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

Ole Raaschou-Nielsen, Aslak H. Poulsen, Matthias Ketzel, Lise M. Frohn, Nina Roswall, Ulla A. Hvidtfeldt, Jesper H. Christensen, Jørgen Brandt, and Mette Sørensen

INCLUDES A COMMENTARY BY THE INSTITUTE'S REVIEW COMMITTEE

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with a Commentary by the HEI Review Committee

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ABOUT HEI

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.

ABOUT THIS REPORT

Research Report 222, *Cardiometabolic Health Effects of Air Pollution, Noise, Green Space, and Socioeconomic Status: The HERMES Study*, presents a research project funded by the Health Effects Institute and conducted by Dr. Ole Raaschou-Nielsen at the Danish Cancer Institute in Copenhagen, Denmark, and his colleagues. The report contains three main sections:

The **HEI Statement**, prepared by staff at HEI, is a brief, nontechnical summary of the study and its findings; it also briefly describes the Review Committee's comments on the study.

The **Investigators' Report**, prepared by Raaschou-Nielsen and colleagues, describes the scientific background, aims, methods, results, and conclusions of the study.

The **Commentary,** prepared by members of the Review Committee with the assistance of HEI staff, places the study in a broader scientific context, points out its strengths and limitations, and discusses the remaining uncertainties and implications of the study's findings for public health and future research.

This report has gone through HEI's rigorous review process. When an HEI-funded study is completed, the investigators submit a draft final report presenting the background and results of the study. Outside technical reviewers and a biostatistician first examine the draft report. The report and the reviewers' comments are then evaluated by members of the Review Committee, an independent panel of distinguished scientists who are not involved in selecting or overseeing HEI studies. During the review process, the investigators have an opportunity to exchange comments with the Review Committee and, as necessary, to revise their report. The Commentary reflects the information provided in the final version of the report.

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PREFACE

HEI's Research to Assess Health Effects of Traffic-Related Air Pollution and to Improve Exposure Assessment for Health Studies

INTRODUCTION

Traffic emissions are an important source of urban air pollution and have been linked to various adverse health outcomes (Atkinson et al 2018; Health Canada 2016; HEI 2010; HEI 2022a; Huangfu and Atkinson 2020; US Environmental Protection Agency [US EPA] 2016). Over the last several decades, air quality regulations and improvements in vehicular emission control technologies have steadily decreased emissions from motor vehicles. As a result, ambient concentrations of several major traffic-related air pollutants have decreased in most high-income countries, even as vehicle miles traveled and economic activity have increased and older or malfunctioning vehicles have remained on the roads (HEI 2022a; US EPA 2023).

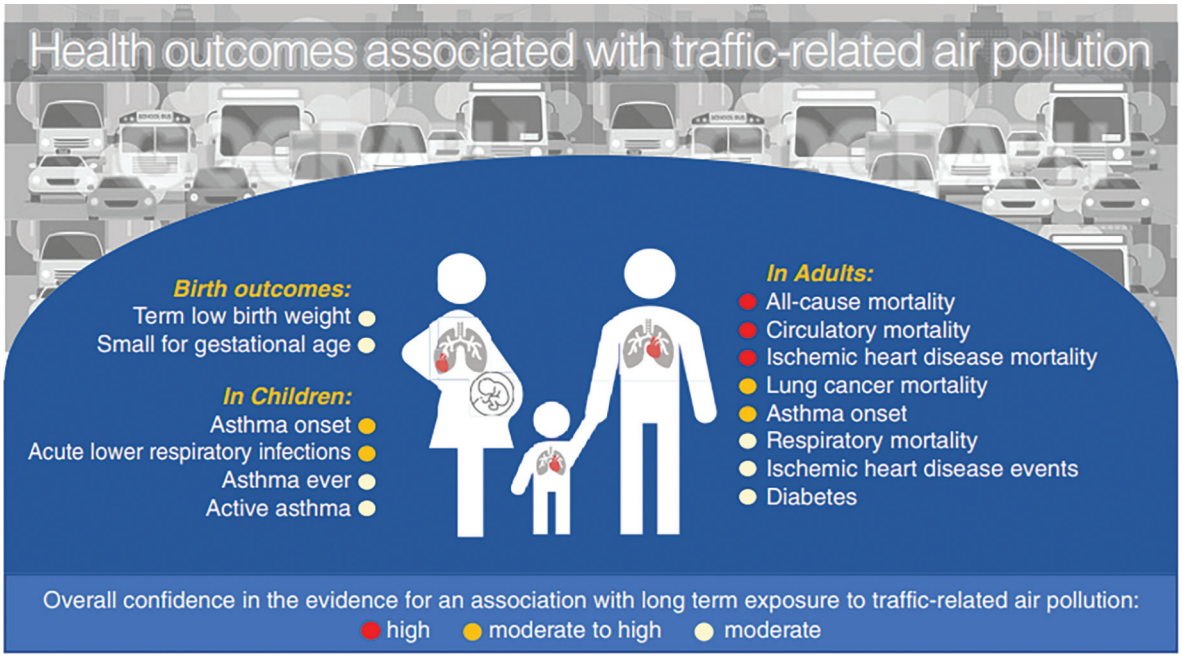
Following HEI's widely cited 2010 Report (HEI 2010), HEI published *Special Report 23*, a systematic review of more than 350 epidemiological studies on the health effects of long-term exposure to emissions of primary traffic-related air pollutants (HEI 2022a). The report found a high level of confidence that strong connections exist between traffic-related air pollution and early death due to cardiovascular diseases. A strong connection was also found between traffic-related air pollution and lung cancer mortality, asthma onset in children and adults, and acute lower respiratory infections in children (**Preface Figure**). The confidence in the evidence was considered moderate, low, or very low for the other selected outcomes, such as coronary events, diabetes, and adverse birth outcomes.

Although traffic-related 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 such as collisions, noise, climate change, temperature, stress, and the lack of physical activity and green space (Glazener et al. 2021). As tailpipe emissions from internal combustion engines decrease and electric vehicles increase market share, more studies are needed to quantify human exposures to nontailpipe particulate matter better and to assess the health effects associated with those exposures. Relatively few studies evaluate how influential factors such as green space, heat exposure, noise pollution, and physical activity interact with or modify air pollution health effects. Evaluation of those factors and exposures are critical because they reflect real-world conditions and might further advance our understanding of the implications of transportation activities on traffic-related air pollution and health (Khreis et al. 2020).

Moreover, better understanding is needed of the role of specific pollutants including nitrogen dioxide (NO_2) and ultrafine particles (UFPs), the health effects of short-term exposures versus long-term exposures, the effects on a broader range of health outcomes (such as neurological and birth outcomes) that have not been extensively examined, and the ways in which marginalized communities are affected. However, a challenge for exposure assessment of traffic-related air pollution is that traffic emits a complex mixture of pollutants in particulate and gaseous forms, many of which are also emitted by other sources. In addition, traffic-related air pollution is characterized by high spatial and temporal variability, with the highest concentrations occurring at or near major roads. Therefore, it has been difficult to identify an appropriate exposure metric that uniquely indicates traffic-related air pollution and to model the distribution of exposure at a sufficiently high degree of spatial and temporal resolution.

Various air quality models—such as dispersion, land use regression, and hybrid models—have been developed to estimate long-term exposure to air pollution (HEI 2022a; Hoek 2017; Jerrett et al. 2005). Recent developments in measurement technologies and approaches to modeling long-term exposure to air pollution have increasingly been used to provide air pollution estimates at fine spatial scales for epidemiological studies of large populations. Advances include novel air pollution sensors, mobile monitoring, satellite data, hybrid models, and machine-learning approaches (Hoek 2017).

Moreover, many improvements in exposure models have occurred over time with the advance of geographic information system approaches and the application of more sophisticated statistical methods; see, for example, several studies previously funded by HEI: Apte 2024, Barratt 2018, Batterman 2020, Frey 2022, and Sarnat 2018. However, the usefulness of exposure estimates still depends on the model assumptions and input data quality, and there remain limitations and challenges when predicting air pollution exposure, particularly for such pollutants as UFPs, NO_2,



Preface Figure. Overall confidence in the evidence for an association between long-term exposure to traffic-related air pollution and selected health outcomes. Health outcomes for which the overall confidence in the evidence was low to moderate, low, or very low are not in the figure. Reproduced from HEI 2022a.

and black carbon (BC) that vary highly in space and time. Few studies have compared the performance of different models and evaluated exposure measurement error and possible bias in health estimations.

Thus, HEI issued complementary requests for applications in 2017 (RFA 17-1) and 2019 (RFA 19-1) to evaluate traffic-related health effects in the context of spatially correlated factors—specifically traffic noise, socio-economic status, and green space—and to improve exposure assessment for health studies.

OBJECTIVES OF THE RFAs

OBJECTIVES OF RFA 17-1

RFA 17-1, *Assessing Adverse Health Effects of Exposure to Traffic-Related Air Pollution, Noise, and Their Interactions with Socioeconomic Status*, solicited studies that sought to assess adverse health effects from exposure to traffic-related air pollution and to disentangle the effects from spatially correlated confounding or modifying factors — most notably, traffic noise, socioeconomic status, and the built environment, including green space. The RFA had five major objectives:

1. In the proposed health studies, develop, validate, and apply improved exposure assessment methods and models suitable for estimating exposure to traffic-related air pollution that take into account other air pollution sources in urban areas (such as airports, [sea]ports, industries, and other local point sources) and that would be able to distinguish between tailpipe and nontailpipe traffic emissions.
2. Propose ways in these studies to disentangle the relationship of adverse health effects of traffic-related air pollution and traffic noise.
3. Develop, evaluate, and apply indicators of socioeconomic status at the individual and community level in the proposed health studies; if such indicators are novel, compare with socioeconomic status indicators commonly used in the literature.
4. Explore the role of other factors that might confound or modify the health effects of traffic-related air pollution at the individual (e.g., age, smoking status, diet, physical activity, and health status) and community level (e.g., presence of green space, other factors related to the built environment, and walkability).
5. Investigate — to the extent that the measurements and patterns of a range of different indicators of traffic-related air pollution allow it (e.g., NO_2, UFPs, BC, and indicators of nontailpipe emissions) — whether one or more of them can be shown to have health effects independent of the other pollutants.

OBJECTIVES OF RFA 19-1

RFA 19-1, *Applying Novel Approaches to Improve Long-Term Exposure Assessment of Outdoor Air Pollution for Health Studies*, solicited studies to assess exposures to air pollution using new and conventional exposure assessment approaches, to evaluate quantitatively exposure measurement error to determine the added value of the novel approaches, and to apply the exposure estimates in epidemiological analyses to evaluate the potential effect of exposure measurement error on chronic health estimates. The RFA had four major objectives:

1. Conduct a new monitoring campaign designed to determine long-term exposure to outdoor air pollutants with high spatial and temporal variability by using sensors, mobile monitoring, location tracking, or other approaches.
2. Develop several exposure assessment approaches suitable to estimate long-term exposure to air pollution at relevant spatial and temporal scales for use in an ongoing or future health study.
3. Quantify exposure measurement error by evaluating and comparing the performance of models of long-term air pollution exposure developed under this RFA to the performance of previous models.
4. Apply the various exposure estimates in an ongoing health study to evaluate the potential impact of exposure measurement error in health estimates or explain how the exposure assessments would be directly applicable to future health studies.

