HEI

Health Effects Institute

NUMBER 222

DECEMBER 2024

COMMENTARY BY THE HEI REVIEW COMMITTEE

Cardiometabolic Health Effects of Air Pollution, Noise, Green Space, and Socioeconomic Status: The HERMES Study

Raaschou-Nielsen et al.

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Cardiometabolic Health Effects of Air Pollution, Noise, Green Space, and Socioeconomic Status: The HERMES Study

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with a Commentary by the HEI Review Committee

Research Report 222
Health Effects Institute
Boston, Massachusetts

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The Health Effects Institute is a nonprofit corporation chartered in 1980 as an independent research organization to provide high-quality, impartial, and relevant science on the effects of air pollution on health. To accomplish its mission, the Institute

- identifies the highest-priority areas for health effects research
- competitively funds and oversees research projects
- provides an intensive independent review of HEI-supported studies and related research
- integrates HEI's research results with those of other institutions into broader evaluations
- communicates the results of HEI's research and analyses to public and private decision-makers.

HEI typically receives balanced funding from the US Environmental Protection Agency and the worldwide motor vehicle industry. Frequently, other public and private organizations in the United States and around the world also support major projects or research programs. HEI has funded more than 380 research projects in North America, Europe, Asia, and Latin America, the results of which have informed decisions regarding carbon monoxide, air toxics, nitrogen oxides, diesel exhaust, ozone, particulate matter, and other pollutants. These results have appeared in more than 260 comprehensive reports published by HEI, as well as in more than 2,500 articles in the peer-reviewed literature.

HEI's independent Board of Directors consists of leaders in science and policy who are committed to fostering the public–private partnership that is central to the organization. The Research Committee solicits input from HEI sponsors and other stakeholders and works with scientific staff to develop a Five-Year Strategic Plan, select research projects for funding, and oversee their conduct. The Review Committee, which has no role in selecting or overseeing studies, works with staff to evaluate and interpret the results of funded studies and related research.

All project results and accompanying comments by the Review Committee are widely disseminated through HEI's website (*www.healtheffects.org*), reports, newsletters, annual conferences, and presentations to legislative bodies and public agencies.

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Research Report 222, *Cardiometabolic Health Effects of Air Pollution, Noise, Green Space, and Socioeconomic Status: The HERMES Study*, O. Raaschou-Nielsen et al.

INTRODUCTION

Traffic emissions are an important source of urban air pollution, and exposure to traffic-related air pollution (TRAP*) has been associated with various adverse health effects. HEI's most recent review on the health effects of TRAP included more than 350 epidemiological studies on the health effects of long-term exposure to emissions of primary traffic-related air pollutants (HEI 2022) and found a high level of confidence that strong connections exist between TRAP and premature death due to cardiovascular diseases. A strong connection was also found between TRAP and lung cancer mortality, asthma onset in children and adults, and acute lower respiratory infections in children. The confidence in the evidence was considered moderate, low, or very low for other selected outcomes, such as coronary events, diabetes, and adverse birth outcomes.

Although TRAP emissions have decreased over the past decades, further research is warranted in several areas. Emerging evidence suggests that transportation can affect health through many intertwined pathways beyond direct exposures to air pollution such as collisions, noise, climate change, temperature, stress, and the lack of physical activity and green space (Glazener et al. 2021). Few studies evaluate how influential factors — such as a lack of green space, greater heat exposure, noise pollution, and reduced physical activity — interact with or modify air pollution health effects. Evaluation of those factors and exposures is critical because they reflect real-world conditions and might further advance our understanding of the implications of transportation activities on TRAP and health (Khreis et al. 2020).

In 2017, HEI issued Request for Applications (RFA) 17-1, Assessing Adverse Health Effects of Exposure to Traffic-Related Air Pollution, Noise, and Their Interactions with Socioeconomic Status. HEI funded three studies under RFA 17-1 and then five other studies related to the improvement of exposure assessment of TRAP for health studies under RFA 19-1 (see *Preface*).

In response to RFA 17-1, Dr. Ole Raaschou-Nielsen and colleagues from the Danish Cancer Institute (formerly Danish Cancer Society Research Center) proposed a 4-year study, "Cardiometabolic Health Effects of Air Pollution, Noise, Green Space, and Socioeconomic Status: The HERMES Study." They aimed to investigate the role of TRAP and specific traffic-related pollutants — particulate matter ≤2.5 µm in aerodynamic diameter ($PM_{2.5}$), nitrogen dioxide (NO_2), elemental carbon (EC), and ultrafine particles (UFPs) — and the independent effects of air pollution, noise, and green space. They were also interested in identifying susceptible subgroups defined by sociodemographic characteristics, stress conditions, and comorbidity in relation to cardiometabolic health and in identifying biological pathways in air pollution exposure and disease development.

The HEI Research Committee recommended the application from Dr. Raaschou-Nielsen and colleagues for funding because it had several strong features, including the rich individual-level data source, large sample size, strong exposure assessment for TRAP and noise, and the inclusion of biomarker data in a large sample.

This Commentary provides the HEI Review Committee's independent evaluation of the study. It is intended to aid the sponsors of HEI and the public by highlighting the strengths and limitations of the study and by placing the results presented in the Investigators' Report into a broader scientific and regulatory context.

