388.8]
GBD-2019	302.2 [200.5; 412.4]
STE-2000	485.7 [258.2; 728.1]
STE-2005	508.3
STE-2010	302.3
WHO-2016	459.2 [348.9; 571.3]

Table A 17 Annual mortality per 100,000 persons and per 10 µg/m³ PM_{10} (difference between population exposure and counterfactual scenario) attributed to PM across AP-HRAs, years and counterfactual scenarios (Switzerland 2021).

Type of impact	Outcome disease	Population group [1]	STE		STE	STE	STE	EEA	EEA	FCAH	FCAH	GBD	GBD	WHO	CITIES	CITIES
			1996		2000	2005	2010	2009	2018	2010	2010	1990	2019	2016	2015	2015
										Low [2]	High[2]				Low [2]	High[2]
Premature deaths	All causes	Adults	34		45		30	32	31			28	20	31	35	35
		Infants			0.3		0.1					0.1	0.1			
		Workers					4									
	Lung cancer	Adults			4					3	3	4	4	3		
Working YLLs	All causes	Adults			63		30									
		Infants					4									
YLLs	All causes	Adults			486	508	302	363	344			490	302	459	427	434
		Infants			21	22	8					12	11	31		

Abbreviations: YLLs = Years of life lost.

[1] Age ranges of the population groups differ across AP-HRAs.

[2] FCAH and CITIES, include two assessments – respectively called high and low - because they each use a lower and a higher counterfactual scenario.

Table A 18 Annual morbidity per 100,000 persons and per 10 µg/m³ PM_{10} (difference between population exposure and counterfactual scenario) attributed to exposure to PM across AP-HRAs, years and counterfactual scenarios (Switzerland 2021).

Type of impact	Outcome disease	Population group [1]	STE	STE	STE	STE	GBD	GBD	WHO
			1996	2000	2005	2010	1990	2019	2016
Attacks	Asthma	Adults							
		Children	241	490	489	483			
Attacks (person-days)	Asthma	Adults	638			1,163			
Cases (incidence)	Acute bronchitis	Children							
	Chronic bronchitis	Adults	43	12	12	33			
Cases (prevalence)	Acute bronchitis	Children	463	487	480	187			
	Chronic bronchitis	Adults							
DALYs	All causes	Adults					554	409	506
		Infants					12	11	1
Hospital admissions	CVD	All	30			12			
	RD	All	13			12			
Hospital days	CVD	All		118	107	118			
	RD	All		70	65	101			
Invalidity cases	Chronic bronchitis	Adults							
Medication intake (person-days)	Asthma	Adults							
RADs	All causes	Adults	28,143	21,143	21,054	50,986			
Symptom days	RD	All							
		Children							
Work loss days	All causes	Workers				12,227			
YLDs	All causes	All					65	108	

Note: DALYs = Disability-adjusted life years. CVD = Cardio-vascular diseases. RD = Respiratory diseases. RADs = Restricted activity days YLDs = Years lived with disability.
[1] Age ranges of the population groups differ across AP-HRAs.

Concentration-response function

Table A 20 shows the CRFs in form of relative risk of both mortality and morbidity impacts attributed to outdoor PM_{10} exposure, including the lower and upper bound of the CI and re-scaled from $PM_{2.5}$ to PM_{10} (if needed).

Table A 21 shows the excess relative risk (relative risk minus one) and the corresponding ratios for morbidity outcomes. The prevalence of bronchitis in children and the restricted activity person-days (RADs) show the largest differences between STE-2000 and STE-2010 (being the STE-2010 in both cases lower). For bronchitis in children, STE-2000 carried out an own meta-analysis based on six studies (5-10), while STE-2010 based on a more recent study in nine countries (11). For RAD, STE-2010 used a different definition and an estimate from an older study than the one used in STE-2000, following WHO recommendations.

Table A 19 summarizes the main specific methodological differences among AP-HRAs.

Table A 19 Main differences in methodological approaches for the quantification of health impacts in the AP-HRAs (Switzerland 2021).

Particularities		STE	STE	STE	EEA	GBD	WHO	CITIES
Topic	Description	1996	2000	2010	2009 - 2018	1990 - 2019	2012 & 2016	2015
All-cause CRF	Aggregation of disease-specific for all-cause mortality					X	X	
	Aggregation of stratified sex- and/or sex specific mortality			X	X	X	X	X
Shape of exposure-response function	Linear exposure-response function (instead of log-linear)	X	X					
	Integrated exposure-response function for CRF					X	X	
PAF	Different concentrations across spatial units of analysis (instead of single exposure level)					X	X	X
Quantification of mortality impacts	Life table approach for premature deaths			X				
	Life table approach for YLLs			X	X			X
	Life table approach for YLLs with discount rate			X				

Notes: We excluded STE-1993, STE-2005 and FCAH from this table due to the following reasons. No information on these specific aspects of the methodology is available for STE-1993. We assumed that STE-2005 uses the same methodology as STE-2000, because STE-2005 is an update of some input data, which mainly replicate the methodology of the STE-2000. FCAH focuses on lung cancer using a very simplified method (see Supplementary Material).

Health impacts can be calculated as in Equation A 3, by multiplying the reported baseline health data and the population attributable fraction (PAF). The health data are equal to baseline health rates (per inhabitant) multiplied by the population at risk at the corresponding age Equation A 4. The PAF can be calculated for the whole population, when considering only an average concentration as in as in STE-2010 (only for morbidity), STE-2000 and EEA (Equation A 5).

Alternatively, when considering multiple exposure levels in grids (Equation A 6 and Equation A 7), PAF can be calculated using the Miettinen's formula (12) and the Levin's formula (13), but both are mathematically equivalent (14). GBD, CITIES an WHO use this PAF for multiple exposure levels (GBD and CITIES based on Miettinen's and WHO based on Levin's formulation). It should be noted that PAFs for counterfactual cases different to zero can also be referred as Potential Impact Factor (PIF) (15).

The exposure-response functions (CRF) enables the estimation of relative risk values for concentrations different to the one provided in the literature (e.g. normally 10 µg/m^3 PM). These functions can vary depending on the study. Thus, STE-2000 (ARE, BAG et al. 2004) apply Equation A 8, while STE-2010, EEA, and CITIES use Equation A 9. In contrast, GBD and WHO applies an integrated exposure response function to derive the relative risk (Equation A 10). FCAH uses a very simplified method based on excess rates as in Equation A 11.

STE 2010 applies a life table approach for assessing premature deaths and years of life lost considering separately adult males, adult females and infants. STE-2000 and consequently the short update for 2005 as well as EEA and CITIES use this life table approach for assessing years of life lost. This life table approach involve more numerous and more complex calculations as the general approach presented in the equations above. Therefore, such equations are not normally published, being EEA an exception.

Equation A 3 Health impact.

$$I = H_B * PAF_E$$

I = Assessed health impact of an air pollution exposure E.
H_B = Baseline health data (e.g. reported annual hospital days due to respiratory diseases in Switzerland) including the effect of exposure.
AF_E= Attributable fraction for an exposure E. By definition: 1- H_A/H_B, being H_A the initial baseline health data without the effect of exposure E.

Equation A 4 Baseline health data.

$$H_B = HR_B * PR$$

H_B = Baseline health rate.
HR_B = Baseline health rate, normalized by population (at risk).
PR = Population (at risk), i.e. population within a specific age range determined by the denominator of the baseline health rate.

Equation A 5 Population attributable fraction for single concentration level as in STE-2010 (for morbidity) (16), STE-2000 (17) and EEA (18).

$$PAF_E = 1 - \frac{1}{RR_E}$$

PAF_E = Population attributable fraction for an exposure E.
RR_E = Relative risk for an exposure E.

Equation A 6 Population attributable fraction for multiple concentration levels based on Miettinen's formula as in GBD (19) and CITIES (20).

$$PAF_E = \frac{\sum P_{B,i} * RR_i - \sum P_{A,i} * RR_i}{\sum P_{B,i} * RR_i}$$

PAF_E = Population attributable fraction for an exposure E.
$P_{B,i}$ = Proportion of the population for a population exposure i.
$P_{A,i}$ = Proportion of the population in the counterfactual case at concentration level i (normally equals to 1 for outdoor air pollution, i.e. 100% of people are exposed to counterfactual scenario) .
RR_i = Relative risk in concentration level i.

Equation A 7 Population attributable fraction for multiple concentration levels based on Levin's formula as in WHO (21).

$$PAF_E = \frac{\sum P_i * (RR_i - 1)}{1 + \sum P_i * (RR_i - 1)}$$

PAF_E = Population attributable fraction for an exposure E.
P_i = Proportion of the population at concentration level i.
RR_i = Relative risk in concentration level i.

Equation A 8 Concentration-response function as in STE-2000 (17).

$$RR_E = 1 + \frac{(RR_D - 1)}{D} * (C_B - C_A)$$

RR_E = Relative risk for an exposure E.
RR_D = Relative risk for a difference in concentration D as in the literature.
D = Difference in concentration of the relative risk as in the literature (e.g. 10 in $\mu g/m^3$ for PM).
C_B = Population-weighted concentration of the pollutant (population exposure).
C_A = Minimum considered concentration (counterfactual scenario).

Equation A 9 Concentration-response function as in STE-2010 (22), EEA (23), and CITIES (20).

$$RR_E = e^{\frac{\ln(RR_D)}{D}*(C_B - C_A)}$$

RR_D = Relative risk for a concentration D as in literature.
D = Difference in concentration of the relative risk as in the literature (e.g. 10 in μg/m^3 for PM).
C_B = Population-weighted concentration of the pollutant (population exposure).
C_A = Minimum considered concentration (counterfactual scenario).

Equation A 10 Concentration-response function based in integrated exposure-response function as in GBD (19) and WHO (21).

$$RR_E = 1 + x * \left(1 - e^{y*(C_B - C_A)^z}\right)$$

C_B = Population-weighted concentration of the pollutant (population exposure).
C_A = Minimum considered concentration (counterfactual scenario).
x, y , z = Parameters estimates of the integrated exposure-response function.