DESCRIPTION OF THE RESEARCH PROGRAM

Three 4-year studies were funded under RFA 17-1 and five 3-year studies were funded under RFA 19-1 to cover the various RFA objectives; they are summarized below (**Preface Table**). The study by Raaschou-Nielsen and colleagues described in this report (Research Report 222) is the second to be published.

STUDIES FUNDED UNDER RFA 17-1

HEI funded two studies in Europe and one study in the United States to evaluate various aspects of the association between long-term traffic-related air pollution and health by using existing cohorts (Denmark, USA) and a newly recruited cohort (Spain). Two studies focused on health outcomes during pregnancy (Dadvand) and childhood (Franklin), and one study focused on cardiometabolic outcomes in adults (Raaschou-Nielsen).

"Traffic-Related Air Pollution and Birth Weight: The Roles of Noise, Placental Function, Green Space, Physical Activity, and Socioeconomic Status (FRONTIER)," Payam Dadvand and Jordi Sunyer, Barcelona Institute for Global Health (ISGlobal), Spain Dadvand, Sunyer, and colleagues established a new cohort, named Barcelona Life Study Cohort (BiSC) of 1,080 healthy pregnant women in Barcelona, Spain, in 2018. They estimated exposure to various traffic-related pollutants by using hybrid models that included dispersion models, land use data, time-activity data, and personal and home-outdoor air pollution monitoring data. They linked the exposure to various birth outcomes including birth weight, small for gestational age, and fetal growth trajectories. They evaluated the role of traffic noise and green space and also took into account socioeconomic status and maternal stress (in review).

"Intersections as Hot Spots: Assessing the Contribution of Localized Non-Tailpipe Emissions and Noise on the Association between Traffic and Children's Respiratory Health," Meredith Franklin, University of Southern California, Los Angeles Franklin and colleagues developed novel exposure models of tailpipe and nontailpipe air pollutants and noise and applied those models to children's respiratory health in a large Southern California cohort that was also studied in a previous HEI-funded study led by Frank Gilliland; see *HEI Research Report 190*. They made use of the most recent Children's Health Study (CHS) cohort that was initiated in 2003 and included about 2,000 children in eight communities. Longitudinal data on asthma and lung function were collected at various time points (2008–2012) at ages 11 through 16. Air pollution models were supported by particulate matter filters at more than 200 locations in the eight Southern California communities (in review).

"Cardiometabolic Health Effects of Air Pollution, Noise, Green Space and Socioeconomic Status: The HERMES Study," Ole Raaschou-Nielsen, Danish Cancer Institute, Copenhagen, Denmark Raaschou-Nielsen and colleagues evaluated effects of traffic-related air pollution, traffic noise, lack of green space, and other factors on myocardial infarction, stroke, diabetes, and related biomarkers in three cohorts, including an administrative cohort of about 2.6 million Danish adults in the period 2005–2017. They assessed traffic-related air pollution using a chemical transport model for various pollutants, including UFPs and NO_2. In addition, they assessed noise, individual- and neighborhood-level socioeconomic status, and various residential green space exposure metrics (current report).

STUDIES FUNDED UNDER RFA 19-1

HEI funded five studies in North America and Europe to evaluate different aspects of improvements to exposure assessment and the application of different exposure assessment approaches to existing cohorts. Three studies are focused on combining novel methods for measuring air pollution and diverse exposure assessment approaches to improve exposure assignment, including machine learning and mobile monitoring (Weichenthal and Hoek) and mobility (de Hoogh). Two studies are testing the added value of incrementally more complex statistical modeling approaches to improving exposure assessment in London (Katsouyanni) and Seattle (Sheppard) and applying their findings to estimating health effects in epidemiological studies.

"Long-Term Exposure to Outdoor Ultrafine Particles and Black Carbon and Effects on Mortality in Montreal and Toronto, Canada," Scott Weichenthal, McGill University, Montreal, Canada Weichenthal and colleagues estimated associations between long-term exposures to UFPs, BC, and other pollutants and mortality in Toronto and Montreal, Canada, using several exposure modeling approaches. They conducted mobile monitoring campaigns in both cities and used those newly collected data to develop various high-resolution exposure models, including land use regression and machine learning. They then evaluated how the effect estimates for nonaccidental and cause-specific mortality in the Canadian Census Health and Environment Cohort (CanCHEC) are influenced by different exposure models (Research Report 217).

"Comparison of Long-Term Air Pollution Exposure Assessment Based on Mobile Monitoring, Low-Cost Sensors, Dispersion Modelling and Routine Monitoring-Based Exposure Models (CLAIRE)," Gerard Hoek, Utrecht University, The

Preface Table. Key Characteristics of HEI's Research to Assess Health Effects of Traffic-Related Air Pollution and to Improve Exposure Assessment for Health Studies

Principal Investigator	Study Name	Location	Study Period	Study Population	Sample Size	Outcomes	Main Air Pollutants	Monitoring Data	Exposure Assessment
RFA 17-1, Assessing Adverse Health Effects of Exposure to Traffic-Related Air Pollution, Noise, and Their Interactions with Socioeconomic Status									
Dadvand	FRONTIER (BiSC)	Barcelona, Spain	2018–2022	Newborns	1,080	Birth weight, small for gestational age, fetal growth trajectories, and placental function	BC, NO_2, $PM_{2.5}$, Cu, Fe, and Zn	Personal, indoor, and outdoor home measurements	LUR, dispersion, and hybrid models
Franklin	CHS	Southern California	2008–2012	Children	2,000	Asthma and lung function	PM_{coarse}, $PM_{2.5}$, Cu, Fe, Zn, and many other elemental components	Outdoor home and school measurements and measurements near road intersections	Machine learning and LUR models
Raaschou-Nielsen (this report)	HERMES (DK-POP, DNHS, DCH–NG)	Denmark	2005–2017	Adults	2.9 million	Myocardial infarction, stroke, and diabetes	UFPs, EC, NO_2, and $PM_{2.5}$	NA	Chemical transport model
RFA 19-1, Applying Novel Approaches to Improve Long-Term Exposure Assessment of Outdoor Air Pollution for Health Studies									
Weichenthal	CanCHEC	Montreal and Toronto, Canada	1991–2016	Adults	1.5 million	Mortality	UFPs, BC	Mobile	Machine learning and LUR models
Hoek	CLAIRE (DUELS, EPIC-NL, PIAMA)	Netherlands	1993–2019	Children and adults	10 million	Mortality, cardiovascular disease, lung function, and asthma	UFPs, NO_2, BC, and $PM_{2.5}$	Mobile, outdoor low-cost sensors, regulatory monitors	LUR, dispersion, machine-learning, and hybrid models

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Preface Table *(continued)*. Key Characteristics of HEI's Research to Assess Health Effects of Traffic-Related Air Pollution and to Improve Exposure Assessment for Health Studies

Principal Investigator	Study Name	Location	Study Period	Study Population	Sample Size	Outcomes	Main Air Pollutants	Monitoring Data	Exposure Assessment
de Hoogh	MOBI-AIR (EPIC-NL, SAPALDIA, SNC)	Netherlands, Switzerland	1991–2018	Adults	3.5 million	Mortality, cardiovascular disease, lung function, and, blood pressure	NO_2, $PM_{2.5}$	Personal measurements, location tracking	Agent-based, LUR, and machine-learning models
Katsouyanni	MELONS (BLW, COPE, DEMiSt, PASTA, London segment of UK Biobank)	London, UK	2006–2024	Adults	62,000	Mortality	BC, NO_2, $PM_{2.5}$, and O_3	Personal measurements, regulatory monitors	LUR, dispersion, machine learning, and hybrid models
Sheppard	ACT Air pollution study	Seattle	1994–2020	Older adults	5,400	Cognitive function	UFPs, NO_2	Mobile, outdoor low-cost sensors	Universal kriging and machine-learning models

ACT = Adult Changes in Thought; BiSC = Barcelona Life Study Cohort; BLW = Breathe London Wearables; CanCHEC = Canadian Census Health and Environment Cohort; CHS = Children's Health Study; COPE = Characterisation of COPD Exacerbations using Environmental Exposure Modelling; DCH–NG = Diet, Cancer and Health–Next Generations cohort; DEMiSt = Driver Diesel Exposure Mitigation Study; DK–POP = Danish Population cohort; DNHS = Danish National Health Survey; DUELS = Dutch Environmental Longitudinal Study; EPIC–NL = European Prospective Investigation on Cancer and Nutrition–Netherlands; PIAMA = Prevention and Incidence of Asthma and Mite Allergy; NA = not applicable; PASTA = Physical Activity through Sustainable Transport Approaches; SAPALDIA = Swiss Study on Air Pollution and Lung Disease in Adults; SNC = Swiss National Cohort.

Netherlands Hoek and colleagues prepared maps of modeled annual average air pollution across the Netherlands, validated the maps using new measurements from 90 sites, and evaluated the performance of several exposure models. They conducted cross-comparisons to evaluate how different exposure assessment methods compare in their ability to predict long-term pollutant concentrations, with a particular focus on spatial variability of pollutants. They applied the various models to three major cohorts in the Netherlands — an administrative cohort of about 10 million adults (DUELS), the European Prospective Investigation into Cancer and Nutrition Netherlands (EPIC-NL), and the Prevention and Incidence of Asthma and Mite Allergy (PIAMA) birth cohort — to evaluate how they influence health effect estimates in epidemiological studies (in review).

"Accounting for Mobility in Air Pollution Exposure Estimates in Studies on Long-Term Health Effects (MOBI-AIR)," Kees de Hoogh, Swiss Tropical and Public Health Institute, Basel, Switzerland Kees de Hoogh and colleagues used location tracking using a mobile phone application and GPS units for about 700 individuals in the Netherlands and Switzerland. They then compared exposure estimates accounting for individual mobility to those accounting only for home addresses in three major cohorts: the Study on Air Pollution and Lung Disease in Adults (SAPALDIA) in Switzerland, participants in the European Prospective Investigation into Cancer and Nutrition Netherlands (EPIC-NL), and the Swiss National Cohort (SNC) (in review).

"Investigating the Consequences of Measurement Error of Gradually More Sophisticated Long-Term Personal Exposure Models in Assessing Health Effects: The London Study (MELONS)," Klea Katsouyanni, Imperial College, United Kingdom Katsouyanni and colleagues evaluated whether increasingly detailed estimates of long-term exposures to outdoor air pollution yielded different estimates of the health effects. They leveraged personal exposure data from four earlier studies in London. They compared predictions from various exposure models that accounted for exposure to indoor sources and mobility by using several types of air pollution models (dispersion, land use regression, machine learning, and hybrid models). Finally, exposures were applied to the London segment of the UK Biobank study with about 62,000 participants to evaluate associations with mortality (in review).

"Optimizing Exposure Assessment for Inference about Air Pollution Effects with Application to the Aging Brain," Lianne Sheppard, University of Washington, Seattle Sheppard and colleagues compared and contrasted scientific and logistic benefits of different study designs to develop air pollution exposure estimates. They leveraged detailed air pollution data and cognitive function data from about 5,000 participants in the Adult Changes in Thought (ACT) Air Pollution study in Seattle. They developed several exposure models that used air pollution data from mobile monitoring of UFPs, NO_2, and other pollutants, and low-cost sensors. In particular, they used statistical techniques to assess the bias and precision of health effect estimates and compared the time and costs spent on more sophisticated exposure assessment activities to guide future studies in efficient selection of exposure assessment methods (in review).