SCIENTIFIC AND REGULATORY BACKGROUND

The health effects of TRAP continue to be an important public health interest across the globe, with the highest exposures in urban settings and residences near busy roadways. In conservative global estimates, vehicle tailpipe emissions were associated with an estimated 361,000 deaths in 2010 and 385,000 in 2015 (Anenberg et al. 2019). The World Bank Group estimated 184,000 deaths worldwide in 2010 attributable to TRAP as indicated by $PM_{2.5}$ derived from vehicular emissions (Global Road Safety Facility 2014). Similarly, Lelieveld and colleagues (2015) estimated that TRAP is responsible for one-fifth of deaths from air pollution in the United States, the United Kingdom, and Germany (Lelieveld et al. 2015).

Dr. Ole Raaschou-Nielsen's 4-year study, "Health Effects of Air Pollution Components, Noise and Socioeconomic Status (HERMES)" began in July 2018. Total expenditures were $999,311. The draft Investigators' Report from Raaschou-Nielsen and colleagues was received for review in March 2023. The first revised report was received in September 2023. A second revised report was received and accepted for publication in November 2023. During the review process, the HEI Review Committee and the investigators had the opportunity to exchange comments and clarify issues in both the Investigators' Report and the Review Committee's Commentary.

* A list of abbreviations and other terms appears at the end of this volume.

The US Environmental Protection Agency recently lowered the National Ambient Air Quality Standards for $PM_{2.5}$ from 12 µg/m^3 to 9 µg/m^3, and the European Union recently lowered the air quality standard for $PM_{2.5}$ from 25 µg/m^3 to 10 µg/m^3 (Council of the European Union 2024; US EPA 2024a). These changes in $PM_{2.5}$ air quality standards were the first since 2012 in the United States and since 2008 in the European Union (Council of the European Union 2024; US EPA 2024a). The World Health Organization (WHO) released new Air Quality Guidelines in 2021 and recommended that annual mean concentrations of $PM_{2.5}$ should not exceed 5 µg/m^3 (World Health Organization 2021). The current NO_2 annual average air quality standard is 53 parts per billion in the United States and 20 µg/m^3 in the European Union (recently lowered from 40 µg/m^3) (Council of the European Union 2024; US EPA 2024b). The WHO's new Air Quality Guidelines recommend that annual mean concentrations of NO_2 should not exceed 10 µg/m^3 (WHO 2021). There are no specific ambient air quality standards or guidelines for UFPs and EC, and regulatory agencies do not commonly measure them. Although no air quality guidelines were developed for UFPs and BC, WHO provided "good practice statements" for these pollutants geared toward additional monitoring, mitigation, and epidemiological research (WHO 2021).

Exposure to TRAP and spatially correlated factors such as noise, green space, and socioeconomic status (SES) can either confound or modify the health effects of TRAP. Therefore, these factors need to be considered to advance our understanding of the health effects of TRAP and to obtain important information for more effective mitigation policies aimed at protecting public health.

EXPOSURE ASSESSMENT OF TRAFFIC-RELATED AIR POLLUTANTS

TRAP is a complex mixture of gases and particles resulting from the use of motor vehicles. Motor vehicles emit a variety of pollutants, including NO_2, EC, UFPs, and $PM_{2.5}$. Exposure assessment of TRAP can be challenging because the highest TRAP concentrations occur within a few hundred meters away from major roads depending on the pollutant, geographic and land-use characteristics, and meteorological conditions, thus requiring exposure assessments to consider gradients across very fine spatial scales.

The most commonly used TRAP exposure metrics are measured or modeled concentrations of individual pollutants considered to be indicators of TRAP (such as NO_2 or black carbon) and simple indicators of traffic (such as distance of the residence from busy roads or traffic density near the residence). UFPs are another indicator of TRAP used in various recent studies. It should be noted that UFP measurement is challenging, and most studies measure particle number concentration to estimate exposure, a topic that is discussed in detail elsewhere (Ohlwein et al. 2019; Samoli et al. 2020). Exposure to TRAP is often estimated using a range of models, such as dispersion, land use regression, and hybrid models. This approach is imperfect, however, because many of the traffic-related pollutants are also emitted by other sources such as airports, (sea)ports (Masiol and Harrison 2014; Muller et al. 2011), and combustion processes not related to traffic.

TRAFFIC NOISE

In addition to air pollution, other factors such as traffic noise are associated with traffic exposure and can either confound or modify the health effects of TRAP. In a 2014 WHO assessment of six European countries, noise ranked second only after air pollution as the most important environmental exposure (Hanninen et al. 2014). In 2018, the WHO released environmental noise guidelines for Europe, which include recommendations for reducing road traffic noise (WHO 2018). In the United States, it has been estimated that at least 146 million people (46% of the population) were at potential risk of hypertension due to noise in 2013 (Hammer et al. 2014).

Since the 1970s, successive Europewide directives have laid down specific noise emissions limits for road vehicles, airplanes, and many types of outdoor equipment, and EU Directive 2002/49/EC harmonized noise assessment and mandated European Union member states to produce strategic noise maps for large cities, major roads and railways, and major airports. Noise levels are modifiable and opportunities to reduce traffic-related noise exposure include traffic and urban planning measures such as lowering speed limits (Rossi et al. 2020), implementation of noise barriers (Tezel-Oguz et al. 2023), vegetation cover (Gaudon et al. 2022), changes to building materials and increased building insulation (Amundsen et al. 2013), and implementation of sound-absorbing technologies in pavement (Vázquez et al. 2016) and motor vehicle brake systems (Stojanovic et al. 2023).