Equation A 11 Health impacts as in FCAH (24).

$$I = PR * HR_B * ln(RR_D) * \frac{(C_B - C_A)}{D}$$

I = Assessed health impact of an air pollution exposure E.
HR_B = Baseline health rate (i.e. by population)
PR = Population at risk (population within a specific age range determined by the denominator of the baseline health rate).
RR_D = Relative risk for a difference in concentration D as in the literature.
D = Difference in concentration of the relative risk as in the literature (e.g. 10 in μg/m^3 for PM).
C_B = Population-weighted concentration of the pollutant (population exposure).
C_A = Minimum considered concentration (counterfactual scenario).

Table A 20 Relative risk coefficients per 10 µg/m³ PM_{10} (including lower and upper bound between squared brackets) across AP-HRAs, years (Switzerland 2021).

Type of impact	Outcome disease	Population group [1]	STE	STE	STE	STE	EEA	FCAH	GBD	CITIES
			1993	1996	2000 & 2005	2010	2009 - 2018	2010	1990 - 2019	2015
Premature deaths or YLLs	All causes	Adults	1.044	1.043 [1.026; 1.061]	1.059 [1.031; 1.088]	1.045 [1.029; 1.060]	1.045 [1.029; 1.060]			1.051 [1.029; 1.065]
		Infants			1.056 [1.026; 1.088]	1.04 [1.02; 1.07]				
	Lung cancer	Adults			1.106 [1.042; 1.174]			1.060 [1.020; 1.080]	1.112 [1.063; 1.129]	
Attacks	Asthma	Adults		1.044 [1.027; 1.062]	1.029 [1.013; 1.045]	1.029 [1.013; 1.045]				
		Children		1.039 [1.019; 1.059]		1.028 [1.006; 1.051]				
Cases (incidence)	Chronic bronchitis	Adults		1.098 [1.009; 1.194]	1.051 [1; 1.150]	1.117 [1.040; 1.189]				
Cases (prevalence)	Acute bronchitis	Children		1.306 [1.135; 1.502]	1.353 [1.095; 1.671]	1.080 [0.980; 1.190]				
Hospital admissions	CVD	All		1.012 [1.007; 1.019]		1.007 [1.001; 1.012]				
	RD	All		1.013 [1.001; 1.025]		1.014 [0.999; 1.029]				
Hospital days	CVD	All	1.009		1.007 [1.004; 1.009]					
	RD	All	1.015		1.008 [1.006; 1.011]					
RADs	All causes	Adults	1.105	1.094 [1.079; 1.109]	1.094 [1.080; 1.110]	1.034 [1.030; 1.038]				
Work loss days	All causes	Workers	1.105			1.033 [1.028; 1.038]				

Abbreviations: YLLs = Years of life lost. CVD = Cardio-vascular diseases. RD = Respiratory diseases. RADs = Restricted activity person-days.

[1] Age ranges of the population groups differ across AP-HRAs.

Table A 21 Mean excess relative risk of morbidity impacts across AP-HRAs, years expressed as per 10 µg/m³ PM_{10} and as a ratio in relation to the reference value (most recent STE, in bold). The ratio is calculated by dividing the AP-HRA value by the reference value (Switzerland 2021).

Type of impact	Outcome disease	Population group [1]	STE	STE	STE	STE	EEA	FCAH	GBD	CITIES
			1993	1996	2000&2005	2010	2009-2018	2010	1990-2019	2015
Mean excess relative risk per 10 µg/m³ PM_{10}										
Attacks	Asthma	Adults		0.044	0.029	0.029				
		Children		0.039		0.028				
Cases (incidence)	Chronic bronchitis	Adults		0.098	0.051	0.117				
Cases (prevalence)	Acute bronchitis	Children		0.306	0.353	0.080				
Hospital admissions	CVD	All		0.012		0.007				
	RD	All		0.013		0.014				
Hospital days	CVD	All	0.009		0.007					
	RD	All	0.015		0.008					
RADs	All causes	Adults	0.105	0.094	0.094	0.034				
Work loss days	All causes	Workers	0.105			0.033				
Ratio in relation to reference value (last STE) [2]										
Attacks	Asthma	Adults		1.52	1.00	1				
		Children		1.39		1				
Cases (incidence)	Chronic bronchitis	Adults		0.84	0.44	1				
Cases (prevalence)	Acute bronchitis	Children		3.82	4.41	1				
Hospital admissions	CVD	All		1.71		1				
	RD	All		0.93		1				
Hospital days	CVD	All	1.29		1					
	RD	All	1.87		1					
RADs	All causes	Adults	3.09	2.76	2.76	1				
Work loss days	All causes	Workers	3.18			1				

Abbreviations: YLLs = Years of life lost. CVD = Cardio-vascular diseases. RD = Respiratory diseases. RADs = Restricted activity person-days.

[1] Age ranges of the population groups differ across AP-HRAs.

[2] Examples for interpretation of the ratio: 1.1 = 1.1 times the ref. value = 10% higher. 2.0 = 2 times the ref. value = 100% higher. 0.4 = 0.4 times the ref. value = 60% lower.

Table A 22 shows the CRFs in form of relative risks of the EEA and GBD before and after re-scaling using the equation above .

Table A 22 Relative risks before and after re-scaling from $PM_{2.5}$ to PM_{10} (Switzerland 2021).

Author	Type of impact	Outcome disease	Population group	Relative risk per 10µg/m³	
				$PM_{2.5}$	PM_{10} (re-scaled)
EEA	Premature deaths	All causes	Adults	1.062 [1.04; 1.083]	1.045 [1.029; 1.06]
CITIES	Premature deaths	All causes	Adults	1.07 [1.04; 1.09]	1.051 [1.029; 1.065]
GBD	Premature deaths	Lung cancer	Adults	1.155 [1.086; 1.179]	1.112 [1.063; 1.129]

Baseline health data among population at risk

Table A 23 and Table A 24 show the age ranges of population at risk for mortality and morbidity outcomes respectively. Regarding morbidity, the previous STEs had higher numbers in the baseline health data than STE-2010 except for: bronchitis and restricted activity person-days in STE-2000; asthma and bronchitis in children in STE-1996; and hospital days due to cardiovascular diseases and restricted activity person-days for STE-1993, which report lower values than in STE-2010.

Furthermore, the main divergences can be found in the definition of adult and children for asthma and bronchitis. STE-2010 considered as adults people at the age 18 or older, while the previous STEs assumed 15 years old or older for asthma and 25 for bronchitis. Children were considered to be between 5 and 17 years old for STE-2010 and younger than 15 for previous STEs.

Table A 23 Mortality outcomes assessed and age groups assessed in the selected AP-HRAs (empty cells show non-assessed outcomes) (Switzerland 2021).

Type of impact	Outcome disease	Population group	STE	STE	STE	STE	STE	EEA	FCAH	GBD [1]	WHO	CITIES
			1993	1996	2000	2005	2010	2009-2018	2010	1990-2019	2012 & 2016	2015
Premature deaths	All causes	Adults	≥30	≥30	≥30		≥30	≥30		≥30	≥25	≥20
		Infants			<1		<1			<1	<5	
		Workers					30-85					
	Lung cancer	Adults			≥30				≥30	≥30	≥25	
Working YLLs	All causes	Adults			≥30		≥30					
		Infants					<1					
YLLs	All causes	Adults			≥30	≥30	≥30	≥30		≥30	≥25	≥20
		Infants			<1	<1	<1			<1	<5	

Abbreviations: YLLs = Years of life lost.

[1] The GBD data set contains assessments for more than 350 causes (diseases) and more than 50 age ranges. This table only shows diseases and ages that are comparable to other selected AP-HRAs.

Table A 24 Morbidity outcomes assessed and ages assessed in the selected AP-HRAs (empty cells show non-assessed outcomes) (Switzerland 2021).

Type of impact	Outcome disease	Population group	STE	STE	STE	STE	STE	GBD [1]	WHO
			1993	1996	2000	2005	2010	1990-2019	2012 & 2016
Attacks	Asthma	Adults		≥15	≥15	≥15	≥18		
Attacks	Asthma	Children		<15			5-17		
Attacks (person-days)	Asthma	Adults	≥15						
Cases (incidence)	Acute bronchitis	Children	<15						
Cases (incidence)	Chronic bronchitis	Adults		≥25	≥25	≥25	≥18		
Cases (prevalence)	Acute bronchitis	Children		<15	<15	<15	5-17		
Cases (prevalence)	Chronic bronchitis	Adults	≥25						
DALYs	All causes	Adults						≥30	≥25
DALYs	All causes	Infants						<1	<5
Hospital admissions	CDV	All		All			All		
Hospital admissions	RD	All		All			All		
Hospital days	CDV	All	All		All	All	All		
Hospital days	RD	All	All		All	All	All		
Invalidity cases	Chronic bronchitis	Adults	≥25						
Medication intake (person-days)	Asthma	Adults	≥15						
RADs	All causes	Adults	≥20	≥20	≥20	≥20	≥18		
Symptom days	RD	Children	<15						
Symptom days	RD	All	All						
Work loss days	All causes	Workers	≥15				≥15		
YLDs	All causes	All						All	

Abbreviations: DALYs = Disability-adjusted life years. RADs = Restricted activity person-days. YLDs = Years lived with disability. CVD = Cardio-vascular diseases. RD = Respiratory diseases.

[1] The GBD data set contains assessments for 364 diseases and 58 age ranges. This table only shows diseases and ages that are comparable to other AP-HRAs.

Table A 25 Morbidity baseline health data expressed as per 100,000 all-age persons and as a ratio in relation to the reference value (most recent STE). The ratio is calculated by dividing the AP-HRA value by the reference value (Switzerland 2021).