FURTHER RESEARCH UNDERWAY

Given the large number of people exposed to traffic-related air pollution — both in and beyond the near-road environment — exposures to traffic-related air pollution remain an important public health concern and deserve greater attention from the public and from policymakers.

Although emissions from automobile exhaust systems have decreased in recent years, emissions from the use and wear of brakes, tires, and other nontailpipe sources now contribute a higher fraction of the particulate emissions. Therefore, HEI funded two ongoing studies funded under *RFA 21-1*, *Quantifying Real-World Impacts of Non-Tailpipe Particulate Matter Emissions*. The two studies involve measurements of mass and composition of ambient particles from nontailpipe motor vehicle sources to disentangle nontailpipe and tailpipe pollution and better understand how each effects human health. One study is measuring concentrations of nontailpipe particulate matter across Toronto, Canada, to determine how much nontailpipe pollution people might breathe in everyday life and how to improve measurement of these exposures in the future. The other study is a panel study in which asthmatic adults rode stationary bicycles on sidewalks in three different exposure environments in London, United Kingdom, to measure how exposure to traffic with different mixtures of nontailpipe and tailpipe emissions affects lung function.

Building on its prior and ongoing research and the recommendations from its systematic traffic review, HEI issued *RFA 23-1*, *Assessing Health Effects of Traffic-Related Air Pollution in a Changing Urban Transportation Landscape*. Investigators funded under RFA 23-1 will conduct epidemiological and health impact assessment studies to assess current and potential future population-level health effects and health burdens associated with current and future transportation systems and traffic-related air pollution. The studies began in late spring 2024. HEI also publishes reports on the State of Global Air to communicate the relationship between air quality and health around the world; see, for example, a recent report on cities and NO_2 (HEI 2022b).

Looking ahead, HEI continues to support improvements in exposure assessment via the use of new technologies, such as satellite remote sensing data. HEI held a *workshop* to discuss applications of high-quality satellite remote sensing data, which have opportunities for increased use in large epidemiological studies, studying the health effects of wildfires, and addressing environmental justice concerns. Challenges include the complexities of data assimilation and accessibility, and current data and algorithmic limitations. HEI is developing an RFA to support research using or assessing the limitations of new approaches to incorporate satellite data products in health studies.

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HEI STATEMENT

Synopsis of Research Report 222

Cardiometabolic Effects of Air Pollution, Noise, and Green Space in Denmark

BACKGROUND

Traffic emissions are an important source of urban air pollution, and exposure to traffic-related air pollution has been associated with various adverse health effects. The health effects of traffic-related air pollution continue to be an important factor affecting public health across the globe, especially for people living in cities and close to busy roadways. Exposure to traffic-related air pollution and other closely correlated factors, such as noise, lack of green space, and socioeconomic status might confound or modify the associated health effects. Therefore, it is important to understand the influence of those other factors on the associations between traffic-related air pollution and health to design more effective policies to protect people's health.

APPROACH

The overarching goal of Dr. Raaschou-Nielsen and colleagues' study was to investigate the associations between long-term exposure to four traffic-related air pollutants and the risk of cardiometabolic diseases and how these effects might vary given other related factors such as noise and green space. The investigators used data from three existing longitudinal cohort studies of Danish adults, covering roughly 2.6 million people. The three cohorts were a nationwide registry-based cohort and two smaller cohorts that had detailed individual-level information to evaluate the influence of lifestyle factors (the Danish National Health Survey cohort) and information on cardiometabolic biomarkers and blood pressure (Diet Cancer and Health – Next Generations cohort). Thus, the study benefited from two complementary sources of data, using one large cohort with less detailed information and two smaller cohorts with highly detailed information.

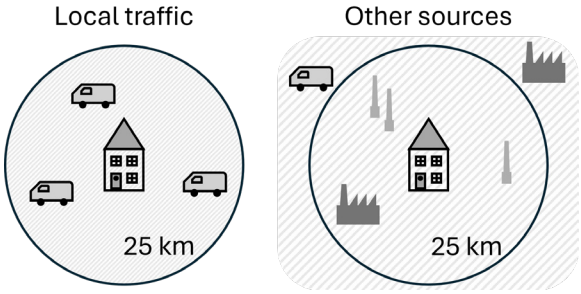
The investigators estimated exposure to four traffic-related air pollutants (fine particulate matter, nitrogen dioxide, ultrafine particles, and elemental carbon) using an advanced chemical transport model system. They also used a noise model to estimate exposure to noise, a high-resolution land use map to assess access to green space near the home, and Danish registries to estimate individual and neighborhood sociodemographic factors. Finally, they estimated air pollutant exposures from local traffic sources (less than 25 km away) and air pollutant exposures from all other sources, including nonlocal traffic, using the chemical transport model system (**Statement Figure 1**).

The study team focused on the following cardiometabolic outcomes: type 2 diabetes, heart attack, stroke, blood pressure, and related biomarkers (cholesterol, blood pressure, C-reactive protein, and blood sugar concentrations). They used Cox proportional hazards models to investigate the associations between these air pollutants and contextual factors and cardiometabolic

What This Study Adds

- This study investigated four traffic-related air pollutants (fine particulate matter, nitrogen dioxide, ultrafine particles, and elemental carbon), noise, and green space in relation to cardiometabolic health in 2.6 million adults in Denmark.
- Individually, all air pollutants, noise, and lack of green space were associated with a higher risk of type 2 diabetes, stroke, and heart attack, while associations adjusted for other exposures were less strong.
- Air pollution from local traffic sources was more strongly associated with a higher risk of type 2 diabetes, while air pollution from all other sources was more strongly associated with a higher risk of heart attack and stroke.
- Exposures to traffic-related air pollutants, noise, and a lack of green space were associated with increases in cholesterol and blood pressure, which are known contributors to cardiometabolic disease.
- This study shows that exposures to traffic-related air pollution, noise, and a lack of green space are associated with a higher risk of cardiometabolic diseases, but that air pollutant sources, presence of other risk factors, and exposure to multiple other factors influence those risks.

This Statement, prepared by the Health Effects Institute, summarizes a research project funded by HEI and conducted by Dr. Ole Raaschou-Nielsen at the Danish Cancer Institute and his colleagues. Research Report 222 contains the detailed Investigators' Report and a Commentary on the study prepared by the HEI Review Committee.



Statement 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").

diseases. They also used multivariate linear regression models to investigate the associations between these air pollutants and cardiometabolic biomarkers and blood pressure.

Dr. Raaschou-Nielsen and colleagues conducted several multiexposure analyses with mutual adjustment for air pollution, noise, and green space. The investigators estimated additive effects (i.e., absolute risk) to assess interactions between these environmental factors.

KEY RESULTS

Adults in the nationwide cohort were exposed to average air pollutant concentrations around or below the US National Ambient Air Quality Standards and new European standards for annual fine particulate matter and nitrogen dioxide concentrations. For all four traffic pollutants, Dr. Raaschou-Nielsen and colleagues observed higher mean concentrations from other sources compared to mean concentrations from local traffic sources. Correlations were moderate to high across pollutants (r > 0.73) and sources (r: 0.42 to 0.72), but low to moderate for the relationships between air pollutants and traffic noise (r: 0.19 to 0.53) and air pollutants and lack of green space (r: –0.07 to 0.40).

In the nationwide cohort, the investigators found that higher ambient (outdoor air) concentrations of each of the four air pollutants were associated with higher risks of each of the cardiometabolic disease outcomes, confirming findings from other studies. For example, a 5-μg/m^3 increase in annual average fine particulate matter was associated with a 12% higher risk of type 2 diabetes, a 15% higher risk of heart attack, and a 22% higher risk of stroke (**Statement Figure 2**). The investigators found that additionally adjusting for detailed lifestyle information beyond adjusting for multiple individual- and neighborhood-level registry-based sociodemographic factors did not meaningfully change the magnitude of the effects, presented as hazard ratios. Factors that did seem to have some modifying effect on cardiometabolic outcomes were gender, level of education, income, and experience of financial stress in the last 5 years. Furthermore, the air pollution source also had some effect on cardiometabolic outcomes: air pollution from local traffic sources was generally more strongly associated with a risk of type 2 diabetes, whereas air pollution from all other sources was more strongly associated with a risk of heart attack and stroke (Statement Figure 2).

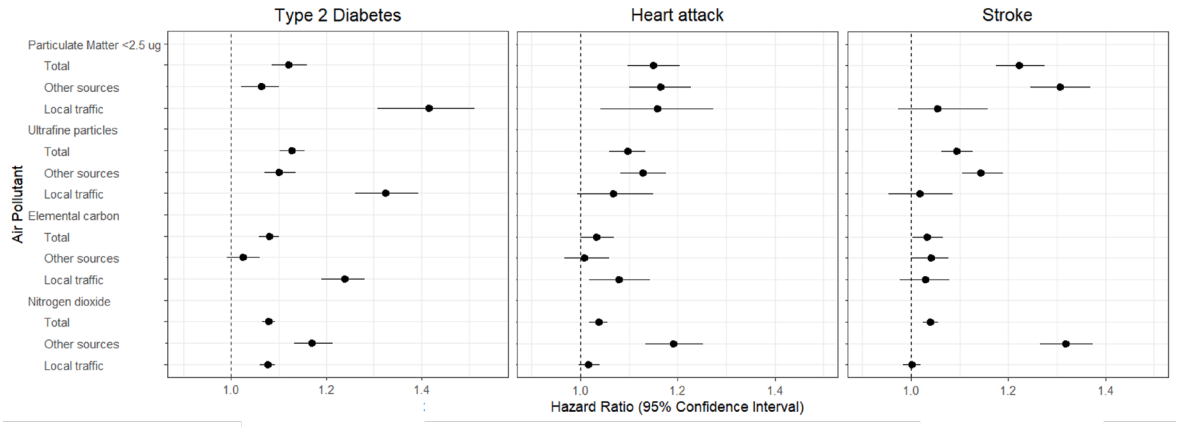
The investigators observed consistent patterns of higher hazard ratios among single-exposure analyses than for the multiexposure analyses with mutual adjustment for air pollution, noise, and green space. In the multiexposure analyses, air pollution, noise, and a lack of green space all influenced the risk of type 2 diabetes and heart attack, whereas only air pollution and noise influenced the risk of stroke.

In the smaller Diet Cancer and Health – Next Generations cohort, Dr. Raaschou-Nielsen, and colleagues found that exposure to traffic-related air pollutants was associated with higher cholesterol and blood pressure, while associations with other biomarkers were mixed. Cholesterol and blood pressure are known contributors to cardiometabolic disease.

INTERPRETATION AND CONCLUSIONS

In summary, this study represents an important contribution to our knowledge about exposure to multiple, co-occurring environmental factors related to traffic concerning the risk of cardiometabolic diseases and their suspected biological mechanisms. This study found that higher levels of ambient traffic-related air pollutants, noise, and lack of access to residential green space are all individually associated with a higher risk of type 2 diabetes, heart attack, and stroke. However, the magnitude of the associations varied depending on the sources of air pollutants, exposure mixtures, and individual and neighborhood-level contextual factors. Additionally in this study, associations between exposure to individual pollutants and chronic cardiometabolic diseases were stronger compared to associations adjusted for other exposures. Finally, the study found associations between exposure to traffic-related air pollutants and increases in cholesterol and blood pressure, which are known contributors to cardiometabolic disease, supporting the primary findings.