Traffic noise has been associated with various adverse health outcomes, including cardiovascular morbidity (such as hypertension and ischemic heart disease) and mortality (Babisch 2014), impaired neurocognitive development and function in children and adults (Stansfeld et al. 2005; Tzivian et al. 2015; van Kempen et al. 2012), adverse birth outcomes (Ristovska et al. 2014), and possible metabolic outcomes such as diabetes mellitus (Dzhambov 2015). All those outcomes are also linked to exposure to air pollution. However, questions remain about whether, or to what extent, the reported associations of TRAP are confounded by traffic noise because both originate from the same source. Additionally, it is unclear how simultaneous exposure to TRAP and traffic noise might interact and possibly enhance each other´s effect. A challenge that might hamper such analyses is the correlation between exposure estimates for TRAP and traffic noise. However, some studies have observed that when noise is modeled with greater detail, correlations between exposure to TRAP and traffic noise decrease (Foraster et al. 2014).

GREEN SPACE

There is also evidence that factors related to the built environment, such as the presence or absence of green space, can either confound or modify the health effects of TRAP (Dadvand et al. 2014; Hystad et al. 2014; James et al. 2015). Mechanisms by which access to green space might influence health outcomes are not yet clear but might include a reduction in stress, enhancing social cohesion, an increase in physical activity, or a buffering from other exposures, such as air pollution and noise (Jimenez et al. 2021). Regarding green space and air pollution, green space can have both beneficial and detrimental effects on air quality depending on the setting, scale, air pollutant, vegetation type, and allergenicity. Higher levels of green space are usually associated with lower levels of air pollution at the neighborhood level (Nowak et al. 2018; Tallis et al. 2011). Green space in epidemiological studies is generally measured using satellite-based vegetation indices or land use databases linked to participants' residential addresses.

SOCIOECONOMIC STATUS

A final important factor to consider in epidemiological studies of exposure to TRAP is individual and neighborhood SES (Gray et al. 2024). In many settings, low-SES communities reside in the vicinity of roads and transportation corridors and therefore are disproportionately exposed to air pollution; such communities might also be more susceptible to air pollution owing to other underlying disparities (Patterson and Harley 2019). However, some studies have reported opposite associations between SES and air pollution exposure, for example in New York and Rome, highlighting the importance of investigating the SES–air pollution associations in a specific setting (Cesaroni et al. 2010; Hajat et al. 2013). Most cohort studies assessing air pollution have reported somewhat higher effect estimates for those with the lowest SES (Chen et al. 2024; Chi et al. 2016). However, it has been difficult so far to disentangle whether differences in susceptibility, exposure, or other factors contribute to those observations.

STUDY OBJECTIVES

The overarching goal of Dr. Raaschou-Nielsen and colleagues' study was to investigate the associations between long-term exposure to TRAP ($PM_{2.5}$, UFPs, EC, and NO_2) and risk of type 2 diabetes, myocardial infarction (MI), and stroke through addressing the following objectives:

- Develop a chemical transport model to assess residential UFP concentrations
- Investigate the contributions of air pollution from local road traffic and other sources in observed associations with cardiometabolic outcomes
- Investigate the effects of adjusting for lifestyle variables after adjusting for registry-based sociodemographic variables and investigate if associations differed by sociodemographic variables, financial stress, and comorbidity
- Analyze joint residential exposure to air pollutants, road traffic noise, and green space in relation to the cardiometabolic outcomes
- Investigate associations of air pollution and noise in relation to cardiometabolic biomarkers and blood pressure.

Dr. Raaschou-Nielsen and colleagues used data from three existing longitudinal cohort studies of Danish adults, covering roughly 2.6 million people. They assessed exposure to four traffic-related air pollutants ($PM_{2.5}$, UFPs, EC, and NO_2). They used a chemistry transport model system, a noise model, a high-resolution land use map, and Danish registries to estimate exposure to air pollutants, noise, green space, and individual and area-level sociodemographic factors.

They focused on the following health outcomes: type 2 diabetes, MI, stroke, cardiometabolic biomarkers, and blood pressure. They investigated the associations between the air pollutants and contextual factors and various health outcomes using Cox proportional hazards models. They also investigated the associations between air pollutants, cardiometabolic biomarkers, and blood pressure using multivariate linear regression models.

Due to computational limitations, Dr. Raaschou-Nielsen and colleagues were not able to complete the original goal of conducting multiexposure analyses. They did conduct some multiexposure analyses with mutual adjustment for other environmental factors and provided a detailed description of their pursued multiexposure approach.

SUMMARY OF METHODS AND STUDY DESIGN

STUDY POPULATION

Dr. Raaschou-Nielsen and colleagues used three existing, nationwide Danish population-based cohort studies (see **Commentary Table 1**). First, a nationwide registry-based cohort (DK-POP) provided a very large dataset that allowed the investigators to evaluate air pollution exposure in relation to type 2 diabetes, MI, and stroke. The DK-POP registry uses a unique personal identification number system for all people in Denmark born after 1920 and contains a continuous Danish address history between January 1, 1979, and January 1, 2005 (n = 2.6 million age 35+, 2 million age 50+). Second, the Danish National Health Survey (DNHS) of almost 250,000 participants ages 16 and older, was much smaller but provided detailed individual-level information to evaluate the influence of lifestyle factors in the associations between air pollution and cardiometabolic chronic disease. Third, the Diet Cancer and Health – Next Generations cohort (DCH-NG) of almost 33,000 participants ages 18 and older was included because it had information on cardiometabolic biomarkers and blood pressure to investigate potential biological mechanisms. Thus, the study benefited from two complementary approaches, using one large cohort with less detailed information and two smaller cohorts with highly detailed information.