Type of impact	Outcome disease	Population group [1]	STE	STE	STE	STE	FCAH	CITIES
			1993	1996	2000	2010	2010	2015
Baseline health data								
Attacks	Asthma	Adults		17,337	17,471	17,199		
		Children		5,766		42,817		
Cases (incidence)	Chronic bronchitis	Adults		502	248	319		
Cases (prevalence)	Acute bronchitis	Children		2,161	1,926	2,545		
Hospital admissions	CVD	All		2,471		1,862		
	RD	All		1,033		895		
Hospital days	CVD	All	10,894		17,936	17,897		
	RD	All	7,573		8,361	7,449		
RADs	All causes	Adults	400,134		251,241	1,556,074		
Ratio in relation to reference value (last STE) [2]								
Attacks	Asthma	Adults		1.01	1.02	1		
		Children		0.13		1		
Cases (incidence)	Chronic bronchitis	Adults		1.57	0.78	1		
Cases (prevalence)	Acute bronchitis	Children		0.85	0.76	1		
Hospital admissions	CVD	All		1.33		1		
	RD	All		1.15		1		
Hospital days	CVD	All	0.61		1	1		
	RD	All	1.02		1.12	1		
RADs	All causes	Adults	0.26		0.16	1		

Abbreviations: YLLs = Years of life lost. CVD = Cardio-vascular diseases. RD = Respiratory diseases. RADs = Restricted activity person-days.

Note: We did not found baseline health data in EEA, GBD and WHO.

[1] See age ranges of the population groups, which differ across AP-HRAs.

[2] Examples for interpretation of the ratio: 1.1 = 1.1 times the ref. value = 10% higher. 2.0 = 2 times the ref. value = 100% higher. 0.4 = 0.4 times the ref. value = 60% lower.

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5. DISCUSSION

The following discussion on the health effects of traffic-related air pollution regarding diabetes and stroke and the methods of health risk assessments shall be reflected under consideration of the initially introduced public health action cycle to show how research should shape policy.

5.1 Public Health Action Cycle

Research and policy-making are interactive and iterative, and policies may change as evidence evolves (Samet, 2000). Initially, I proposed to use the concept of the Public Health Action Cycle by Rosenbrock et al. (1995) to illustrate the constant cycle between problem definition or assessment, strategy formulation, implementation and evaluation (see).

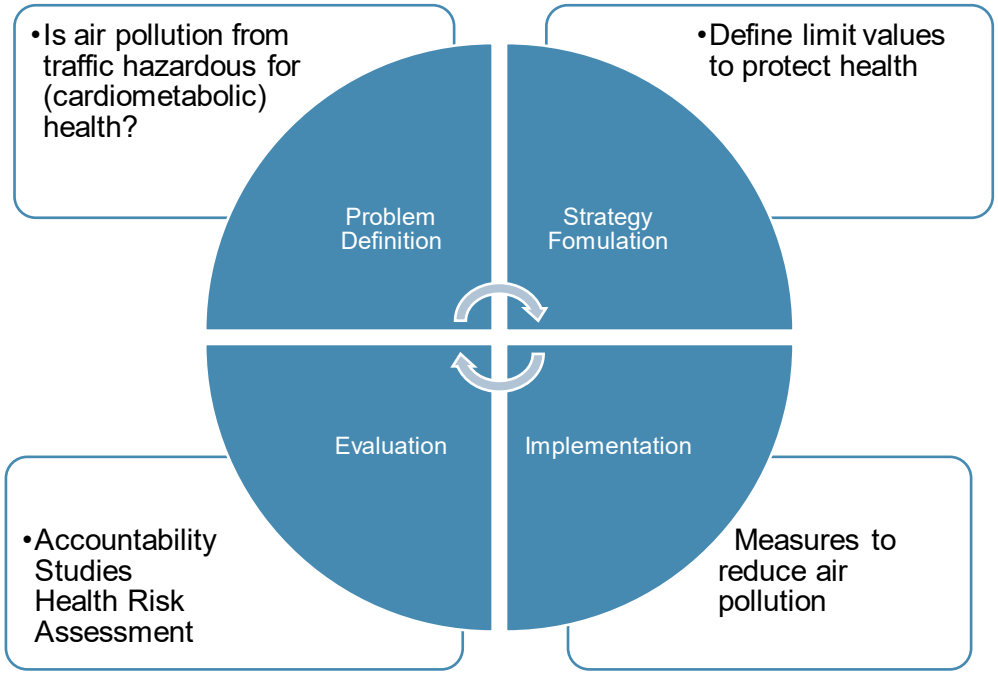

Fig. 5.1: Public Health Action Cycle (own figure).

Künzli and Perez (2009) have introduced the concept of evidence based public health similar to the paradigm of evidence based medicine, in 2009. They developed the following steps mirroring the steps in patient treatment in clinical work: cause(s) (inner Box A) of health problems (B) result in a doctors' diagnosis. The assessment of the overall situation of the patient (C) determines the treatment strategy (D) to positively affect the causes. In public health, some "exposure" (A) may cause health problems in the population (B). The assessment of its

relevance (C) may result in a policy (D) to abate the exposure (A) and improve public health (B) (Fig. 5.2) (Künzli & Perez, 2009).

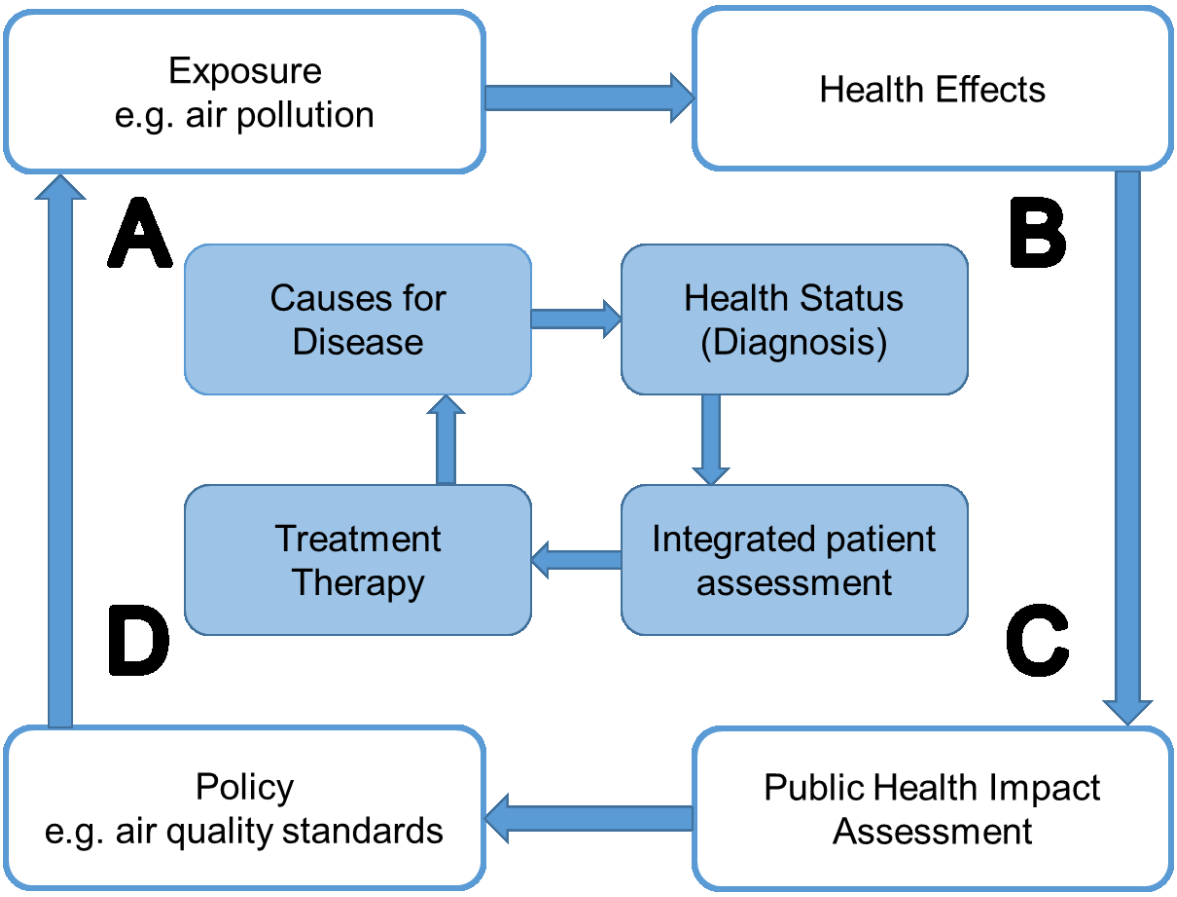

Fig. 5.2: Evidence based public health cycle (own figure adapted from Künzli and Perez (2009)).

The concept or cycle is similar to the public health action cycle but differs in the placement order of the health risk assessment and lacks the explicit step to evaluate effectiveness of measures taken. In the public health action cycle the last step from the policy to abatement of exposure and improvement of public health is comprised in the evaluation step, with accountability studies showing the effect of the measures taken.

The paper of Künzli and Perez (2009) was only discovered during the course of the thesis. It appears that health risk assessment serves as a crucial step in comprehending the relevance of various risk factors to public health. This bridges the gap between problem definition and strategy formulation by assessing the relevance of the problem. However, the concept is less refined regarding the policy to action and impact path. Of course, one can argue that health risk assessments should be part of the problem definition. However, I consider it to be a crucial part of giving arguments to take action. Therefore, I propose a public health evidence based action

cycle combining both cycles with six steps to be a good model for public health (air pollution) policy making (Fig. 5.3).

The former problem definition comprises the study of exposures to a risk factor (1) and their health effects (2). In a next step the relevance of this risk factor for the health on the population level is calculated in a health risk assessment (3). This informs policy makers, whether to take action if the problem is relevant or big enough compared to other risk factors to take action. Strategies (4) to reduce or abate the risk factor are developed and measures (5) are taken or implemented. Evaluation (6) should reveal whether the actions taken were successful to reduce or eliminate the underlying risk factor and whether health improved.

Fig. 5.3: A new evidence based Public Health Action Cycle for environmental risk policy setting (own figure).