The report presents important progress in better understanding exposure to multiple correlated traffic-related environmental factors in relation to cardiometabolic outcomes. The finding that air pollutants from local traffic sources were less strongly associated



Statement Figure 2. Associations between air pollutants per fixed unit increase and risk of type 2 diabetes, heart attack, and stroke among the Danish Nationwide Cohort. 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.

with increased risk of heart attack and stroke and more strongly associated with increased risk of type 2 diabetes than all other sources presents interesting differences that warrant further study to inform local regulations to protect public health. This study was unable to differentiate between sources of air pollution greater than 25 km away from the residence, and it is possible that the main contribution of all sources farther away 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).

Other important contributions are the high-resolution spatiotemporal exposure assessment of noise and modeled ultrafine particle exposure — which is challenging and not readily available in many epidemiological studies — and the efforts toward modeling exposures to multiple environmental factors to improve understanding of the public health risks of joint exposures, better reflecting real-world exposure scenarios.

Ultimately, this study has documented that exposure to traffic-related air pollutants, noise, and a lack of green space is associated with an increased risk of type 2 diabetes, heart attack, and stroke, and the air pollutant sources, presence of other risk factors, and exposure to multiple other factors influence those risks.

INVESTIGATORS' REPORT

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

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ABSTRACT

Introduction We conducted the HERMES study to address the role of source-specific air pollution and the independent effects of air pollution, noise, and green space as well as the identification of susceptible subgroups defined by sociodemographic characteristics, stress conditions, and comorbidity in relation to cardiometabolic health. We studied three cohorts, a chemistry transport model (CTM*) system, a noise model, a high-resolution land use map, and Danish registries on health and sociodemographic variables at individual and small-area levels.

Methods Using Danish registries we defined a cohort of about 2 million persons living in Denmark. We also used data from the Danish National Health Survey (DNHS) (n = 246,766) and the Diet Cancer and Health – Next Generations cohort (DCH-NG) (n = 32,851). The Danish registries provided sociodemographic data at individual and small-area levels and allowed identification of medical diagnoses, comorbidity, and financial stress. The other two cohorts included information on lifestyle habits and measurements of blood pressure and biomarkers. We used Cox models for analyses of associations between exposures and type 2 diabetes, myocardial infarction (MI), and stroke. For analyses of interactions, we used both Cox and Aalen models and multivariate linear regression models for the analyses of air pollution and biomarkers.

Results Air pollution concentrations correlated well with measurements. Analyses of associations between air pollution and type 2 diabetes, MI, and stroke adjusted for individual and area-level sociodemographic variables showed that further adjustment for individual lifestyle had minimal effect on the risk estimates. All four air pollutants were associated with a higher risk of each of the three endpoints. The local traffic contribution to air pollution seemed more important for risk of type 2 diabetes than the contribution from all other sources combined, whereas for MI and stroke, the contribution from all other sources seemed most important. The most consistent interaction was a stronger association between air pollution and type 2 diabetes, MI, and stroke among those with comorbidity. For MI and stroke, we found several interactions on the absolute scale that could not be detected on the relative scale. In multiexposure analyses, we found that particulate matter ≤2.5 µm in aerodynamic diameter ($PM_{2.5}$) was most important for cardiovascular diseases, and ultrafine particles (UFPs) were most important for type 2 diabetes. We also found that noise and lack of green space were associated with all three endpoints. Analyses of the DCH-NG cohort showed associations between exposure to air pollution and higher concentrations of non–high-density lipoprotein, lower concentrations of high-density lipoprotein, and higher blood pressure. The contribution to air pollution from sources other than local traffic seemed mainly responsible for these associations.

Conclusions We found that $PM_{2.5}$, UFPs, elemental carbon (EC), and nitrogen dioxide (NO_2) were all associated with type 2 diabetes, MI, and stroke in single-pollutant models. However, in multiexposure analyses that included noise and green space, only UFPs for type 2 diabetes and $PM_{2.5}$ for MI and stroke remained associated, suggesting that these are the main air pollutants responsible for increasing the risk of cardiometabolic disease. Noise and lack of green space were also associated with cardiometabolic diseases in multiexposure models. We found that air pollution from local traffic was most important for risk of type 2 diabetes, whereas air pollution from other sources was most important for the risk of MI and stroke, which could relate to different air pollution mixtures and/or different biological pathways. Associations between air pollution and type 2 diabetes, MI, and stroke were consistently stronger among individuals with comorbidity, indicating higher susceptibility to negative air pollution effects in this subpopulation. The results of the interaction

This Investigators' Report is one part of the Health Effects Institute Research Report 222, which also includes a Commentary by the Review Committee and an HEI Statement about the research project. Correspondence concerning the Investigators' Report may be addressed to Dr. Ole Raaschou-Nielsen, Danish Cancer Institute, Strandboulevarden 49,2100 Copenhagen, Denmark; email: *ole@cancer.dk*. No potential conflict of interest was reported by the authors.

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

analyses showed that higher risk estimates among those of low socioeconomic status could be detected when estimating absolute risk but not when estimating relative risk, indicating that the best picture of effect modification is provided when expressed by both relative and absolute risk. The biomarker study showed expected associations between exposure to air pollution and blood lipid levels and blood pressure.

INTRODUCTION

Previous research has demonstrated associations between air pollution and the risk of various major diseases, including MI, stroke, and diabetes, which are all widespread and have major impacts on lost life years and quality of life. However, six important research questions remain open:

1. Which source(s) of air pollution is responsible for the observed health effect? This question is of major importance for the development of efficient prevention strategies, and traffic-related air pollution has attracted much attention (HEI 2010, 2022).
2. Which air pollutant, or submixture of air pollutants, is most important for the health effect under study? This is an analytical challenge because air pollution always occurs as a mixture of many correlated air pollutants.
3. What are the health effects of UFPs? They are potentially more harmful than larger particle fractions because they dominate the particle number concentration, have a large reactive surface area, can pass from the airways into the bloodstream, and translocate to other organs. The health effects of UFPs are an understudied research area, most likely because modeling and measuring UFPs are challenging.
4. What are the associations of residential exposure to air pollution, road traffic noise, and lack of green space — correlated aspects of modern urban living — to negative health effects? These three environmental domains should preferably be studied in parallel to best establish their individual and combined effects on health.
5. What are the associations between air pollution and health effects when considering sociodemographic factors, stress conditions, and comorbidity? Identification of susceptible subgroups may facilitate focused prevention measures. Previous studies have provided mixed results, and analyses of relative and absolute risk might provide different results.
6. (6) What are the biological pathways by which air pollution exerts influence on the development of diseases? Shedding light on these pathways could facilitate a better understanding of the causal links between air pollution and health effects and make stronger conclusions possible.

For comprehensive introductions and previous literature related to these research questions, we refer to our scientific articles, published as part of the HERMES project. For type 2 diabetes, we refer to Sørensen and colleagues (2022b, 2022c, and 2023); for MI, we refer to Poulsen and colleagues (2023a, 2023b, and 2023c); for stroke, we refer to Poulsen and colleagues (2023d, 2023e, and 2023f); and for biological mechanisms, we refer to Roswall and colleagues (2023).

We conducted the HERMES study to address these questions. We took advantage of both nationwide registry-based cohorts and questionnaire-based Danish cohorts, a state-of-the-art CTM system, the assessment of air pollution at high spatial and temporal resolution, a high-quality noise model, a high-resolution land use map, and high-quality Danish registry information on health and sociodemographic variables at the individual and small-area level.

The HERMES study has resulted in 19 scientific articles and the present report summarizes the results from these articles. Therefore, in the present report, we often refer to these articles for more comprehensive and detailed reporting of, for example, methods, results, and the data on which figures are based. We have provided a full list of the articles from the HERMES study at the end of this report.

OBJECTIVES

The overall aim of the HERMES project was to provide answers to the questions asked in the *Introduction* regarding the associations between air pollution and risk of type 2 diabetes, MI, and stroke.

Objectives included

- developing a CTM to assess concentrations of UFPs at address-level resolution
- investigating the importance of additional adjustments for lifestyle variables in analyses of air pollution and cardiometabolic diseases that had already been adjusted for registry-based sociodemographic variables
- analyzing associations between air pollutants ($PM_{2.5}$, UFPs, EC, and NO_2) and risk of type 2 diabetes, MI, and stroke, including assessment of risk in association with the contributions to air pollution from local road traffic and other sources
- investigating if associations between air pollution and type 2 diabetes, MI, and stroke differed according to sociodemographics, financial stress, and comorbidity
- analyzing concomitant residential exposure to air pollutants, road traffic noise, and green space in relation to risk of type 2 diabetes, MI, and stroke
- investigating associations between air pollution and noise, and cardiometabolic biomarkers and blood pressure.

METHODS, DATA, AND STUDY DESIGN

THE THREE STUDY POPULATIONS

Danish Population

A unique personal identification number has been allocated to all Danish residents since 1968. The identification

number allows all residents to be traced in and across all health and administrative registers (Schmidt et al. 2014). For the Danish Population (DK-POP) cohort, we identified Danish residents in the Civil Registration System (C.B. Pedersen 2011), which also provided information about emigration from Denmark. We identified all people in Denmark born after 1920 who were residing in Denmark on January 1, 1979, and who had a continuous Danish address history from January 1, 1979 (or birth) until January 1, 2005. Because the studies on long-term health effects addressed disease incidence, we excluded those people with the disease under study at baseline. We also excluded those missing data for a covariate. The cohort for the first study of type 2 diabetes, which addressed overall associations, consisted of people 35 years or older who were followed up from January 1, 2005, or the date when a participant turned 35 years old, whichever came last (baseline). The cohort for the two other type 2 diabetes studies and the MI and stroke studies, consisted of people 50 years or older who were followed up from January 1, 2005, or the date when a participant turned 50 years old, whichever came last (baseline). We chose to start follow-up for type 2 diabetes at an earlier age than for cardiovascular diseases because type 2 diabetes is diagnosed in relatively large numbers at younger ages than MI and stroke. For example, in 2017, 22.6% of the incident type 2 diabetes cases in Denmark were diagnosed in people younger than 50 years of age (84% of these people were diagnosed between 35 and 50 years of age). In contrast, only a few people are diagnosed with MI and stroke before 50 years of age. For example, a report from 2009 by Kildemoes and Hanehøj found that for ischemic heart disease, 12% of the incident cases in Denmark were diagnosed in people below 50 years of age. Therefore, we started follow-ups for MI and stroke at the age of 50 years. Subsequent analyses using Aalen models required starting follow-up of the type 2 diabetes study at age 50 (see below about Aalen models).

Danish National Health Survey

From February to April of 2010, 298,550 people were invited to participate in the Danish National Health Survey (DNHS) and three years later a second set of invitations were sent from February to April 2013 to 300,450 people (Christensen et al. 2022; Sørensen et al. 2022a). In total, 324,988 people accepted the invitation. At enrollment, all participants filled in a questionnaire, which included questions on smoking, diet, physical activity, height, and weight. Participants were followed from baseline in 2010 or 2013 until December 31, 2017.