Commentary Table 1. Characteristics of Three Existing, Nationwide Danish Study Populations Used to Investigate Associations Between Exposure to TRAP, Noise, Green Space, Sociodemographic Factors, and Cardiometabolic Outcomes

	Study Populations		
Characteristics	**DK-POP**	**DNHS**	**DCH-NG**
Years of Follow-up	2005–2017	2010–2017, 2013–2017	One-time participation in 2015–2019
Population Size	Age 35+: 2.6 million for type 2 diabetes Age 50+: 1.9 million for type 2 diabetes, 2 million for MI risk, 2 million for stroke risk	Age 16+: 246,766; 234,018 for type 2 diabetes risk, 241,056 for MI risk, 241,988 for stroke risk	Age 18+: 32,851
Inclusion Criteria	Continuous Danish address history between January 1, 1979, and January 1, 2005		
Exclusion Criteria		Missing address or exposure information at any time during follow-up, presence or history of outcome of interest at baseline	Missing address, lifestyle, SES, or biomarker data; previous diagnosis of diabetes, MI, or stroke; use of blood pressure or cholesterol medication or low-dose aspirin; change of address within 90 days before blood draw or blood pressure measurement
Outcomes	Type 2 diabetes risk, MI risk, stroke risk	Type 2 diabetes risk, MI risk, stroke risk	Biomarkers of cardiometabolic diseases, blood pressure
Statistical Analyses	Incidence: Cox proportional hazards models, interaction: Aalen additive hazards models	Incidence: Cox proportional hazards models, interaction: Aalen additive hazards models	Multivariate linear regression

DCH-NG = Diet, Cancer, and Health – Next Generations; DK-POP = Danish Population; DNHS = Danish National Health Survey.

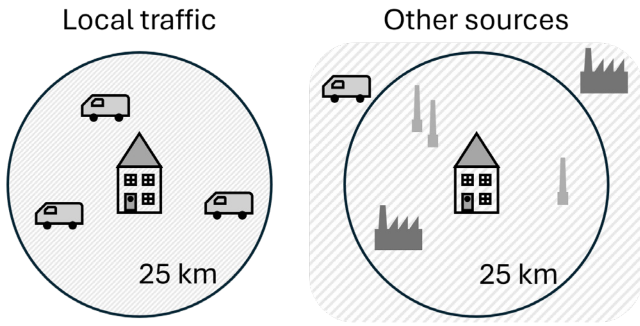
EXPOSURE ASSESSMENT

Traffic-Related Air Pollution

The investigators used an advanced chemical transport-based air pollution modeling system, which was developed by the Department of Environmental Science at Aarhus University, Denmark, and which has been extensively validated and applied in earlier studies (Brandt et al. 2001, 2012; Hvidtfeldt et al. 2018; Jensen et al. 2017; Khan et al. 2019). The investigators used the system to model ambient air pollution concentrations of TRAP ($PM_{2.5}$, EC, and NO_2) as 5-year running averages at each residential address and for each time period on an hourly basis for the entire study population over the course of follow-up or over the 30 days before assessment of cardiometabolic markers. Additionally, the investigators added a novel module to the air pollution modeling system to estimate particle number concentrations larger than 10 nm in diameter as a proxy for UFPs. The system uses different types of input data to model air pollution exposure, which the investigators leveraged to distinguish between exposure to air pollution from local road traffic ("local traffic"), which captures air pollutants from road traffic sources within 25 km, and all other sources of air pollution ("other sources"), which captures air pollutants from all other sources, including nonlocal road traffic (**Commentary Figure 1).**

Noise

The investigators used the Nordic Prediction Method (Bendtsen 1999) to model road traffic noise at the most- and least-exposed façades of each residence for 2000, 2005, 2010, and 2015 (Thacher et al. 2020). The noise model incorporates landscape elements (three-dimensional building polygons, roads, and terrain) and traffic information (traffic data, traffic speeds, vehicle distributions, and noise barriers). The investigators applied the noise model to estimate average noise levels at the center, most-, and least-exposed facades for each residential address. Average noise levels at each residential address were estimated using A-weighted sound levels, which represent sound levels humans can hear, during the



Commentary Figure 1. The investigators assessed exposure to air pollution from local road traffic within 25 km ("local traffic"), and all other sources of air pollution, including nonlocal road traffic ("other sources").

day (7 a.m. to 7 p.m.), evening (7 p.m. to 11 p.m.), night (11 p.m. to 7 a.m.), as well as 24-hour weighted averages for each year between 2000 and 2017. The estimates for the most- and least-exposed facades were used to investigate associations with cardiometabolic outcomes.

Green Space

The investigators used a detailed land use map of Denmark (Basemap) for 2016 to assess the proportion of green space near each residence. The investigators estimated the proportion of publicly accessible green space within 1,000 m of the residence to capture green space that could encourage physical activity and the proportion of private and publicly accessible green space within 150 m of the residence as an indicator of green space potentially visible from the residence. The investigators included the lack of green space within 150 m and within 1,000 m of the residence in the statistical models.