Following this cycle, the results of the papers comprised in this thesis and its policy implications are discussed.

5.2 Relevance of traffic-related air pollution for Public Health

5.2.1 Exposure

Exposure to a specific risk factor is part of the Public Health Action Cycle's problem definition. The traffic sector is an important source of air pollution. In 2022, the contribution of traffic to emissions of PM_{10}, $PM_{2.5}$, NO_x, CO and Black Carbon in Germany were 19.2%, 26.5%. 39.9%, 32.3%, and 47.8% (Umweltbundesamt, 2022) (see Fig. 1.3). In Switzerland the contributions to emissions of PM_{10}, $PM_{2.5}$, NO_x, CO and Black Carbon were 31%, 23% 56% 43% and 23% in 2021 (Eidgenössische Kommission für Lufthygiene (EKL), 2023). TRAP emissions from the transportation sector have declined very substantially during the past several decades in most high-income countries mainly due to impressive improvements in motor vehicle technologies and fuels (Public Health Action Cycle: Implementation) as well as aggressive regulatory actions (Public Health Action Cycle: Policy) to combat TRAP emissions (HEI Panel on the Health Effects of Long-Term Exposure to Traffic-Related Air Pollution, 2022). Although some countries like China and also India have made progress in controlling motor vehicle emissions, motor vehicle emissions in many other low- and middle- income countries are quite high due for example to lower emission standards and fuel quality standards (e.g. regarding its sulfur content, see Public Eye (2016)). Additionally, decreases in emissions from individual motor vehicles, while substantial, do not fully compensate for the rapid growth and increased vehicular congestion of the motor vehicle fleet due to population growth, urbanization, and economic activity, as well as to the continued presence of older or malfunctioning vehicles on the roads (HEI Panel on the Health Effects of Long-Term Exposure to Traffic-Related Air Pollution, 2022).

The adoption of new technologies such as electric vehicles, will certainly reduce local tail-pipe emissions, however non-tailpipe emissions will not be affected. Thus, brake wear and tire wear, which are considered especially toxic due to their high content of metals and high oxidative potential (Piscitello et al., 2021), as well as road wear, will still be emitted with the electrification of the transport sector (Amato et al., 2014). In high-income countries, non-tailpipe emissions comprise over half of the PM from traffic (Piscitello et al., 2021). Since electric vehicles tend to be heavier and the trend still goes towards larger cars, their share is even expected to rise disproportionally. The overall environmental benefit of electric vehicles is closely tied to the degree of decarbonization of the electric grid: the more renewable or clean the source of energy is, the smaller the climate footprint and lastly emissions of electric vehicles will be (HEI Panel on the Health Effects of Long-Term Exposure to Traffic-Related Air Pollution, 2022).

Therefore, despite improvements in air quality related to reduced motor vehicle (tail-pipe) emissions concerns about TRAP and their impact on human health, even at reduced levels, are likely to continue in the near and medium-term.

5.2.2 Health effects: Traffic-related air pollution and diabetes and stroke

Understanding health effects of a risk factor is part of the Public Health Action Cycle's problem definition. Multiple health outcomes are associated with air pollution, as well as source specific air pollution from traffic as was shown in the overarching systematic review report of selected health effects of long-term exposure to traffic-related air pollution (Fig. 5.5) (HEI Panel on the Health Effects of Long-Term Exposure to Traffic-Related Air Pollution, 2022). Paper I and II have shown, that traffic-related air pollution is associated with diabetes and stroke with moderate and low to moderate evidence.

More evidence with particulate matter

Newer studies support these findings. The diabetes paper and updated search and analysis showed additional to the significantly elevated risk of diabetes prevalence in association with NO_2 strengthened associations with $PM_{2.5}$ and diabetes incidence (RR 1.09; 95%-CI: 0.99-1.20) and reduced confidence intervals in general (Fig. 5.4).

More recent publications of large cohort data support the findings. The UK-Biobank analysis including over 390,000 adults found significantly increased diabetes incidence risks with $PM_{2.5}$ HR 1.05 (95%-CI: 1.01-1.10) per 1.3 µg/m^3 and with NO_2 HR 1.07 (1.02-1.11) per 9.8 µg/m^3 (Hu et al., 2023). These were assessed in land use regression models. The analysis of over 10 million cases of diabetes (incidence) in the US Medicare cohort showed that the risk for first diabetes occurrence was increased by HR 1.074 (95%-CI 1.058; 1.089) for 5 µg/m^3 increase in $PM_{2.5}$, and 1.055 (95%-CI 1.050; 1.060) for 5 ppb (9.4 µg/m^3) increase in NO_2 (Yitshak Sade et al., 2023). However, the high resolution exposure assessments were aggregated at ZIP code level and thus for rural areas rather coarse and not as informative on TRAP exposure as the studies included in the HEI review. Nevertheless, newer studies seem to further strengthen associations with exposure to $PM_{2.5}$.

Compared to the diabetes analysis, the stroke analysis did not find associations with NO_2 or NO_x, however elevated risks with EC and PM-measures. In the extended analysis the association with $PM_{2.5}$ and stroke were strengthened as well and became significantly elevated (RR 1.12; 95%-CI: 1.03-1.21 per 5 µg/m^3), while the NO_2 association was slightly strengthened becoming RR >1.00, but still including unity. Where a distinction between fatal and non-fatal cases were possible, associations seemed stronger with fatal cases and exposure to NO_2 and NO_x (Appendix Paper II Fig. 2 A and B).

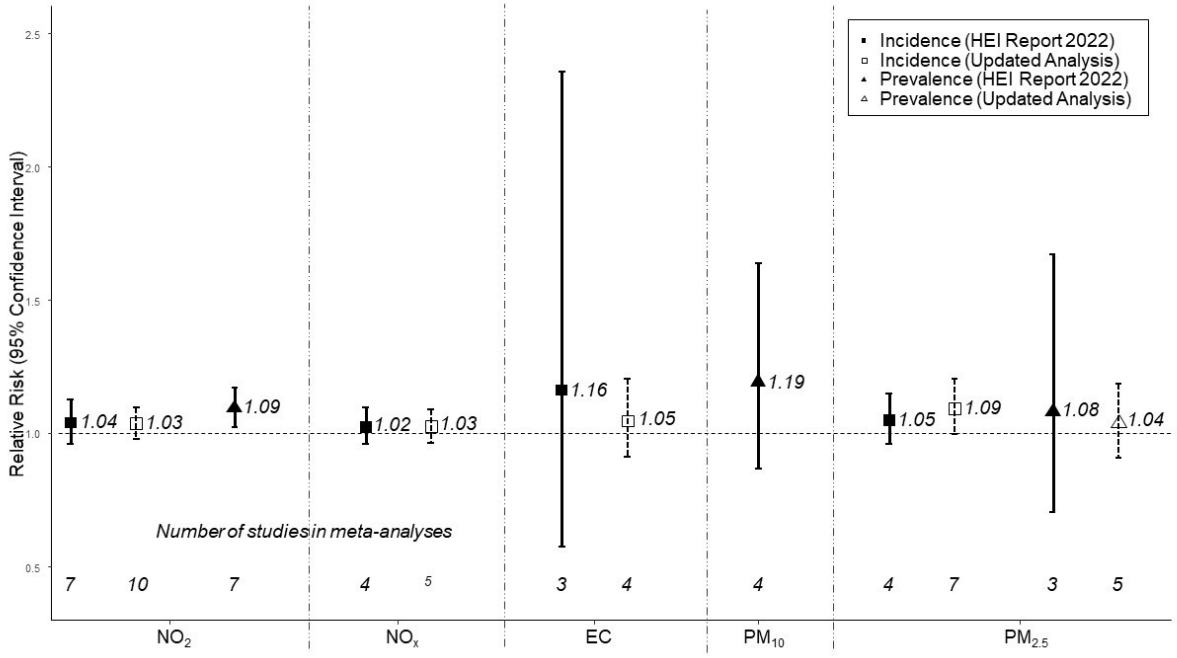

Fig. 5.4: Comparison of meta-analytic results of associations between traffic-related air pollutants and diabetes incidence (squares) and prevalence (triangles) from original analyses including studies up to July 2019 (HEI Report filled triangle/square) and the updated analysis including studies up to May 2022 (Updated Analysis empty triangle/square) (Supplementary figure from (Kutlar Joss et al., 2023)).

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. No new studies were added from the update for the prevalence analysis with NO_2 and PM_{10}.

Abbreviations: EC, elemental carbon (soot); NO_2, nitrogen dioxide, NO_x, nitrogen dioxide and nitric oxide; PM_{10}, particulate matter with aerodynamic diameter ≤ 10 µm; $PM_{2.5}$, particulate matter with aerodynamic diameter ≤ 2.5 µm; µg/m^3; microgram per cubic meter.

The separate analysis of data on stroke mortality within the same review project combining six studies only showed slightly elevated risks with NO_2 exposure including unity (RR 1.01; 0.98-1.04), whereas the association with $PM_{2.5}$ was significantly elevated (RR 1.04; 1.01-1.07), combining three studies (Table 5.1) (Boogaard et al., 2022; HEI Panel on the Health Effects of Long-Term Exposure to Traffic-Related Air Pollution, 2022). The overall confidence in an association of stroke mortality with TRAP was judged to be low to moderate whereas mortality due to all cardiovascular diseases and ischemic heart disease showed high confidence in an association. Additionally, the quality of the evidence and confidence for an association of outcomes relating to ischemic heart disease showed a stronger, i.e. moderate, evidence compared to the stroke analysis, based on consistent associations with PM_{10} with evidence suggesting a monotonic exposure-response function, and suggestive evidence for an association with EC and $PM_{2.5}$ (Table 5.1).