Diet, Cancer, and Health — Next Generations

Between 2015 and 2019, 183,764 individuals were invited to become part of the Diet, Cancer, and Health — Next Generations (DCH-NG) cohort (Petersen et al. 2022). Inclusion criteria were age ≥18 years, registered in the Danish Civil Registration System, and living at an address in Denmark. Of these, 41,980 accepted the invitation and delivered a blood sample, and were thus eligible for the biomarker study. At enrollment, all participants completed a questionnaire about lifestyle and food frequency, underwent a physical exam, and delivered biological samples at the study centers.

The HERMES study was approved by the Institutional Review Board at the Danish Cancer Institute. Participants in the DNHS and DCH-NG cohorts gave written informed consent and were not paid.

DATA ON CIVIL STATUS AND HEALTH

The Civil Registration System provided data on marital/cohabitant status and dates of birth, emigration, and death. We identified incident diabetes cases using the National Prescription Register (Kildemoes et al. 2011) and the National Patient Register (Lynge et al. 2011). The Prescription Register holds information on all dispensed drugs. We defined a type 2 diabetes case as a person with two contacts with either a hospital (International Classification of Diseases Eighth Revision [ICD 8]: 250 or International Classification of Diseases Tenth Revision [ICD10]: E11) and/or a pharmacy using the Anatomical Therapeutic Chemical system (ATC) codes A10AE54, A10AE56, and A10B, though for A10B excluding A10BJ02 Saxenda (but including A10BJ02 Victoza) as well as women receiving A10BA02 in combination with G03GB02 or G03HB or a diagnosis of polycystic ovary syndrome (ICD10: E282). We registered a person as a case from the second contact. A type 1 diabetes diagnosis was defined as ICD8: 249 or ICD10: E10 or at least one dispensed prescription with ATC A10A (insulins and analogues), excluding A10AE54 and A10AE56. These algorithms were developed and are currently used by Danish health authorities (Agency 2021). Until 2012, diabetes was diagnosed in Denmark using a combination of data in the National Patient Register, registration of chiropody (as diabetic patient) in the National Health Service Register, five blood-glucose measurements in a 1-year period in the National Health Service Register, two blood-glucose measurements per year in 5 consecutive years in the National Health Service Register, and the Prescription Register. However, such registration of diabetes is no longer updated (closed in 2012) because identification of diabetes based on chiropody and blood-glucose measurements was later found to be associated with a high risk of misclassification.

We identified all cases of MI (ICD8: 410 or ICD10: I21) and stroke (ICD8: 431–434, 436 or ICD10: I61–I64) recorded as a primary diagnosis in the National Patient Register or with the same codes as the primary cause of death in the Danish Register of Cause of Death.

Individuals identified as having cases of diabetes (type 1 or type 2), MI, or stroke in one of these registries — from the start of the registration (Patient Registry: 1977; Mortality Registry: 1970; Prescription Register: 1994) until baseline — were excluded in the analyses of type 2 diabetes, MI, and stroke, respectively. All persons with a first incident diagnosis after baseline were counted as cases.

We used the National Patient Registry (Lynge et al. 2011) to calculate the Charlson comorbidities index, which is a standard method of categorizing comorbidities of patients based on ICD codes (Roffman et al. 2016). We calculated the index as a time-dependent variable, summing up the score based on diseases during 5 previous years, with a 1-year lag period to minimize the risk that the disease under study would impact the index. For the analyses, we categorized the comorbidity index score into 0, 1, or ≥2.

SOCIODEMOGRAPHIC AND STRESS VARIABLES

We selected covariates a priori. The registries at Statistics Denmark provided annually updated information about the highest attained educational level (mandatory, secondary/vocational, medium/long), individual income (quintiles), household per capita income (quintiles), occupational status (high level white-collar, low level white-collar, blue-collar, unemployed, retired), cohabiting status (married/cohabiting, other), and country of origin (Denmark, other). Quintiles of individual and household income were determined separately for each sex and calendar year combination to allow for inflation and sex-specific income disparities. The data included 2,160 parishes, with a mean area of 16 km^2 and a median population of 1,032 people. We obtained annual information about population density for each parish and retrieved yearly information on parish-level socioeconomic indicators: the proportion of inhabitants with a criminal record, living in single-parent households, having only mandatory education, engaged in manual labor, having an income in the lowest quartile of the national distribution, living in social housing, being unemployed, and having a non-Western background. A Western background was defined as either being a citizen or having at least one parent being a citizen of a Western country (the European Union, the United Kingdom, Norway, Iceland, Liechtenstein, Switzerland, Andorra, San Marino, the Vatican, Australia, New Zealand, the United States of America, and Canada).

We used the registers of Statistics Denmark to identify people experiencing one or more "financial stress event(s)" defined as family income below the Danish relative poverty limit, personal or family income drop of 50% or more between 2 consecutive years, and/or loss of job. Based on this, we created a time-dependent dichotomous variable of one or more financially stressful event(s) in the last 5 years (yes/no).

LIFESTYLE IN THE DNHS

The following information on lifestyle habits was obtained from the baseline questionnaire: smoking status (current, occasional, former, and never), smoking intensity (among current smokers, g tobacco/day), intake of alcohol (drinks/week), intake of fruit (0–2 times/week, 3–6 times/week, 1–4 times/day, ≥5 times/day), intake of salad (never/rarely, 1–2 times/week, 3–4 times/week, ≥5 times/week), intake of red meat (never/rarely, 1–2 times/week, 3–4 times/week, ≥5 times/week), physical activity during leisure time (highly active, ≥4 hours/week of sport; medium active, mainly light physical activity, such as walking and gardening, and <4 hours/week of sport; inactive, only limited physical activity), height (cm), and weight (kg).

For 35,698 people, we lacked information on one or more of the following nine covariates (percentage missing of the total cohort): educational level (1.4%), smoking status (2.4%), smoking intensity (2.7%), intake of alcohol (5.4%), intake of fruit (2.9%), intake of salad (1.6%), intake of red meat (1.4%), physical activity (3.5%) and/or body mass index (BMI) (3.6%). All other covariates were complete. We lacked information on only one or two of these covariates for most (84.3%) of these people. We assumed that missing covariates were missing at random and imputed missing information for the above covariates (to reduce bias) according to the fully conditional specification method (25 imputations, 20 iterations for each imputation).

THE DEHM/UBM/AIRGIS MODELING SYSTEM

Integration of Three Models

The air pollution modeling system (DEHM/UBM/AirGIS) is based on emissions, meteorology, and atmospheric physics and chemistry and is a fully deterministic CTM system (*http://au.dk/AirGIS/*) (Jensen et al. 2017; Ketzel et al. 2011; Khan et al. 2019) (**Figure 1**). The system consists of a coupling of three air pollution models: (1) the Danish Eulerian Hemispheric Model (DEHM), which models air pollution in the Northern Hemisphere and provides air pollution concentrations at a 5.6 km × 5.6 km resolution within a domain covering Denmark (Brandt et al. 2012; Christensen 1997); (2) the Urban Background Model (UBM), which uses results from the DEHM and detailed Danish emissions as input to give concentrations with a 1 km × 1 km resolution over Denmark (Berkowicz 2000; Brandt et al. 2003; Frohn et al. 2022); and (3) the Operational Street Pollution Model (OSPM), which uses results from the UBM model, street traffic emissions, and street geometry as input and provides concentrations for every street with more than 500 vehicles/day (Ketzel et al. 2012; Ketzel et al. 2021). The DEHM, UBM, and OSPM models cover hemispheric/regional, local/urban, and street scale, respectively, and apply emission inventories and meteorological data from a numerical weather forecast model. The integration of modeling results carefully avoids counting the same emissions twice. All three models handle the physical (atmospheric transport and dispersion) and chemical processes in the atmosphere by numerically solving the basic governing equations.

Emissions

The data for anthropogenic emissions outside of Denmark are obtained from the EMEP WebDab emission database (EMEP-CEIP 2023; Mareckova et al. 2008) and the ECLIPSE V6b database (Klimont et al. 2017). Emissions from wildfires are based on the reanalysis of the tropospheric chemical

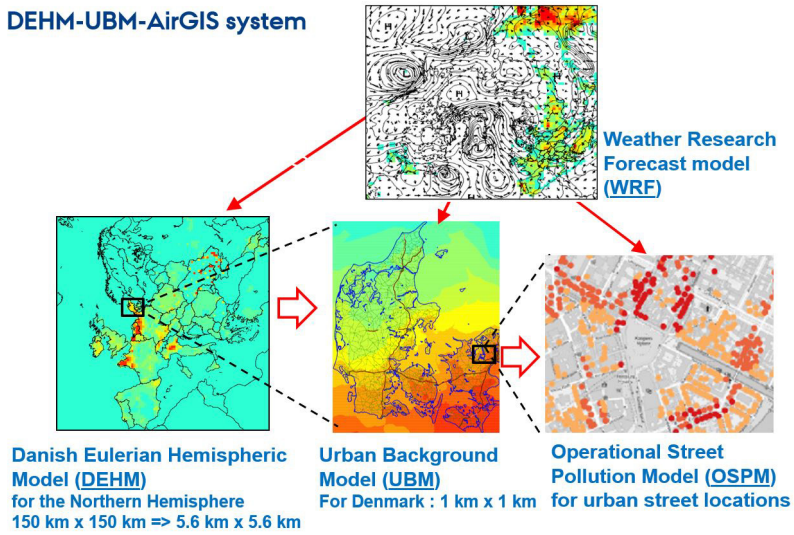

Figure 1. Integration of several models in the DEHM/UBM/AirGIS modeling system.

composition inventory (RETRO) compiled by Schultz and colleagues (2008) for the period before 2003, and on the Global Fire Assimilation System (GFAS) database from 2003 and onward, which is provided by the Copernicus Atmospheric Modeling Service (CAMS), and is based on satellite detections of wildfires. Natural emissions of biogenic volatile organic carbons (VOCs) from vegetation are based on the MEGAN model implemented in DEHM (Guenther et al. 2006) while other natural emissions are based on the Global Emissions Initiative (GEIA) (Frost et al. 2013). Emissions from ships are based on the inventory from the EPITOME project (Geels et al. 2021), which is compiled from data from the Ship Traffic Emission Assessment Model (STEAM) (Johansson et al. 2017). The ship emissions have global coverage up to 73°N for the year 2015. We extrapolated this detailed spatial distribution for 2015 to all other years of our modeling period using annually updated emission factors and taking into account the effects of the sulfur emission control area and trends in shipping activities.

The emission data for Denmark are obtained from the Danish national emission inventory model SPREAD (Plejdrup et al. 2021) for the period 1990–2020. These Danish national emissions are based on registers of high quality and detail (for example, the Civil Registration System, the Building and Dwelling Register, the Central Husbandry Register, the General Agricultural Register, the Danish Land Use Matrix, annual databases from the Danish Energy Agency, detailed data from the Danish Association of Chimney Sweepers, and the National Road and Traffic Database) (Jensen et al. 2019). These emission data include, for example, information on stack emissions, traffic, industries, other mobile sources, and agriculture down to details of single farms and individual animals (Plejdrup et al. 2021). The emission inventories are subject to annual review from international experts to ensure that the calculations are done following best practices and meet the internationally established quality criteria.