Sociodemographic Factors

The investigators obtained information on an array of sociodemographic and financial stress-related factors from the Statistics Denmark registries, which are updated annually. Their sociodemographic and financial stress-related factors included individual-level factors such as level of education, individual and household per capita income, occupational status, and country of origin, and area-level factors such as population density and proportion with a criminal record, proportion living in a single-parent household, and proportion unemployed. The investigators also assessed the occurrence of one or more financial stress events in the last 5 years, defined as family income below the Danish relative poverty limit, personal or family income drop of 50% or more between 2 consecutive years, and job loss.

HEALTH OUTCOME ASSESSMENT

Dr. Raaschou-Nielsen and colleagues assessed five outcomes related to cardiometabolic health: risk of type 2 diabetes, risk of MI, risk of stroke, cardiometabolic biomarkers, and systolic and diastolic blood pressure.

In the large DK-POP cohort (2.6 million participants), Dr. Raaschou-Nielsen assessed the risk of developing type 2 diabetes, risk of MI, and risk of stroke. Participants were followed from either January 1, 2005, the date when they turned 35 (for overall associations with type 2 diabetes) or the date when they turned 50 (for other associations with type 2 diabetes, risk of MI, and risk of stroke). Participants were followed until the date of diagnosis based on ICD-10 codes, death, emigration, more than 14 consecutive days of unknown address, or the end of follow-up on December 31, 2017, whichever came first. In addition to the follow-up conditions described above, follow-up for type 2 diabetes further ended at the date of first diagnosis of type 1 diabetes. This cohort did not have information on individual-level lifestyle covariates.

In the smaller DNHS cohort that included detailed individual lifestyle information (246,766 participants), Dr. Raaschou-Nielsen and colleagues evaluated the same cardiometabolic outcomes as in the large DK-POP cohort from the date of enrollment in 2010 or 2013 until the end of follow-up on December 31, 2017. Reasons for ending follow-up sooner were the same as for the DK-POP cohort. For this cohort, the investigators obtained information on potential individual-level confounders related to smoking status and intensity, alcohol consumption, diet, leisure-time physical activity, height, and weight.

In the smaller DCH-NG cohort that had biomarker information (32,851 participants), Dr. Raaschou-Nielsen and colleagues assessed cardiometabolic biomarkers that were measured once in blood, including high-density lipoprotein (HDL), non-HDL lipoprotein, C-reactive protein (CRP, a marker of inflammation), and hemoglobin A1c, a prediabetes marker related to blood glucose regulation. They also assessed systolic and diastolic blood pressure (measured three times). All biomarkers were measured between 2015 and 2019. For this cohort, the investigators obtained information on individual-level confounders related to smoking status, exposure to second-hand smoke, alcohol consumption, physical activity, and body mass index.

STATISTICAL ANALYSES

In the large DK-POP and smaller DNHS cohorts, Dr. Raaschou-Nielsen and colleagues used Cox proportional hazards models to estimate associations between exposure to four air pollutants and risk of three cardiometabolic outcomes using hazard ratios (HRs) and 95% confidence intervals (CIs) per interquartile range (IQR) and fixed unit of exposure. Additionally in the DK-POP cohort, the investigators assessed the source contributions for each air pollutant to differentiate between air pollution exposure from local road traffic and other sources. They assessed exposure to air pollutants, noise, and lack of green space as 5-year running averages that were updated every 3 months.

The investigators adjusted their statistical models for multiple individual- and neighborhood-level registry-based sociodemographic variables in the DK-POP and DNHS cohorts and adjusted the models for lifestyle factors and body mass index in the DNHS cohort. To assess additive interactions between air pollutant exposures, noise, and lack of green space in the DK-POP and DNHS cohorts, the investigators also used Aalen additive hazards models, which estimate the additive effects of covariates (i.e., absolute risk), in contrast to Cox multiplicative proportional hazards models, which estimate the multiplicative effects of covariates (i.e., relative risk) (Vanderweele and Knol 2014).

Furthermore, the investigators investigated how the air pollutants, noise, and green space might have interacted by fitting one-, two-, three-, and four-pollutant models for the four air pollutants, one- and two-factor models for noise (most- and least-exposed façade), and one- and two-factor models for lack of green space (accessible within 150 m and within 1000 m of the residence). The investigators assessed correlations between the individual exposures. They were interested in identifying exposures that were consistently associated with the outcomes of interest when analyzed alone and when adjusted for other exposure metrics. They also calculated a cumulative risk index, assuming additive effects of the combined exposures, to quantify the cumulative burden of the traffic-related exposures. Furthermore, the investigators used Cox multiplicative proportional hazards models and Aalen additive hazards models to investigate the potential effect modification of TRAP and the outcomes of interest in the DK-POP cohort.

In the smaller DCH-NG cohort, the investigators used multivariate linear regression to assess associations between traffic-related air pollutants and cardiometabolic biomarkers and blood pressure, adjusting for sex, sociodemographic, and lifestyle factors.

SUMMARY OF KEY RESULTS

EXPOSURE TO TRAFFIC-RELATED AIR POLLUTION

Adults in the nationwide cohort had average $PM_{2.5}$ concentrations of 10.0 µg/m^3 (range: 5.9–31.7), UFP counts of 10,665 number/cm^3 (range: 3,691–93,677), EC concentrations of 0.7 µg/m^3 (range: 0.2–20.3), and NO_2 concentrations of 15.0 µg/m^3 (range: 4.9–69.0). The average levels are at or below the current and new (lower) European standards for annual $PM_{2.5}$ and NO_2 concentrations; there are no existing European standards for UFPs or EC. Dr. Raaschou-Nielsen and colleagues observed higher mean concentrations from other sources compared to mean concentrations from local traffic sources for all four pollutants.