Table 5.1: Overall confidence assessment and meta-analytical summary estimates with confidence intervals of associations between long-term exposure to the most common traffic-related air pollutants and selected cardiometabolic and mortality outcomes adapted from (Boogaard et al., 2022). (Note: the individual pollutants are considered as indicators of TRAP)

Health outcome		Overall confidence assessment	NO_2 per 10 µg/m³		EC per 1 µg/m³		$PM_{2.5}$ per 5 µg/m³	
			N	Relative risk	N	Relative risk	N	Relative risk
Cardiometabolic outcomes	**Stroke events (incidence)**	Low-to-moderate	7	0.98 (0.92;1.05)	6	1.03 (0.98;1.09)	4	1.08 (0.89;1.32)
	Ischemic heart disease events	Moderate	5	0.99 (0.94;1.05)	5	1.01 (0.99;1.03)	4	1.09 (0.86;1.39)
	Diabetes Incidence	Moderate	7	1.04 (0.96;1.13)	3	1.16 (0.57;2.36)	4	1.05 (0.96;1.15)
	Diabetes Prevalence		7	1.09 (1.02;1.17)	<3	NA	3	1.08 (0.70;1.67)
Mortality	**All–cause**	High	11	1.04 (1.01;1.06)	11	1.02 (1.00;1.04)	12	1.03 (1.01;1.05)
	Circulatory	High	10	1.04 (1.00;1.09)	9	1.02 (1.00;1.04)	11	1.04 (1.01;1.08)
	Ischemic heart disease	High	6	1.05 (1.03;1.08)	6	1.05 (0.99;1.11)	7	1.07 (1.04;1.10)
	Stroke	Low-to-moderate	6	1.01 (0.98;1.04)	<3	NA	3	1.04 (1.01;1.07)

Abbreviations: m^3, cubic meter; µg, microgram; EC, elemental carbon (measure for soot); NO_2, nitrogen dioxide; $PM_{2.5}$, particulate matter with aerodynamic diameter ≤ 2.5 µm; N, number of studies included in meta-analysis; NA, not applicable; TRAP, traffic-related air pollution.

Possible mechanisms

Both outcomes show more or strengthening evidence for associations with particulate matter. Several mechanisms that are proposed for environmental exposures to take effect on health (Peters et al., 2021) are also mentioned for the pathway from exposure to air pollution to the development of diabetes and stroke. Especially oxidative stress and subclinical inflammation are discussed in this context (Gorini et al., 2021; Kulick et al., 2023).

Mechanisms described for $PM_{2.5}$ linking it to diabetes include inducing oxidative stress due to increased production of reactive oxygen species (Rajagopalan & Brook, 2012), triggering systemic oxidative stress (Gangwar et al., 2020), inducing visceral adipose tissue inflammation,

and further leading to insulin resistance and metabolic dysfunction (Li et al., 2023; Lim & Thurston, 2019). Other possible mechanisms include a disturbed autonomic nervous system, endothelial dysfunction (Münzel et al., 2018), alteration of the gut microbiome (Zhao et al., 2022), and mitochondrial dysfunction (Mudway et al., 2020; Xu et al., 2011).

A link between vascular inflammation and indicators for insulin resistance (e.g. HOMA-IR, Adiponectin, Leptin) was recently demonstrated in a panel of Chinese adults (Xu et al., 2022). Up to 66% of the short-term air pollution associated increase of markers for insulin resistance was mediated by markers of inflammation, such as IL-2, osteoprotegerin. Adiponectin was found the sole relevant mediator of diabetes incidence and air pollution in a German cohort, suggesting a relevant role in the pathway to diabetes (Lucht et al., 2020).

For stroke, important intermediate risk factors (Kulick et al, 2023; Münzel et al, 2018) such as atherosclerosis, hypertension, arrhythmias and a change in blood coagulability are judged to be causally related with exposure to particulate matter in the US EPA integrated science assessment for particulate matter (U.S. EPA, 2019). Munzel et al. (2017) describes oxidative stress and inflammation as underlying mechanisms for these intermediate outcomes that are on the pathways to stroke. Particle translocation and resulting platelet aggregation and activation, as well as sensory receptor activation resulting in autonomic nervous system imbalance, are also reported as underlying possible mechanisms (Kulick et al., 2023).

NO_x and possible confounding by noise

While the bulk of mechanistic studies concentrate on possible mechanisms with particulate matter exposure, mechanistic studies on NO_2 are scarce (Forastiere & Peters, 2021). It can be argued that NO_2 could be an indicator for other highly correlated pollutants or exposures from the same source. A study with Danish national cohort data and high resolution dispersion modelling exposure assessment indicated significantly increased diabetes incidence risk with $PM_{2.5}$, EC, NO_2 and UFP (PNC 10-10000 nm), and additionally with noise (Sorensen et al., 2022). The multi-pollutant model including the four air pollution indicators resulted in significantly elevated risks with UFP and NO_2 exposure, while the EC and $PM_{2.5}$ results were reduced including unity. When studying the traffic specific contributions in the four-pollutant models, only traffic UFP remained associated with higher risk of diabetes in all models, whereas traffic NO_2 was reduced to unity following adjustment for traffic UFP or traffic EC. The authors concluded, that this could indicate that for air pollution emitted from local traffic, particulate matter is the main causative agent. Additionally, the effect estimate for total NO_2 exposure in multi-pollutant models including noise and greenspace was markedly reduced. The authors suggest, that “this lends some support to the hypothesis that NO_2 is not the main causal agent with regard to increasing diabetes risk, but rather a proxy of other traffic-related pollutants, e.g. road traffic noise” (Sorensen et al., 2022).

Table 5.2: Effect estimates of studies reporting on the association of traffic-related air pollution and diabetes incidence or prevalence in single- and noise adjusted models.

Reference	Study Name	Pollutant	Incidence or prevalence	Effect measure	Increment	Single pollutant results	Noise adjusted
Clark, 2017	British Columbia Diabetes Cohort	NO	Incidence	odds ratio (OR)	13.13 µg/m^3	1.04 (1.01, 1.05)	1.01 (1.00, 1.04)
Eze, 2014	SAPALDIA	NO_2	Prevalence	odds ratio (OR)	10 µg/m^3	1.21 (1.05, 1.39)	1.19 (1.03, 1.38)
Eze, 2017	SAPALDIA	NO_2	Incidence	relative risk (RR)	15 µg/m^3	0.92 (0.67, 1.26)	0.86 (0.61, 1.22)
Renzi, 2018	Rome Longitudinal	NO_2	Incidence	hazard ratio (HR)	10 µg/m^3	1.00 (1.00, 1.01)	1.00 (0.99, 1.01)
Renzi, 2018	Rome Longitudinal	NO_2	Prevalence	odds ratio (OR)	10 µg/m^3	1.00 (1.00, 1.01)	1.01 (1.00, 1.02)
Renzi, 2018	Rome Longitudinal	NO_x	Incidence	hazard ratio (HR)	20 µg/m^3	1.01 (1.00, 1.01)	1.01 (1.00, 1.02)
Renzi, 2018	Rome Longitudinal	NO_x	Prevalence	odds ratio (OR)	20 µg/m^3	1.01 (1.00, 1.01)	1.02 (1.01, 1.02)

Abbreviations: HR, hazard ratio; m, meter; m^3, cubic meter; ng, nanogram; NO, nitric oxide; NO_2, nitrogen dioxide; NO_x, nitrogen dioxide and nitric oxide; OR, odds ratio; PAH (BaP), polycyclic aromatic hydrocarbon (benzo(a)pyrene); PM_{10}, particulate matter with an aerodynamic diameter smaller or equal to 10 micrometer mass concentration; $PM_{2.5}$, particulate matter with an aerodynamic diameter smaller or equal to 2.5 micrometer mass concentration; $PM_{2.5abs}$, light absorption on $PM_{2.5}$ (soot); PM_{coarse}; particulate matter with an aerodynamic diameter between 2.5 and 10 micrometer; vs., versus; SAPALDIA, Swiss cohort study on Air Pollution and Lung Disease In Adults; µg/m^3, microgram per cubic meter.

Yet, the results of the studies included in the review on diabetes including noise in multi-pollutant models with NO_2 or NO_x showed only some attenuation of the effect estimates upon noise adjustment. For example the NO_2 diabetes 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 (Eze et al., 2014) (Table 5.2). The only noise adjusted stroke analysis of NO_2 by (Sorensen et al., 2014) showed strengthened estimates for fatal strokes (IRR 1.47 (1.21-1.80) to 1.90 (1.45-2.47)) but no association with ischemic strokes after noise adjustment (1.11 (1.03-1.20) to 1.02 (0.92-1.12)).

As Vienneau et al. (2023) discuss in their combined analysis of mortality with noise and air pollution exposure (note: not diabetes or stroke) in a Swiss administrative cohort, differences in the quality, specification or resolution of the country specific noise models may play a role regarding the possibility of effect transfer, i.e. when the effect from the less well measured exposure is transferred to (or mopped up by) the better measured one. In their analysis with comparable model quality, air pollution effects modelled with hybrid land-use regression models were more attenuated upon inclusion of noise than vice versa. The NO_2 effect estimates reduced from 1.051 (1.031-1.072) to 1.024 (1.003-1.046) per 10 µg/m^3 NO_2 upon inclusion of total noise and 1.020 (0.998-1.042) upon inclusion of traffic noise. The corresponding traffic noise effect estimates where 1.058 (1.045-1.071) in the single pollutant model and 1.053 (1.039-1.067) in the NO_2-adjusted model. Overall, effects with BC and iron in $PM_{2.5}$ were still significantly elevated, indicating independent effects of air pollution and noise exposure on mortality, but the reduced effect estimates were interpreted as air pollution effects in single pollutant models partially to be related to noise exposure.

Thus, noise could partially confound effects of TRAP with diabetes and stroke. However, the available evidence suggests still a role of TRAP in diabetes and stroke morbidity.

Outcome classification

Kulick et al. (2023) discuss challenges of outcome classification especially for stroke morbidity as stroke can be mild or more severe, while the former is often not diagnosed or misdiagnosed. Research data based on administrative or register data show this distinctive weakness in outcome classification (Kulick et al., 2023). It is likely, that different pathophysiologic mechanisms are more important for different stroke subtypes and that the combination may underestimate the true association between air pollution and stroke, according to the authors. However, the results of studies that have tried to disentangle effects on hemorrhagic versus ischemic stroke have not been entirely consistent. Again, this could be attributed to outcome misclassification.