The inventories organize the emissions according to the Selected Nomenclature for Air Pollution (SNAP) classification (EEA 2007) with the main categories being: SNAP 01, combustion in energy and transformation industries; SNAP 02, nonindustrial combustion plants; SNAP 03, combustion in manufacturing industry; SNAP 04, production processes; SNAP 05, extraction and distribution of fossil fuels and geothermal energy; SNAP 06, solvents and other product use; SNAP 07, road transport; SNAP 08, other mobile sources and machinery; SNAP 09, waste treatment and disposal; SNAP 10, agriculture; and SNAP 11, other sources and sinks

Denmark follows international good practices for inventory compilation (EEA 2019) and the inventories adhere to the EMEP/EEA air pollutant emission inventory guidebook (EEA 2019). The emission estimations are done at the most detailed SNAP level (e.g., SNAP 010101) and can then be aggregated, for example, to match the international nomenclature for reporting (NFR, see EEA, 2019) or to main SNAP categories.

The uncertainty of the data in the Danish emission inventory depends on the emission category (EEA 2007) and the pollutant considered. For some sectors (e.g., large point sources such as power plants [included in SNAP 01] and road transport [SNAP 07]), the data quality is high, with a large share of the emissions covered by direct measurements or very detailed information on technology and abatement. For other sectors, such as small-scale combustion (SNAP 02), the uncertainties are higher due to a large number of small installations for which we have only limited knowledge of the technology and abatement measures. Regarding pollutants, the uncertainty for nitrogen oxides (NO_x) is generally lower than for particulate matter and EC. This uncertainty is related to the main sources of these pollutants. For NO_x, major sources are large combustion plants and road transport, where the data quality is high and uncertainties low. For particulate matter, small-scale combustion and diffuse sources (such as mining and construction) are important sources of emission. We expect the largest uncertainty in the emission estimates will be for UFPs (or its proxy, particle number) because this is a relatively new field without international guidance documents for compiling UFP inventories and no international obligations to report emission inventories. UFP emissions are not currently part of the Danish emission model SPREAD, and the method for deriving UFP emissions is described later in this report.

The contributions from different sources to air pollution differ by time, place, and pollutant as illustrated in **Figure 2**. The figure is based on official emission inventories as described above. This figure reflects that in our databases, "ships" is singled out from the SNAP 08 category where it originally belonged.

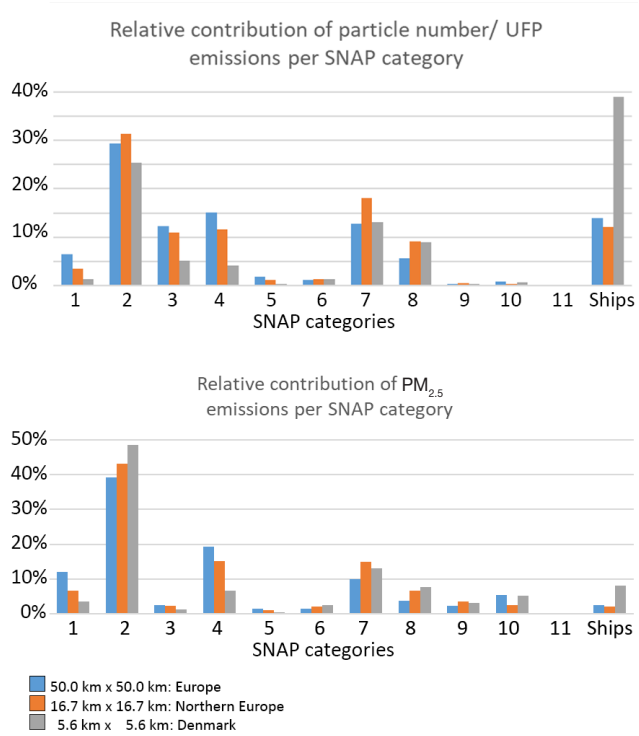

Figure 2. Relative contribution of source categories to emissions of particle number / UFPs (upper) and primary $PM_{2.5}$ (lower) in 2010. Comparisons between Europe (50 km × 50 km resolution, blue), Northern Europe (16.7 km × 16.7 km resolution, orange), and Denmark (5.6 km × 5.6 km resolution, grey).
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In Denmark, nonindustrial combustion plants (SNAP 02, for example, wood stoves), road transport (SNAP 07), and ships contribute most of the emissions of both pollutants.

Meteorology

In addition to emissions, meteorology is an important factor driving the modeling system. The meteorology is based on global reanalyzed data. The global models and the limited-area weather forecast model, which produce input data to the air pollution models, have been rerun back in time to maintain equal and high-quality data throughout the period from 1979 to the present. The meteorological parameters that served as input for the air pollution models included temperature, wind speed, wind direction, global radiation, and humidity. This information is based on measurements and models and is incorporated in the air pollution modeling system in the following way: All air pollution models (DEHM, UBM, and OSPM) receive hour-by-hour updated meteorological variables modeled using the Weather Research Forecast (WRF) model, which is a state-of-the-art weather forecast community model developed and maintained by National Center for Atmospheric Research (USA) and applied globally at many universities and research institutes (Skamarock et al. 2021). The WRF model is driven by nudging and boundary conditions via the newest and probably best global reanalysis, ERA5, which combines vast amounts of historical observations of wind, pressure, temperature, humidity, clouds, surface temperature, snow, and ice cover from, for example, ground stations, radiosondes, and satellites into global estimates using advanced modeling and data assimilation systems (Hersbach et al. 2018).

Modeling Dispersion and Chemistry in the Atmosphere

The DEHM is an Eulerian model using input data from meteorology and air pollution emissions in the Northern Hemisphere, where atmospheric transport and dispersion, chemical reactions in the lower part of the atmosphere, and dry and wet deposition of air pollutants are calculated in a three-dimensional grid covering the Northern Hemisphere. In the vertical direction, the model is divided into 29 layers covering the lowest ~15 km of the atmosphere. The DEHM has a 150 km × 150 km horizontal resolution and a two-way nesting capability, facilitating a higher resolution over limited areas, resulting in a 5.6 km × 5.6 km resolution over Denmark, using four domains in total.

The UBM calculates the local background air pollution in Denmark at a 1 km × 1 km resolution based on the Danish emission inventories, meteorological data, and regional background air pollution concentrations from DEHM. The UBM includes a Gaussian plume approximation for the calculation of the dispersion and transport of the air pollutants from every 1 km × 1 km emission cell within 25 km from a receptor point and a simple chemical model accounting for the photochemical reactions of NO, NO_2, and O_3.

We use the street canyon model, OSPM, to calculate air pollution concentrations at 2 meters above the sidewalk of street addresses (**Figure 3**). Input data include meteorology from the WRF model, background air pollution concentrations from the UBM, emissions from traffic at the street address, and street and building configuration at the address. The model includes simple chemical reactions and dispersion of air pollutants in the street canyon due to meteorological conditions, turbulence induced by traffic, and influence of the street geometry. The OSPM is a parametrized model combining a Gaussian plume model for the direct emissions transported from the vehicles to the receptor point and a box model for the recirculated air "trapped" in the street canyon.

Output

The modeling system operates with an hourly temporal resolution and at an address-level spatial resolution. **Figure 4** shows annual mean concentration maps of Denmark produced by the UBM model with input from DEHM.

The UFP Model

As part of the HERMES project, we developed the DEHM/UBM/AirGIS system to include, for the first time, particle number concentrations (PNC) as a proxy for UFPs (Frohn et al. 2021; Ketzel et al. 2021).

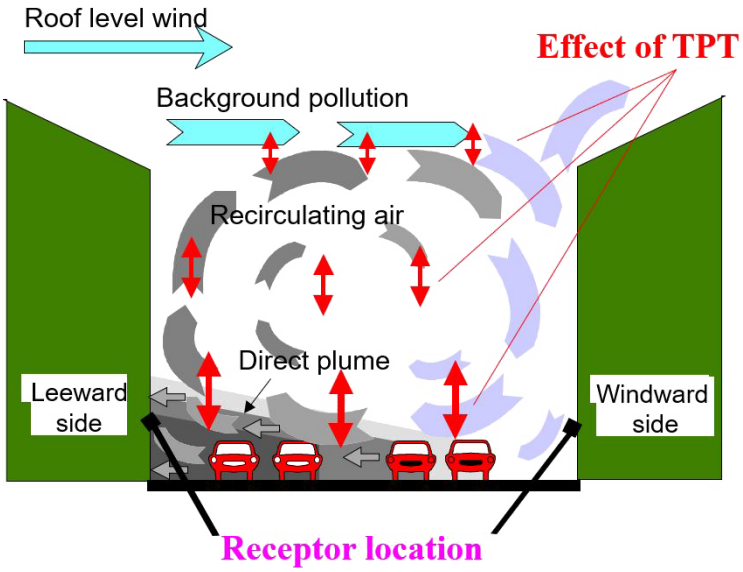

Figure 3. Concept of the OSPM model, including an illustration of the effect of traffic-produced turbulence (TPT) on the dispersion of pollutants near the traffic source.

Emission inventories are a crucial input for deterministic models, but existing emission inventories for PNC are scarce and incomplete, covering only a few emission sectors or a limited particle size range. After some attempts to use activity-based emission factors (e.g., number of emitted UFPs per vehicle-km or per kW), which resulted in unrealistic emission estimates, we developed and implemented a scaling method, where emission ratios were applied that relate PN emissions (in Aitken and Accumulation modes) to known mass emission of $PM_{2.5}$ components for each SNAP source sector. The emission ratios were related to the following $PM_{2.5}$ components: EC, organic matter, sulfates (SO4), or "residual" PM (earlier called "mineral dust" or "ash"). The development of these emission ratios was based on a database for European emissions developed by The Netherlands Organisation for Applied Scientific Research (TNO) (Denier van der Gon 2014). We applied the ratios to the mass emissions of the emission inventories described previously to obtain PNC emissions, which cover the same time span and spatial resolution as the other pollutants in the DEHM/UBM/AirGIS modeling system.

We implemented the M7 particle dynamics module (Vignati et al. 2004) in the DEHM model. The module includes four different aerosol modes in specific size ranges: nucleation (0–10 nm diameter), Aitken (10–100 nm), accumulation (100–1000 nm), and coarse (>1000 nm). The three larger modes appear as soluble and insoluble versions depending on the chemical composition, whereas the nucleation mode is always soluble (because in the model it exclusively consists of sulfuric acid). The processes of nucleation, coagulation, condensation, and particle growth are described in the M7 module. The dry deposition of PNC is calculated by combining the size distribution for each mode with size-dependent dry deposition velocities. When the DEHM model is run with the M7 module included, the chemical model is run simultaneously based on mass concentrations to ensure consistency. The modeled PNC concentrations for the sum of Aitken and accumulation mode particles were used as input for the UBM model. We modeled PNC in UBM and OSPM without including the particle dynamics. Our final modeling output for PNC did not include the very complex processes of particle formation, where nucleation mode particles are formed from gaseous precursors. These formation processes are primarily observed in rural areas. At urban and street level, particles smaller than 30 nm are locally produced and primarily emitted (from traffic, for example). These locally produced UFPs are included in the local emissions in the UBM and OSPM models. Thus, our modeling of PNC included local anthropogenic emissions of nucleation mode particles, but we did not model the complex nucleation processes leading to the formation of new particles at local scale.