RISK OF TYPE 2 DIABETES, MYOCARDIAL INFARCTION, AND STROKE

In the nationwide DK-POP cohort, the investigators found that higher total concentrations of each of the four air pollutants were associated with a higher risk of each of the cardiometabolic outcomes. For example, a 5-µg/m^3 increase in $PM_{2.5}$ was associated with an HR of 1.12 (95% CI: 1.09–1.16) for type 2 diabetes, HR 1.15 (95% CI: 1.10–1.20) for MI, and HR 1.22 (95% CI: 1.17–1.28) for stroke (**Commentary Figure 2**). The investigators observed similar associations in the smaller DNHS cohort and found that adjusting for detailed lifestyle information beyond adjusting for the multiple individual- and neighborhood-level registry-based sociodemographic factors did not meaningfully change the HRs.

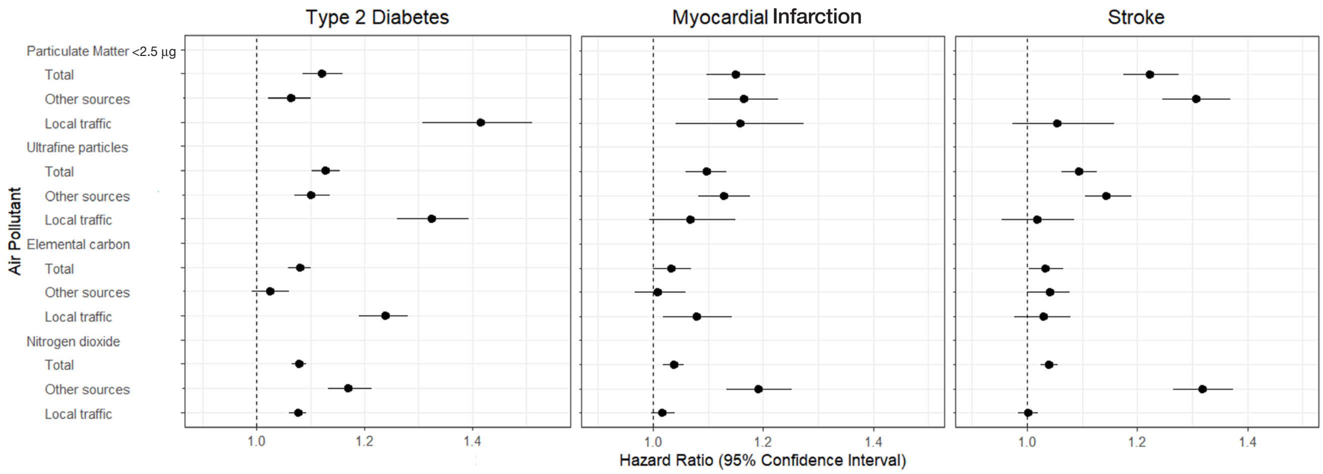
Overall, the investigators found that all four examined traffic-related air pollutants were associated with a higher risk of type 2 diabetes, MI, and stroke. Exposure to air pollution from local traffic sources was generally more strongly associated with a higher risk of type 2 diabetes compared to exposure to air pollution from other sources with an exception for NO_2 (Commentary Figure 2). In contrast, exposure to air pollution from sources other than local traffic was generally more strongly associated with a higher risk of MI and higher risk of stroke compared to exposure to air pollution from local traffic sources with the exception of EC and myocardial infarction.

INTERACTIONS WITH OTHER POTENTIAL RISK FACTORS

In the nationwide DK-POP cohort, the investigators observed consistent effect modifications by other potential risk factors across all four air pollutants in relation to type 2 diabetes, with higher risk estimates for exposure to air pollutants among men, those without financial stress, and those with comorbidities. The investigators further observed effect modification across all four air pollutants in relation to the risk of MI, with higher risk estimates among those with comorbidities, men, those with lower education, those with lower income, and those without financial stress. Finally, the investigators observed effect modification across all four air pollutants in relation to the risk of stroke, with higher risk estimates among those with lower education, those with lower income, and those without financial stress. Associations between traffic-related air pollutants and chronic cardiometabolic disease were not modified by population density, traffic noise, or green space. In relation to traffic-related air pollutant exposures, men and those with comorbidities had higher risks of type 2 diabetes and MI, those with lower education and those with lower income had higher risks of MI and stroke, and those *without* one or more financial stress events in the last 5 years had higher risks of type 2 diabetes, MI, and stroke.

MULTIEXPOSURE ANALYSES OF AIR POLLUTION, NOISE, AND GREEN SPACE

The investigators observed relatively high correlations among the four air pollutants ($r > 0.73$) and moderate to high correlations between the air pollutants from local traffic and other sources (r: 0.42 to 0.72). However, correlations were low to moderate between the four air pollutants and noise (r: 0.19 to 0.53) and lack of green space (r: –0.07 to 0.40). The investigators observed consistent patterns of higher HRs among single-pollutant analyses and generally lower or no associations in



Commentary Figure 2. Associations between air pollutants per fixed unit increase and risk of type 2 diabetes, myocardial infarction, and stroke among the Danish Nationwide Cohort in single-pollutant models (N = 2,631,488 for type 2 diabetes, N = 1,964,702 for MI, N = 1,971,246 for stroke). Air pollutant unit increase: particulate matter ≤2.5 µm in aerodynamic diameter per 5 µg/m^3, ultrafine particles per 10,000/cm^3, elemental carbon per 1 µg/m^3, and nitrogen dioxide per 10 µg/m^3.

the multiexposure analyses with mutual adjustment for the other environmental factors. In the multiexposure analyses, air pollution, noise, and lack of green space all influenced the risk of type 2 diabetes and MI; whereas only air pollution and noise influenced the risk of stroke.