Paper I argued similarly regarding the seemingly missing link of TRAP with diabetes incidence. While there was no significant association in the original meta-analyses, it was pointed out that

studies with in-depth study center examinations have a much higher sensitivity. This could be attributed to the long oligosymptomatic prediagnostic phase of diabetes missing cases that rely on doctor diagnosis or administrative data. Studies using a more rigorous case ascertainment method tended to show elevated incidence risks with TRAP. Thus bias due to outcome misclassification was reduced and the updated analysis with $PM_{2.5}$ even showed significantly elevated diabetes incidence risks.

Evidence for inclusion in HRA

The HEI TRAP review and its resulting papers have shown that the evidence for an association of TRAP is high for various mortality outcomes, the development of asthma and lower respiratory infections and moderate for health endpoints such as diabetes, ischemic heart disease events and birth outcomes (Fig. 5.5) (HEI Panel on the Health Effects of Long-Term Exposure to Traffic-Related Air Pollution, 2022).

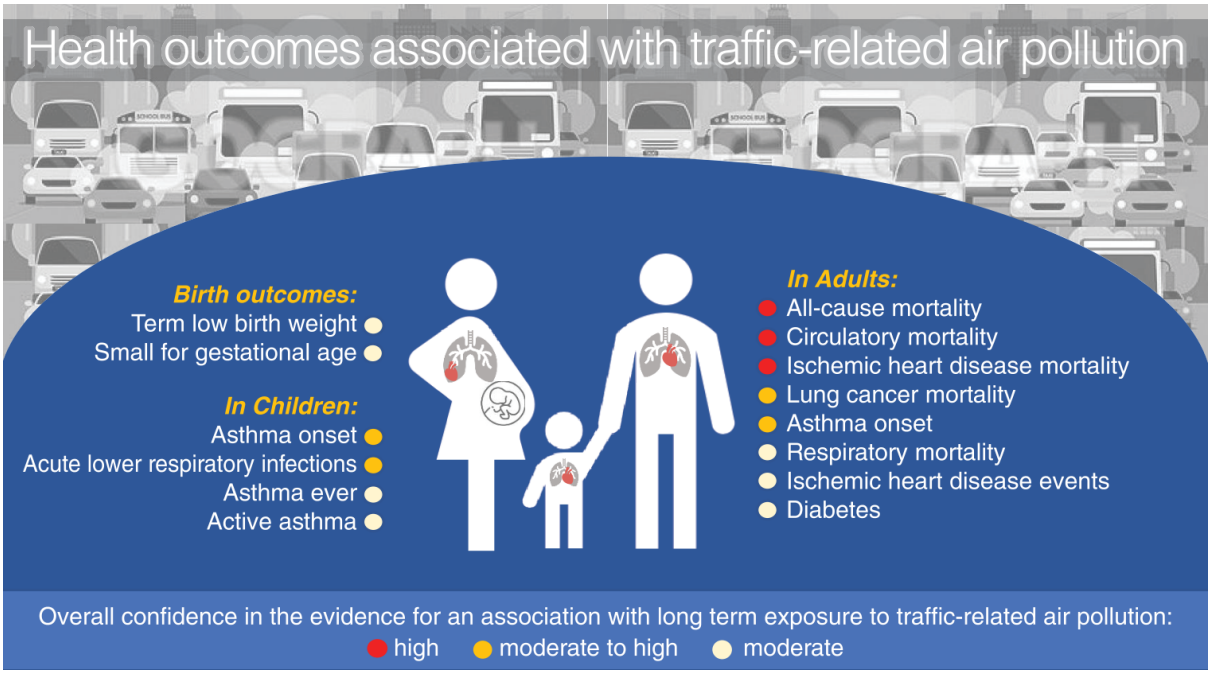

Fig. 5.5: Associations between long-term exposure to ambient TRAP and selected health outcomes with moderate to high evidence not showing health outcomes for which the overall confidence in the evidence was low-to-moderate, low or very low (with kind permission HEI Panel on the Health Effects of Long-Term Exposure to Traffic-Related Air Pollution, 2022)

While evidence for an association of cardiovascular endpoints such as atherosclerosis, increased blood pressure or changed blood coagulability with particulate matter is solid (U.S. EPA, 2019), as well as ischemic heart disease and cardiovascular mortality, the weaker evidence for stroke could be attributed to difficulties in outcome assessment and different pathophysiological pathways regarding short-term and long-term effects. It seems justified to calculate air pollution related burden of disease due to stroke in the global burden of disease

study. However, the evidence base is still too weak to propose stroke incidence or prevalence in health risk assessments of TRAP.

With more studies showing elevated risks for diabetes, especially with markers of particulate matter pollution, the case for an association of TRAP with diabetes becomes stronger. It seems justified to calculate air pollution related burden of disease due to diabetes in the global burden of disease study as well as in health risk assessments of TRAP.

Evidence Synthesis

The HEI Traffic Review did not embark on studying causality, because it did not conduct separate, independent systematic assessments of the mechanistic, toxicological, and human clinical studies relating TRAP to human health (HEI Panel on the Health Effects of Long-Term Exposure to Traffic-Related Air Pollution, 2022). However, it selected health outcomes that already show a strong (causal) association with general ambient air pollution to study the links with TRAP. Using the latest methods developed for evidence synthesis in environmental epidemiology, the Panel provided a systematic review of the epidemiological evidence and discussed the strengths and limitations of the evidence. In a more recent paper Boogaard, Atkinson, et al. (2023), discuss their experiences with the tools used and how they amended them to fit their purpose to study the health effects of TRAP.

The Panel considered the determination of confidence using a formal rating scheme of up- and downgrading of certain factors, the treatment of every factor as equally important, and the lower initial confidence rating of observational studies to be fundamental issues in the OHAT approach. They argue that some observational studies can offer high-confidence evidence in environmental health, especially when studying incidence of diseases, when the exposure precedes the outcome. Heterogeneity in pooled studies, is generally seen as a weakness of studies especially in a clinical setting as the “true” effect (of an agent) cannot be determined. In environmental epidemiology, the exact magnitude of the effect is less important than the understanding whether the exposure is truly harmful. Since epidemiological studies investigate different populations, in different settings, and exposure mixes far from homogenous clinical study populations, heterogeneity could be explained by these factors. Therefore, heterogeneity in magnitude of effect estimates and imprecision of the pooled effect estimate should not automatically weaken the evidence, unless it cannot be explained or the confidence interval includes the null even though the studies had enough statistical power to find an association. Consistency of associations across study designs, populations, and exposure assessment methods may even strengthen confidence in the evidence. Another, finding relates to publication bias, which should be explored beyond statistical methods. Especially when there are not many studies and large and collaborative studies comprise most of the evidence and when accrued

over several decades. Finally, the risk of bias assessment should also not automatically result in downgrading of the level of the quality of the evidence. Rather possible key biases should be identified as well as their most likely direction, and their potential impacts on the results. The Panel argues, that true heterogeneity in effect size unrelated to publication bias may also lead to asymmetrical funnel plots and statistically significant results in statistical publication bias tests. When effects are still visible in stratified analysis of low risk of bias studies the overall evidence should not be downgraded due to some high risk of bias studies.

Overall, the Panel concluded that the OHAT approach and other GRADE-type frameworks require substantial modification to align better with features of environmental health questions and the studies that address them. Therefore, they proposed a broader narrative evidence assessment based on the systematic review and considering evidence not entering the meta-analyses to complement the formal GRADE-type evaluation (Boogaard, Atkinson, et al., 2023). However, Jonathan M. Samet cautions on such an approach in an invited perspective, as it relies on expert judgment to a greater degree than the OHAT approach and therefore might introduce intransparent subjectivity into the synthesis process. According to him, experience shows that for agencies conducting ongoing reviews, adherence to standardized methods is requisite to ensure transparency, given the scrutiny that such reviews may receive (Samet, 2023).

5.2.3 Burden of disease or health risk assessment

Health risk assessments, that translate the observed risks into numbers of death or morbidity to assess the relevance of the problem, are another part of the Public Health Action Cycle's problem definition. However, this step could also be interpreted as part of the Public Health Action Cycle's strategy and policy formulation to prioritize mitigation of different risks that should or could be addressed by policy making. It is estimated that 3.2 million incident cases of diabetes in 2016 (Bowe et al., 2018) and 2.4 million incident cases of stroke worldwide in 2019 were attributable to ambient $PM_{2.5}$ exposure (GBD 2019 Stroke Collaborators, 2021).

While the numbers of health risk calculations are impressive and instrumental in communicating the health risks of ambient air pollution to the public and policy makers, paper III highlighted that the transparent communication of methods and data feeding into such burden calculations are instrumental. The case study of comparing Swiss health risk assessments revealed that estimates of deaths attributable to air pollution ranged from 16 in GBD 2019 to 76 per 100,000 inhabitants in STE 1993 – a difference in a factor of 5. Important determinants of such numbers are the included health endpoints, the counterfactual scenario (TMREL), the year of analysis and health data and the exposure-risk functions.

The same has been shown for the numbers in the EU. With 300,000 deaths per year in the EU (Press Office European Parliament, 2023) or 400,000 across Europe (Taylor & Duncan, 2023), the burden in Europe is high. In light of growing evidence on morbidity endpoints such as stroke and diabetes, these outcomes should be included in future health risk assessments. While the GBD study already incorporates these health endpoints, the widely used AirQ+ software (available at https://www.who.int/europe/tools-and-toolkits/airq---software-tool-for-health-risk-assessment-of-air-pollution) has not yet incorporated these outcomes into their calculations (WHO, 2023b). The AirQ+ software is a tool provided by WHO to conduct health risk assessments. The health outcomes and related exposure-risk functions incorporated into the burden calculations are based on recommendations by the Health risks of air pollution in Europe HRAPIE project in 2013 (WHO, 2013). An update is under way (Holland, 2020) and urgently expected as a new standard for comparable health risk assessment in Europe.