Air Pollution from Local Traffic and Other Sources

The concept of the DEHM/UBM/AirGIS modeling system using emission data as a starting point allowed us to model air pollution both with and without the emissions from Danish road traffic (SNAP 07 code) to the local background (UBM) and without the contribution from the traffic at the street address (OSPM). Subtracting results from modeling with and without these traffic emissions enabled the apportioning of total pollutant levels into local road traffic ("local traffic") and all other contributions combined ("other sources"). "Local" refers to road traffic within 25 km. Note that the "other sources" also include road traffic more than 25 km away. An example of a contribution from "other sources" is nitrate particles formed in the atmosphere from NO_x emitted from road traffic far from the receptor point and transported over a long distance. The local road traffic contribution (i.e., from road traffic within 25 km) would approximate what local politicians, such as a city council, could influence by road traffic restrictions.

Validation of Modeling Results

We compared model predictions with measurements undertaken within the Danish air pollution monitoring network (Ellermann et al. 2022). For $PM_{2.5}$, we only included measurements by low volume sampler (LVS) instruments because these are the most reliable and the inclusion is in accordance with the reference method recommended by the European Air Quality directive. In this report, comparisons for different averaging times are based on identical measurement periods (except from Table 3). The number of measuring locations and available years of data differs between the pollutants and is a limiting factor, especially for the evaluation of the spatial model performance for UFPs and EC, for which

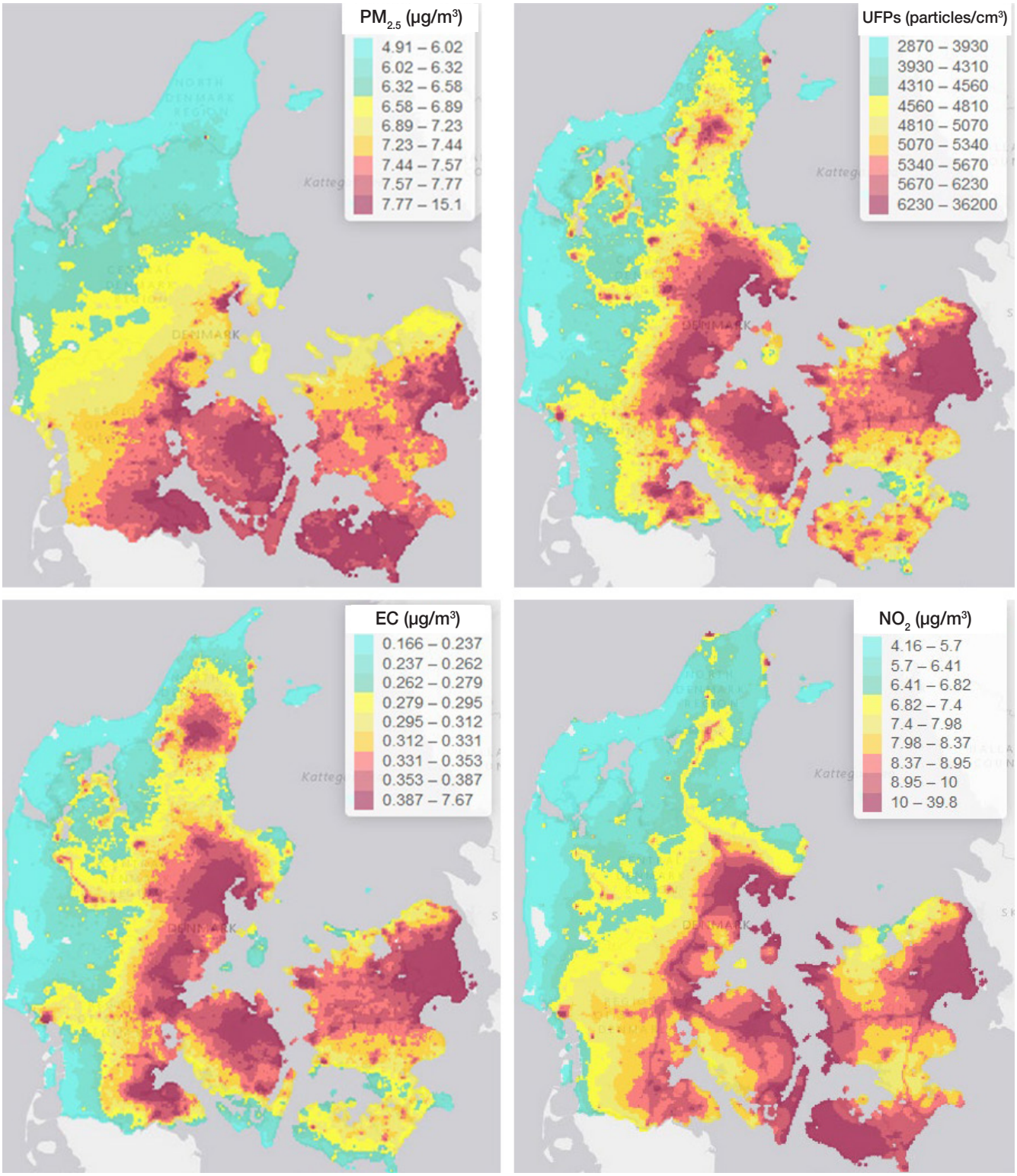

Figure 4. Concentration maps of Denmark for $PM_{2.5}$ (upper left), UFPs (upper right), EC (lower left), and NO_2 (lower right) for 2017, at a 1 km × 1 km spatial resolution, calculated with the UBM model.

there are only three locations with longer time series and one additional shorter time series. For EC, an additional short-term campaign at many locations is available to test the spatial performance of our modeling system. The best data coverage exists for NO_2 — both in number of locations (18) and length of time series. For $PM_{2.5}$, we can compare with data from nine locations.

We have also compared air pollution predictions with measurements from three monitoring campaigns covering many different locations. The first campaign covered 1,224 1-month measurements of NO_2 at 204 different locations (Ketzel et al. 2011), the second campaign covered 98 48-hour EC ($PM_{2.5}$ absorbance) measurements at 30 locations from 1999 to 2000 (Hvidtfeldt et al. 2018), and the third campaign covered 60 14-day EC measurements at 20 locations from 2009 to 2010 (Hvidtfeldt et al. 2018).

Further, **Figure 5** illustrates the ability of the DEHM/UBM/AirGIS system to predict day-to-day variation in $PM_{2.5}$, UFPs, EC, and NO_2 concentrations in a street in Copenhagen.

Tables 1–4 and Figure 5 show a general picture of high correlations between predicted and measured concentrations for all four air pollutants. A comparison between Table 1 and Table 2 shows that when considering both spatial and temporal (global) variation (Table 2), the correlation coefficients were higher than when considering exclusively temporal variation at one location (Table 1). Further, when comparing correlations for different averaging periods (24 hours to 1 year), Tables 1–4 show a consistent pattern of higher correlations for the longer averaging periods, except for EC at the urban background station (HCØ), with a very short time series of only five data points. Moreover, Table 1 indicates that the correlations for UFPs are highest for the street station (HCAB) and lower at urban background (HCØ) and the rural station (LVBY/Risø).

It is not possible to directly validate the separation of the total air pollution concentrations into the contributions from local traffic and other sources by comparing model predictions with measurements because measurements do not distinguish between the sources of the air pollutants. The validity of our source-allocation method, that is, comparing model results with and without the emissions from local street traffic (SNAP 07), relies on the quality of the emission inventory. The Danish emission inventory is of exceptionally high quality and is based on detailed registration of traffic on the entire Danish street network (Jensen et al. 2019) and on other sources of air pollution (Plejdrup et al. 2021). Other pieces of evidence in support of the validity of our method

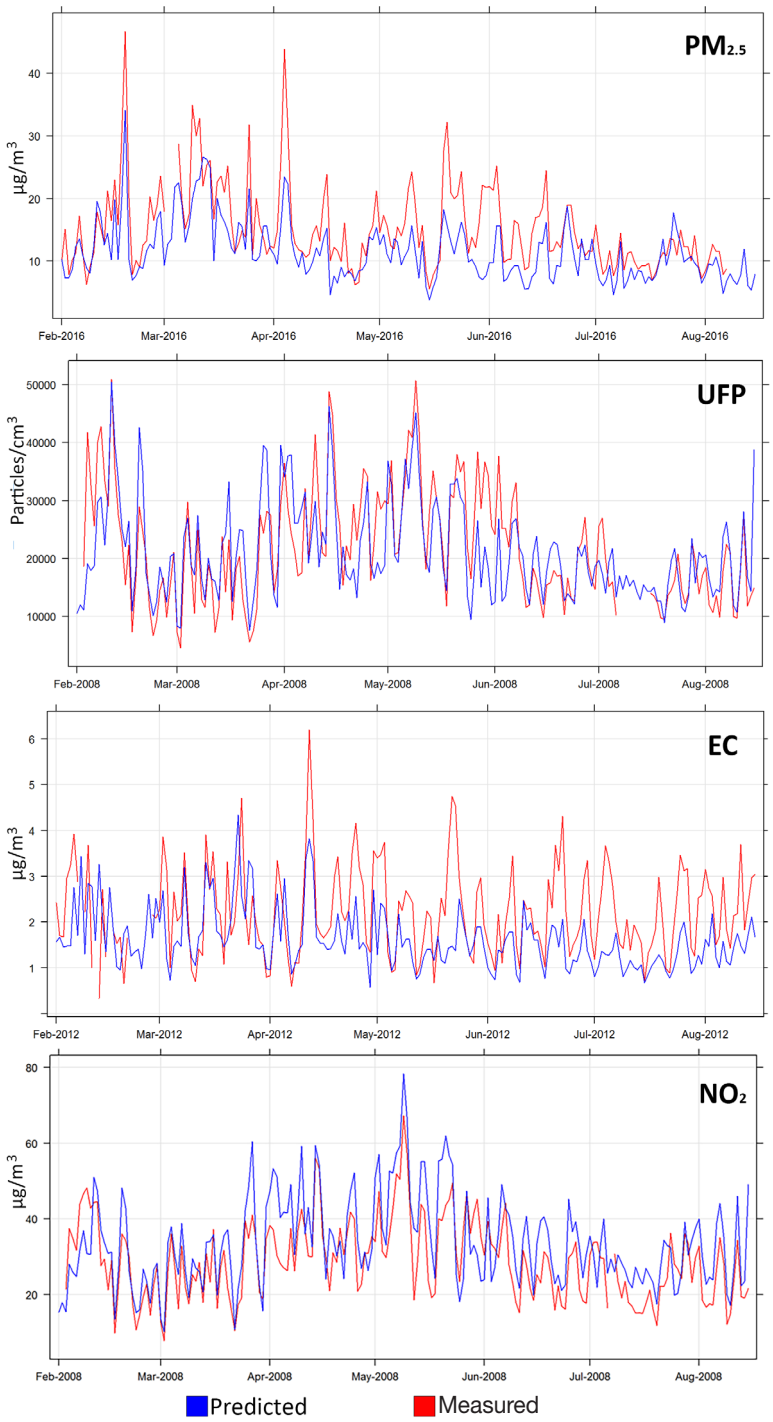

Figure 5. Time series of predicted (blue) and measured (red) daily air pollution concentrations of $PM_{2.5}$, UFPs (PNC>10), EC, and NO_2 at a street monitoring station (HCAB) in Copenhagen (temporal performance). The figure covers February to August, however, for different years due to the availability of measurements.