CARDIOMETABOLIC BIOMARKERS AND BLOOD PRESSURE

In the analysis of biomarkers in the DCH-NG cohort, Dr. Raaschou-Nielsen and colleagues observed consistent associations between exposure to all four air pollutants and lower levels of HDL (“good cholesterol”), higher levels of non-HDL (“bad cholesterol”), and higher systolic and diastolic blood pressure. Unexpectedly, the investigators also found consistent associations between exposure to all four air pollutants and lower CRP (higher levels are a marker of inflammation) and lower HbA1c concentrations (higher levels are a marker of prediabetes).

These results were most consistent for air pollution from other sources compared to local traffic sources for cholesterol and blood pressure, but no systematic difference was observed between air pollution sources in relation to CRP and HbA1c concentrations. The investigators observed that residential noise levels were associated with higher systolic blood pressure and lower HbA1c concentrations, but associations were less consistent for diastolic blood pressure and CRP. Overall, exposure to traffic-related air pollutants was associated with lower levels of HDL, higher levels of non-HDL, and higher systolic and diastolic blood pressure, which are in the biological pathway to cardiometabolic outcomes. However, associations between air pollutants and CRP and HbA1c, as well as exposure to noise in relation to cardiometabolic biomarkers and blood pressure, present mixed results.

HEI REVIEW COMMITTEE’S EVALUATION

In its independent review of the study, the HEI Review Committee commended Dr. Raaschou-Nielsen and colleagues on their highly productive study. The Review Committee emphasized several study strengths, including the use of multiple, data-rich nationwide cohorts, high-resolution assessment of multiple traffic-related factors, efforts toward multiexposure analyses in longitudinal cohort studies, and the ability to differentiate between air pollution from local traffic sources and air pollution from all other sources.

STRENGTHS OF THE STUDY

A major strength of the study was the Danish population-based registries, which use a unique personal identification number system. The national health registries include complete residential address history and near-complete information on healthcare data, which is accessible for research without informed consent under Danish law. Leveraging data from the nationwide cohort of DK-POP bolstered the study with a very large sample size; it was also nationally inclusive and hence not sensitive to bias related to selection and loss to follow-up.

Another major strength of the study was the detailed national-scale exposure model that had been thoroughly evaluated in previous Danish studies and that allows exposure estimations for a range of traffic-related air pollutants for the entire Danish population at a fine spatial and temporal scale. A particularly unique feature of the study was the ability to distinguish between exposure to local traffic sources and other sources of traffic-related air pollutants. A better understanding of local road traffic contributions (i.e., from road traffic within 25 km) might be of interest to policymakers to inform public health strategies.

An additional major strength of the study is the use of a high-quality noise model, which is often a challenge in large cohort studies, and their development of a model to estimate UFP exposure. UFP exposure assessment methods are actively being developed, and there is no standard UFP monitoring network available, which makes investigating exposure to, and health effects associated with, UFPs difficult, so this work adds nicely to the literature. Finally, the comparison of results across cohorts with and without more detailed personal information was perceived as an additional strength, especially because they were able to demonstrate that additionally adjusting for lifestyle factors did not meaningfully alter the observed associations.

Although the Review Committee broadly agreed with the investigator's conclusions, some limitations should be considered when interpreting the results, as explained next.

DIFFERENTIATING BETWEEN TRAFFIC AND OTHER AIR POLLUTION SOURCES

The Review Committee noted some limitations to the study, such as the inability to differentiate between traffic- and nontraffic sources of air pollution greater than 25 km away from the residence. Because the investigators did not differentiate between individual sources (e.g., traffic and nontraffic) of air pollutants farther than 25 km away, it is possible that the main contribution of "other sources" of air pollutants could also be from traffic, yet from nonlocal sources. The ability to disentangle individual sources farther away would allow more direct comparisons and could facilitate further insights into the relative contribution of traffic and nontraffic sources at varying geospatial scales (i.e., near traffic vs. far traffic). The Committee also noted that the single cut-off distance of 25 km for all four air pollutants is too far to reflect primary emissions and might not allow full distinction between local traffic and all other sources, as air pollutants are not transported equally. The Committee further noted that the high correlations between air pollutants raise questions as to how easily associations with air pollutants can be disentangled.

GENERALIZABILITY

The Committee also had some concerns about the generalizability of the study. Although the investigators included a nationwide cohort, the Danish population is relatively homogeneous and well-resourced, they receive relatively high levels of social support and have relatively high levels of education. Thus, the findings might not be generalizable for populations with fewer social supports and greater diversity in resources.

The Committee noted that a sizeable amount of data was missing among the smaller cohorts. The missing data resulted in relatively large numbers of DNHS and DCH-NG participants who were excluded from the analyses, which might have resulted in selection bias and limited generalizability.

MULTIEXPOSURE MODELING

The novel multiexposure analyses proposed originally were considered one of the strengths of the proposed work by the Research Committee. Multiexposure analyses have proven to be a major challenge in epidemiological research due to computational limitations and multicollinearity issues, and statistical methods for multiexposure assessments remain an important area of development (Dominici et al. 2010; HEI 2015; Joubert et al. 2022; Molitor et al. 2016; Pedersen et al. 2024).