Boogaard, Andersen, et al. (2023) pointed out that the disease burden regarding mortality is even underestimated owed to older exposure-response functions applied in the health risk assessments for Europe. Using the latest results from the European ELAPSE study as proposed by (Hoffmann et al., 2022), the attributable mortality estimates were 40% higher for $PM_{2.5}$ and more than double for NO_2 (European Commission & Directorate-General for Environment, 2022).

Thus, air pollution is a non-negligible risk factor for public health and the HEI review (2022) and papers (Boogaard et al., 2022; Haddad et al., 2023; Kutlar Joss et al., 2023) have shown that air pollution from the important source of traffic is certainly related to mortality and to other health endpoints (problem definition).

In view of the reported large differences in estimates for the burden of disease from air pollution, policy makers and the public could easily dismiss such calculations as uncertainties in the science and deny need for action. Such denial has been known as a strategy in other topics such as the harmfulness of tobacco smoke or climate change to prevent (costly) action (Diethelm & McKee, 2009). This was also shown for the car industry in a newspaper article by the Union of Concerned Scientists from 2017 citing the American Automobile Manufacturers Association saying “The effects of ozone are not that serious … what we’re talking about is a temporary loss in lung function of 20 to 30 percent. That’s not really a health effect.”, and a Chrysler representative saying “We believe that the potential impact of [fuel economy standards] on the global issue of planetary warming are [sic] difficult to demonstrate.” (Cooke, 2017).

Nevertheless, differences in calculations should be communicated with the clear message that the science behind such calculations is sound and that there is urgent need for action to clean up the air. There is also enough evidence to tackle air pollution from traffic-related sources.

5.2.4 Strategy / Policy

While air quality has improved tremendously for most pollutants in Germany, Switzerland and many places in Europe (Public Health Action Cycle: Evaluation), there is still large room for improvement, especially since the publication of WHO's new air quality guidelines in 2021. It calls for stricter air quality standards to protect public health as part of a health policy or strategy (Public Health Action Cycle: Policy).

While in 2017, only six countries complied with the WHO guideline values for $PM_{2.5}$ set in 2005 (Kutlar Joss et al., 2017; United Nations Environment Programme, 2021a), today, none of the countries comply with the new guideline values (evaluation of policies, Table 5.3). The gap between what is considered safe by WHO and what countries define as safe or sufficient air quality (for now) for their populations has widened considerably.

Table 5.3: Comparison of EU and national air quality standards and proposed standards with the WHO air quality guideline values 2005 and 2021. References: (World Health Organization. Regional Office for Europe, 2006) and 2021 (World Health Organization, 2021), EU (European Commission, 2022; European Parliament & European Council, 2008), Switzerland (Eidgenössische Kommission für Lufthygiene (EKL), 2023; Schweizerischer Bundesrat, 1985), USA (U.S. EPA, 2023a), China (Wang et al., 2023).

Pollutant	Averaging time	WHO AQG 2005	WHO AQG 2021	EU	EU proposal by 2030	Switzer-land	Swiss FCAH proposal	USA	China
Suspended particulates / particulate matter ($PM_{2.5}$), $\mu g/m^3$	Annual average	10	5	20	10	10	5	12	35
	24h mean value	25	15	-	25	-	15	35	75
Suspended particulates / particulate matter (PM_{10}), $\mu g/m^3$	Annual average	20	15	40	20	20	15	-	70
	24h mean value	50	45[a]	50	45	50	45	150	150
Ozone (O_3), $\mu g/m^3$	Summer season[b]	-	60	-	-	-	60		-
	8h mean value	100	100[a]	120	100 objective	-	-	140	160
	1h mean value		-		-	120[c]	120[c]		200
Nitrogen dioxide (NO_2), $\mu g/m^3$	Annual average	40	10	40	20	30	10	100	40
	24h mean value	1h 200	25[a]	1h 200	50	80[c]	25[a]	1h 188	80
Sulfur dioxide (SO_2), $\mu g/m^3$	Annual average	Not reviewed	Not reviewed	-	20	30[d]	20	-	60
	24h mean value		40[a]	125	(1h 350)	100	40	1h 197	150
Carbon monoxide (CO), mg/m^3	24h mean value		4[a]	10	4	8	4	10.3	4

Abbreviations: AQG, air quality guideline; m^3, cubic meter; EU, European Union; h, hour; µg, microgram; $PM_{2.5}$, particulate matter with aerodynamic diameter ≤ 2.5 µm; PM_{10}, particulate matter with aerodynamic diameter ≤ 10 µm, USA, United States of America; WHO, World Health Organization

[a] 99th percentile (i.e. limit value may be exceeded three times per year).

[b] Average of daily maximum 8-hour mean ozone concentration in the six consecutive months with the highest six-month-running-average ozone concentrations.

[c] Limit value may be exceeded once per year.

[d] Guideline values set to protect ecosystems from adverse effects

EU Air Quality Policy

While the first column of the figure below (Fig. 5.6) implies good achievement of the air quality standards set for the European Union (EU) with less than 1% of the population living in areas exceeding EU air quality limits for $PM_{2.5}$, 96% live in areas with unhealthy levels of $PM_{2.5}$ when applying the WHO air quality guideline values (EEA, 2020). This is due to the EU standard (20 µg/m^3) being four times higher than the WHO Air Quality Guideline value (5 µg/m^3).

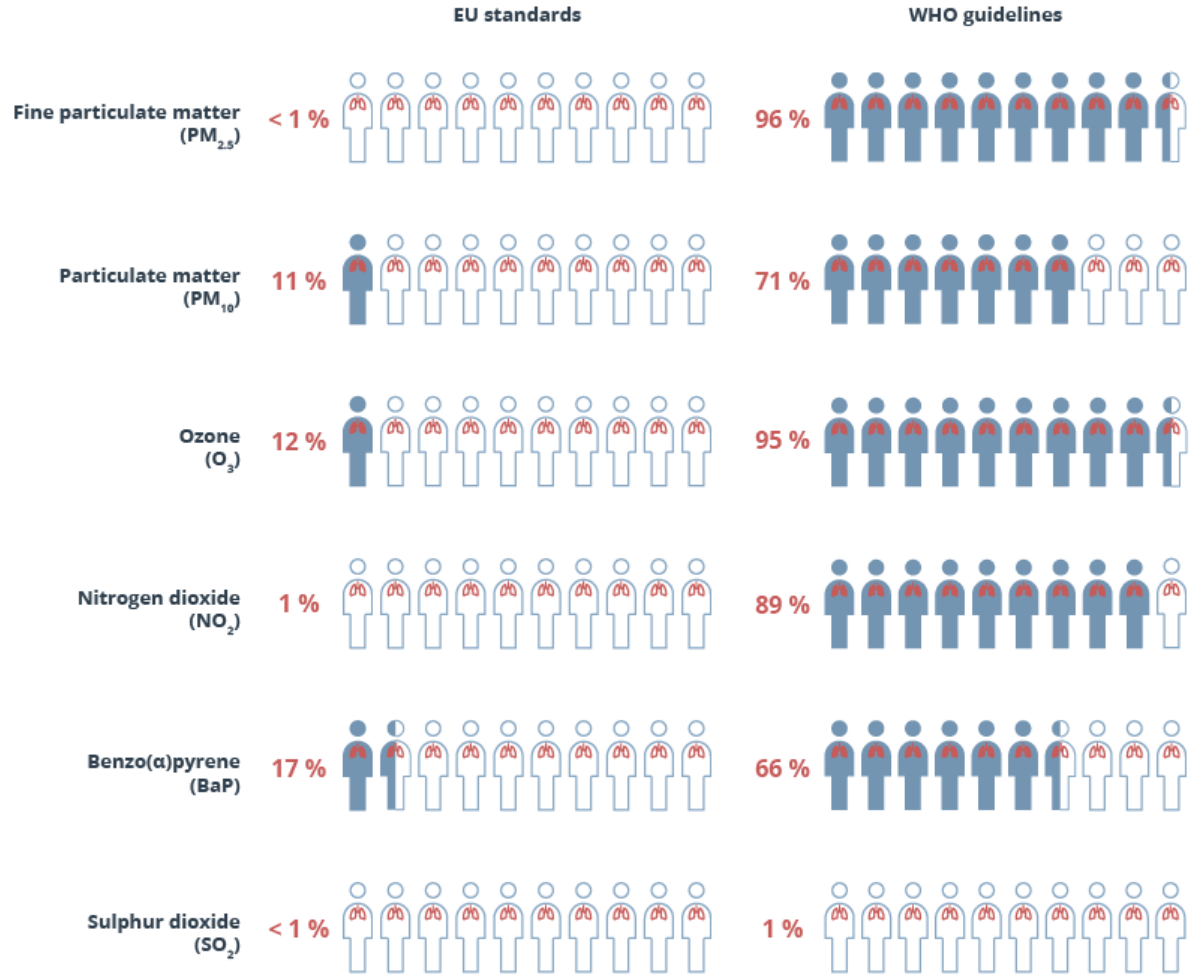

Fig. 5.6: Proportion of the population in the European Union (EU) in 2020, which was exposed to air pollution levels exceeding the EU-Standards (left) and the WHO air quality guideline values (right) (publicly available from European Environment Agency, 2022).

Abbreviations: BaP, Benzo(a)pyrene; EU, European Union; WHO, World Health Organization.