The investigators pursued multiple modeling methods to conduct multiexposure analyses but found that the intended approach was not feasible, as described in the Appendix (see Additional Materials on the HEI website). In particular, the existing computational limitations combined with a very large dataset and high-resolution temporal scale resulted in the outcomes of interest being extremely rare. Although the study did not include the multiexposure analyses as intended, the Review Committee commended Dr. Raaschou-Nielsen and colleagues' efforts and the use of multiexposure analyses using traditional Cox models. However, the Review Committee noted that Dr. Raaschou-Nielsen and colleagues might have been challenged by the inherent multicollinearity of the air pollution data. The Review Committee emphasized that the detailed description of the novel approach and the lessons learned that are included in the Appendix will serve as a valuable resource to other investigators pursuing methodological approaches toward multiexposure analyses.

CONCLUSIONS

In summary, this study represents an important contribution to our knowledge about exposure to multiple spatially correlated traffic-related environmental factors in relation to risk of type 2 diabetes, MI, stroke, and the suspected biological mechanisms. The study's findings suggest that traffic-related air pollutants, traffic noise, and residential green space are all individually associated with a higher risk of type 2 diabetes, MI, and stroke but that local traffic and other sources of air pollutants may be related to different health outcomes. In addition, these associations may be attenuated by mutual adjustment to exposure to traffic-related air pollutants, noise, and green space. Finally, the study found adverse associations between exposure to traffic-related air pollutants and cholesterol and blood pressure, which are known contributors to cardiometabolic disease, further supporting the findings on type 2 diabetes, MI, and stroke. However, other associations with traffic-related air pollution, noise, green space, and cardiometabolic biomarkers present mixed findings.

The report presents important steps in better understanding exposure to multiple spatially correlated traffic-related environmental factors in relation to cardiometabolic outcomes. The report distinguishes between exposure to traffic-related air pollutants from road traffic within 25 km compared to all other sources, which might be of interest to policymakers in informing local road traffic regulations to protect public health. Furthermore, the report used a high-resolution exposure assessment of noise and modeled UFP exposure, which is both challenging in many epidemiological studies. Finally, the report presents important progress toward modeling exposures to multiple environmental factors beyond air pollution alone to better understand public health risks of joint exposures, better reflecting real-world exposure scenarios. In this study, associations between exposure to individual pollutants and chronic cardiometabolic diseases were stronger compared to associations adjusted for other exposures, indicating that the joint associations were less than the sum of the individual associations.

Ultimately, this study has documented that exposure to traffic-related environmental factors is associated with a higher risk of type 2 diabetes, MI, and stroke, but that the sources of traffic-related air pollutants, presence of other risk factors such as comorbidities, and joint exposure to multiple factors influence those risks.

ACKNOWLEDGMENTS

The HEI Review Committee thanks the ad hoc reviewers for their help in evaluating the scientific merit of the Investigators' Report. The Committee is also grateful to Hanna Boogaard for her oversight of the study, to Elise Elliott for assistance with the review of the report and in preparing its Commentary, to Mary Brennan for editing this Report and its Commentary, and to Kristin Eckles and Hope Green for their roles in preparing this Research Report for publication.

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ABBREVIATIONS AND OTHER TERMS

ATC	Anatomical Therapeutic Chemical System
BMI	body mass index
CAFE	corporate average fuel economy
CI	confidence interval
CRI	Cumulative Risk Index
CRP	C-reactive protein
CTM	Chemistry Transport Model
dB	decibel
DCH-NG	Diet Cancer and Health – Next Generations cohort
DK-POP	Danish Population cohort
DNHS	Danish National Health Survey
DEHM	Danish Eulerian Hemispheric Model
EC	elemental carbon
Green1000m	percentage area with green space with 1000 m of the residence
Green150m	percentage area with green space with 150 m of the residence
HbA1c	hemoglobin A1c
HDL	high-density lipoprotein
HR	hazard ratio
ICD	International Classification of Diseases
IQR	interquartile range
LdenMax	noise level, day-evening-night weighted, at the most exposed façade
LdenMin	noise level, day-evening-night weighted, at the least exposed façade
LVS	low volume sampler
MI	myocardial infarction
NO_2	nitrogen dioxide
NO_x	oxides of nitrogen
OSPM	Operational Street Pollution Model
$PM_{2.5}$	particulate matter ≤2.5 µm in aerodynamic diameter
PNC	particle number concentration
RFS	Renewable Fuel Standard Program
SD	standard deviation
SES	socioeconomic status
SNAP	Selected Nomenclature for Air Pollution
SO_4	sulfate
TRAP	traffic-related air pollution
UBM	Urban Background Model
UFP	ultrafine particles
VOC	volatile organic compound

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NUMBER 222
DECEMBER 2024

COMMENTARY BY THE HEI REVIEW COMMITTEE

Publishing history: This document was posted at *www.healtheffects.org* in December 2024.

Citation for document:

HEI Review Committee. 2024. Commentary. In: Raaschou-Nielsen O, Poulsen AH, Ketzel M, Frohn LM, Roswall N, Hvidtfeldt UA, et al. 2024. Cardiometabolic Health Effects of Air Pollution, Noise, Green Space, and Socioeconomic Status: The HERMES Study. Research Report 222. Boston, MA: Health Effects Institute.

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