The EU took note of their short-comings regarding the protection of their populations in the "Fitness Check" (Public Health Action Cycle: evaluation) and concluded to align the air quality standards of the Ambient Air Quality Directive (AAQD) – the central regulatory instrument regarding air quality legislation in the EU – closer with the WHO recommendations (European Commission, 2019). The new proposal for the Ambient Air Quality Directive includes new

standards (Table 5.3) and addresses shortcomings, in monitoring and assessment among others (European Commission & Directorate-General for Environment, 2022). Even though the EU parliament voted for more ambitious air quality standards in September 2023 (Press Office European Parliament, 2023), they do only comply with WHO air quality standards defined almost 20 years ago for PM and still allow double the level of NO_2 that is considered safe by WHO (Table 5.3). The EU council plans to further weaken this proposal by allowing flexibility for EU countries seeking to delay implementation of air quality standards (Pacheco, 2024). A final vote is expected in late April 2024.

It seems that achievability of reaching the standards within a given time seems an unofficial criteria for defining levels of air quality standards in the EU. This is probably due to the actions taken in case of non-compliance. The European Commission has taken action in multiple infringement cases related to the breach of pollutant limit values (a total of 14 cases for PM_{10} and/or $PM_{2.5}$, 14 for NO_2 and 1 for SO_2) (European Commission & Directorate-General for Environment, 2022). Therefore, member states, might not be supportive of air quality standards, that they will not be able to meet and fear the costs of penalties due to non-compliance. It seems, that air quality standards, that are achievable within a given time frame are preferred over those that are best for the population and the environment. The German Sachverständigenrat für Umweltfragen also concluded that air quality standards are not ambitious enough (2023).

Moreover, the current policies do not support further improvements once the air quality standards are reached. For example, the implementation of air quality measures (Public Health Action Cycle: implementation) defined in German air quality plans (Luftreinhaltepläne) are stopped once air quality standards are complied with. Measures to improve air pollution are only warranted when air quality standards are exceeded (Landesanstalt für Umwelt Baden-Württemberg, 2024). This is alarming, since it does not support any further improvements to safer levels of air pollution; especially in the case when air quality standards are higher than recommended by the WHO and in absence of safe levels of air pollution as stated by the WHO (World Health Organization, 2021). At least, the new AAQD proposal shows a promising way by which an achievement of the WHO recommendations are a “vision” by 2050 (European Commission, 2022).

Since air pollution from traffic is an important source, strategies to improve air quality must tackle this sector specifically regarding urban environments where a large share of the population lives and works and is exposed to harmful levels of air pollution.

5.2.5 Implementation / Measures

There are various levels to take action against air pollution (Public Health Action Cycle: implementation). According to Public Health England prevention of air pollution at the source should always be the first step in mitigating air pollution (2019). The German Sachverständigenrat für Umweltfragen also stresses that policy needs to tackle air pollution systemically, since individuals have only limited influence on environmental exposures (Sachverständigenrat für Umweltfragen, 2023).

Therefore, air pollution from the transportation sector should be tackled with a combination of measures like lower emission mobility, increased uptake of public transport and active mobility. The EU directive lists more stringent air pollutant emissions standards for combustion engine vehicles (in the forthcoming Euro 7 proposal) and the proposal for an alternative fuels infrastructure regulation. That includes a comprehensive network of recharging and refueling infrastructure which is needed to facilitate the increased uptake of renewable and low-carbon fuels, including e-mobility (European Commission, 2022).

Electric cars, vans, trucks and buses will play a key role in reducing some of the negative impacts of road transport on human health, the environment and climate. Faced with a growing transport demand, electric vehicles alone cannot be enough to achieve a sustainable road transport in Europe. Moreover, production of electric vehicles will still require substantial resources and generate pollution. Electric vehicles will also not solve the problem of growing transport demand, time spent in traffic or finding a parking spot. They need to be seen within the wider mobility system, with a focus on mobility need and alternative modes of transport. (EEA, 2023)

While the electrification of the transport sector will certainly reduce local tail-pipe (combustion related) emissions, non-tailpipe emissions will not be affected. Since electric vehicles tend to be heavier and the trend still goes towards larger cars, their share is even expected to rise disproportionally. No actions are currently in place to reduce the non-exhaust part of emissions (Amato et al., 2014; Khreis et al., 2020; Timmers & Achten, 2016). Health effects of non-tailpipe emissions are not well understood yet. They might pose higher health risks, due to their high metal content and oxidative potential (Amato et al., 2014).

Improving public transport and making it affordable is an important strategy to reduce demand for individual motorized mobility in cities. Driving restrictions through the implementation of low emissions zones (LEZs) or congestion charging zones (CCZs) are also measures to reduce traffic. LEZs charge or ban vehicles that exceed specific exhaust emission standards and aim to reduce air pollution by encouraging use of lower emission vehicles or physically active forms of transport. CCZs focus on reducing congestion through charging financial penalties for the

majority of vehicles, with little or no differentiation by emission standards (Chamberlain et al., 2023).

According to Public Health England, thinking spatial planning and transport strategy together is one of the most effective ways of increasing public transport use and active travel and reducing emissions from existing vehicles over time (Public Health Action Cycle: strategy). Spatial planning can be used to reduce the need for vehicle use by design, and has a wider role in reducing emissions from buildings through energy-efficiency measures and use of renewable energy technologies. Measures include subsidizing public transport, designating new and priority bus measures, new tram and taxi schemes, providing school buses, providing infrastructure to enable walking and cycling, and promoting walking and cycling, which provide significant health benefits associated with physical exercise. Interventions that separate people from pollution and introduce barriers can reduce people's exposure to pollutants: they include changing road and pavement layouts, well-designed urban greening schemes, and providing active travel routes through green spaces (Public Health England, 2019). Introducing speed limits also increases safety for non-motorized participants in traffic as well as mitigating congestion and improving traffic flow in high trafficked roads (Sachverständigenrat für Umweltfragen, 2023).

Co-benefits of such measures include lower air pollution, lower emissions of greenhouse gases and reduced noise levels as well as a higher quality of life and health promotion regarding the uptake of walking or cycling (Public Health England, 2019).

5.2.6 Evaluation / Accountability

A vital step to check whether strategies and measures taken were successful in mitigating the initially identified problem or risk factor (Public Health Action Cycle: problem definition), is policy evaluation (Public Health Action Cycle: Evaluation). As initially stated, policy makers are often concerned about the costs of clean air measures, and the demands and hurdles for the local industry. Regarding costs of cleaning up the air – or better: not polluting it in the first place – in relation to benefits, the US has calculated a ratio of 1:30, i.e. the costs of air pollution measures are outweighed by a factor of 30 in comparison to the benefits from 1990 to 2020, including avoided morbidity, health care costs, premature deaths and crop loss (U.S. EPA, 2011). The proposed limit values for the EU would result in total gross benefits of 42 billion EUR/year that outweigh by seven times mitigation costs of 5.6 billion EUR/year, according to Turner et al. (2023).

The methodology of health risk / impact assessments has also been important in accountability studies showing that policy measures have led to improvement of air pollution levels which in

turn translate into lower numbers of death and morbidity attributed to air pollution. This has helped to clean up the air in many European countries in the last 30 years.

Public health England has evaluated a great variety of interventions in various sectors to improve outdoor air quality. The evidence was strongest for measures promoting vehicles with low(er) emissions with a medium evidence rating (Public Health England, 2019). A recent systematic review also found some prove for the usefulness of low emission zones on improving health. While low emission zones showed positive effects on cardiovascular health endpoints, congestion charging zones mainly reported on reduced accidents (Chamberlain et al., 2023).

A few epidemiological studies were also able to show health effects of long-term improved air quality. The Swiss SAPALDIA study was one of the first studies to show that improved air quality levels (PM_{10}) led to a slower age-related decline in lung function parameters (Downs et al., 2007). A quasi-experimental study in Canada using data from people relocating to areas with better air quality ($PM_{2.5}$) showed reduced mortality risks, especially for mortality from cardiometabolic causes (Chen et al., 2021). A Swedish study found that the general improvement of air quality over the 24 years of the children's study BAMSE improved lung function growth, especially during adolescence (Yu et al., 2023). Remarkably air pollution levels in Sweden did not improve from high levels to low levels but rather from already low levels (on average 8 µg/m^3) to very low levels (5 µg/m^3) (Yu et al., 2023), still showing gains in health.

Thus air pollution mitigation leads to improved air quality, improved health and lower costs. Targeting air pollution from the transport sector is important due to its high contribution to air pollution especially in urban areas and its harmfulness.

5.3 Conclusion and Outlook

Policy in air pollution control has a history in relying on research and being evidence based. This was discussed for each element of the newly proposed public health evidence based action cycle.

However, recently the new air quality guidelines by WHO have set new ambitious targets. The pace, how they will be met, lies in policy making and technological progress. A promising way forward reflecting the ideas of the public health action cycle, lies in the European Commission's plans on the proposal for the new Air Quality Directive to review the air quality standards by 2030 and as frequently as necessary thereafter, to assess whether they need to be updated based on the latest scientific information (Council of the EU, 2023).

The challenge will be to further reduce emissions in light of ever lower levels. With the expected electrification of the transport sector non-tailpipe emissions and their health effects will gain in

importance. While there is more and more evidence of ambient air pollution as well as traffic-related air pollution on human health, the health effects of non-tailpipe emissions are not yet well understood. This calls – apart from more research in understanding these effects – for more integrated mobility policy strategies, that do not only support the use of lower (tail-pipe) emission vehicles but offer (more healthy) alternatives such as public transport, walking or cycling. International cooperation to tackle transboundary air pollution, cooperation with industry, education of the public and advocating for measures taken are warranted to ensure achievability of the goals for cleaner air. In light of climate change, understanding and communicating co-benefits of air quality measures could further strengthen air quality policy making.

While the role of TRAP has been shown with reasonable certainty to be at least partly responsible for various health effects of residency close to high traffic, the role of other traffic-related exposures needs more attention. There is clear evidence that noise and area-level SES, and to a lesser degree lack of green space, which are all related to traffic as well, have adverse health effects on cardiometabolic health and quality of life (Diez Roux et al., 2016; Schultz et al., 2018; World Health Organization, 2018; Yuan et al., 2021).

Therefore, integrated approaches to improve overall environmental quality are called for. Following the concept of the Public Health Action Cycle can guarantee constant improvement of population health.

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