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Table 1. Correlation Coefficients (Temporal Performance) Between Predicted and Measured Air Pollution Concentrations at Three Monitoring Stations in Denmark (Street, Urban Background, and Rural)[a]

	Correlation Coefficients, $R_{Pearson}/R_{Spearman}$ (*n*)		
HCAB – street	**Daily Means**	**Monthly Means**	**Annual Means**
$PM_{2.5}$	0.75 / 0.75 (2,165)	0.83 / 0.85 (76)	0.87 / 0.86 (7)
UFPs ($PNC_{>10}$)[b]	0.71 / 0.73 (3,371)	0.81 / 0.80 (135)	0.91 / 0.93 (14)
EC	0.60 / 0.64 (3,006)	0.69 / 0.69 (104)	0.90 / 0.95 (9)
NO_2	0.71 / 0.71 (6,294)	0.65 / 0.62 (214)	0.69 / 0.57 (18)

	Correlation Coefficients, $R_{Pearson}/R_{Spearman}$ (*n*)		
HCØ – urban background	**Daily Means**	**Monthly Means**	**Annual Means**
$PM_{2.5}$	0.77 / 0.78 (2,218)	0.86 / 0.84 (77)	0.72 / 0.54 (7)
UFPs ($PNC_{>10}$)[b]	0.44 / 0.48 (3,524)	0.42 / 0.38 (139)	0.77 / 0.87 (16)
EC	0.50 / 0.57 (1,503)	0.73 / 0.75 (52)	0.65 / 0.30 (5)
NO_2	0.78 / 0.79 (6,344)	0.85 / 0.86 (213)	0.94 / 0.94 (18)

	Correlation Coefficients, $R_{Pearson}/R_{Spearman}$ (*n*)		
LVBY/Risø – rural	**Daily Means**	**Monthly Means**	**Annual Means**
$PM_{2.5}$	0.80 / 0.80 (2232)	0.89 / 0.88 (77)	0.82 / 0.82 (7)
UFPs ($PNC_{>10}$)[b]	0.48 / 0.54 (3257)	0.42 / 0.41 (127)	0.88 / 0.86 (13)
EC	0.67 / 0.78 (3068)	0.84 / 0.88 (108)	0.91 / 0.97 (9)
NO_2	0.72 / 0.76 (6398)	0.70 / 0.68 (215)	0.95 / 0.91 (18)

[a] The periods covered 2001–2018 but differed between the pollutants and stations. Results based on a low number of data points should be interpreted with caution, especially those for annual means of EC at the urban background station.

[b] UFPs (PNC>10): Particle number concentration for particles larger than 10 nm in diameter, a close proxy for UFPs.

Table 2. Correlation Coefficients Between Predicted and Measured Air Pollution Concentrations Measured at All Danish Monitoring Stations with Available Data (Temporal and Spatial Performance Combined)[a]

			Correlation Coefficients, $R_{Pearson}/R_{Spearman}$ (*n*)		
	Station (n)	**First Year**	**Daily Means**	**Monthly Means**	**Annual Means**
$PM_{2.5}$	9	2012	0.78 / 0.80 (14,866)	0.89/ 0.89 (506)	0.92 / 0.87 (47)
UFPs (PNC>10)	4	2001	0.69 / 0.68 (14,265)	0.83 / 0.73 (470)	0.91 / 0.88 (42)
EC	4	2010	0.76 / 0.83 (8,671)	0.90 / 0.92 (294)	0.99 / 0.90 (27)
NO_2	18	1982	0.84 / 0.87 (100,163)	0.91 / 0.93 (3,353)	0.94 / 0.94 (294)

[a] First year is given in the table; last year was 2018.

Table 3. Correlation Coefficients Between Predicted and Measured EC Concentrations in Denmark (Temporal and Spatial Performance Combined)

	Correlation Coefficients, $R_{Pearson}/R_{Spearman}$ (n)	
	48-Hour Means, 1999–2000 at 30 Locations	**14-Day Means, 2009–2010 at 20 Locations**
EC	0.67 / 0.74 (98)	0.80 / 0.80 (60)

Table 4. Correlation Coefficients Between Predicted and Measured NO_2 Concentrations at 204 Locations in Denmark, 1994–1995 (Temporal and Spatial Performance Combined)

	Correlation Coefficients, $R_{Pearson}$ (n)	
	1-Month Means	**6-Month Means**
NO_2	0.88 (1,224)	0.92 (204)

include the model's ability to reproduce temporal patterns (diurnal, weekly, and yearly) and absolute concentrations of traffic-related pollutants in streets with dense traffic. This is illustrated below by comparing modeled and measured air pollution at the street station HCAB (Copenhagen, Denmark, dense traffic) (**Figure 6**). The temporal patterns are aggregated for 2002–2016. Figure 6 shows an excellent reproduction by the modeling system of measured temporal patterns and absolute levels.

ADDRESS HISTORIES AND AIR POLLUTION MEASURES

The Civil Registration System provided complete residential histories for our study population, including exact dates of moving in and out. We established geocodes for each residential address in Denmark from the Building and Housing Registry and calculated concentrations of $PM_{2.5}$, UFPs, EC, and NO_2 at each address with the DEHM/UBM/AirGIS modeling system. For participants in the DK-POP and DNHS cohorts, we summarized the hourly concentrations into 1-month averages and subsequently calculated 5-year average concentrations taking into account all addresses during the 5-year period and weighted by time living at the addresses. We calculated running 5-year averages with an update every third month.

For the biomarker study of the DCH-NG participants, the hourly concentrations were summarized into averages over 24 hours, 72 hours, 7 days, 30 days, and 90 days before blood draw and blood pressure measurement.

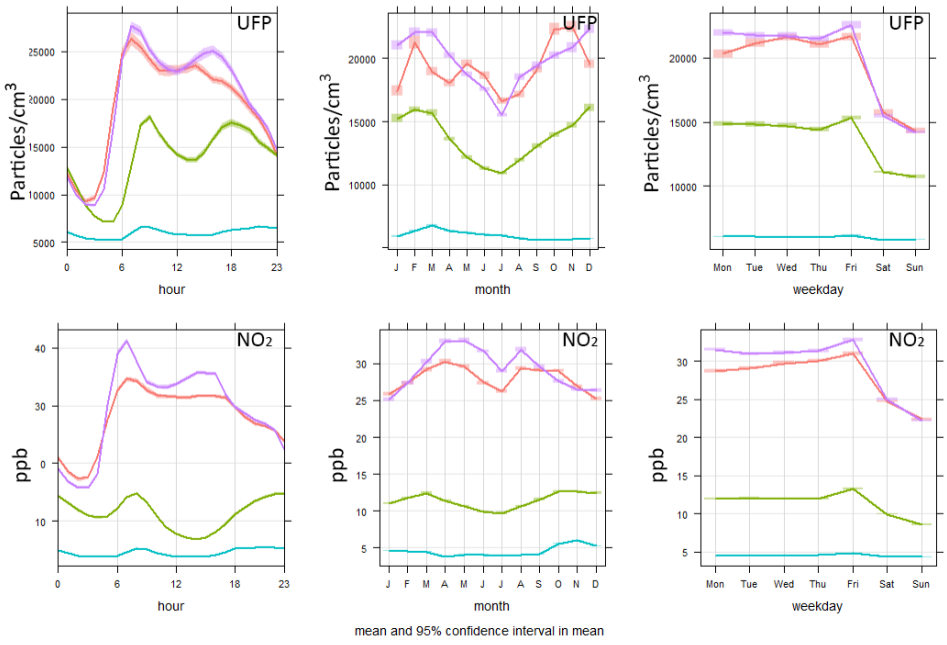

Figure 6. Comparison of temporal patterns of measured and modeled UFPs (upper row) and NO_2 (lower row) at the HCAB street station (temporal performance). Red: measured concentrations; purple: modeled with the DEHM/UBM/AirGIS system; green: urban background concentration modeled with DEHM/UBM; blue: regional background modeled with DEHM.

ROAD TRAFFIC NOISE AND GREEN SPACE

We used the Nordic Prediction Method (Bendtsen 1999) to model road traffic noise at the most- and least-exposed façades (LdenMax and LdenMin, respectively) of each residence for 2000, 2005, 2010, and 2015 (Thacher et al. 2020). Noise calculations were made using SoundPLAN (version 8.0, SoundPLAN Nord ApS). First, we generated a model where all three-dimensional building polygons (linked with address points), roads, and terrain were prepared in SoundPLAN for each year. Secondly, traffic data, traffic speeds, vehicle distributions, and noise barriers were

added. Lastly, noise levels were estimated and linked with each address point. Noise levels were calculated in the center of all facades of each residential building unit, and afterward, the most- and least-exposed facades of all Danish residential buildings were identified. In large blocks of apartments and townhouses, there were often several address points present inside the same building polygon. To control for this, buildings with more than two address points were divided into separate building polygons for each address point.

Input variables included geocode, height, light and heavy vehicle distribution, road type, travel speed, and annual average daily traffic for all Danish road links (Jensen et al. 2019). The model considered screening from buildings, terrain, noise barriers, and first- and second-order reflections. Urban areas, road surfaces, and large bodies of water were assumed to be fully reflecting and all other areas were considered fully absorbent. We used linear interpolation to quantify noise levels for all years between 2000 and 2017. Values below 35 dB were set to 35 dB. We calculated noise as the equivalent A-weighted sound pressure level for day (7 a.m.–7 p.m.), evening (7 p.m.–11 p.m.), and night (11 p.m.–7 a.m.) and aggregated it as $L_{den.}$ A previous validation of the Nordic Prediction Method found a mean difference of 0.3 dB (with a standard deviation of 3.0 dB) when comparing measured and calculated road LdenMax from different locations across the Nordic countries (Ström 1997).

We used a detailed land use map of Denmark (Basemap) for 2016 to assess the proportion of green space at the residences. Basemap includes 36 land use classes at a 10 m × 10 m resolution (Levin et al. 2017). We defined two green space variables: (1) the proportion of recreational areas, forests, and open nature areas within 1000 m of the residence ("Green1000m"), with which we aimed to capture publicly accessible green space near the residence that could encourage physical activity; and (2) the proportion of household gardens, green space between multistorage buildings, agricultural areas, recreational areas, forests, and open nature areas within 150 m of the residence ("Green150m"), which served as an indicator of greenness potentially visible from the residence and which could potentially be considered antistressful.

DCH-NG COHORT: ENDPOINTS AND LIFESTYLE COVARIATES

Participants provided blood samples and underwent a physical examination with measurements of blood pressure, anthropometrics, and bioelectrical impedance. We included the following clinical measurements: high-density lipoprotein (HDL), often characterized as "the good cholesterol," and non-HDL lipoprotein, often characterized as "the bad cholesterol;" systolic and diastolic blood pressure; C-reactive protein (CRP, a marker of inflammation); and hemoglobin A1c (HbA1c), which is a prediabetes marker related to blood glucose regulation. A detailed description of the collection of these can be found in Petersen and colleagues (2022). In brief, nonfasting blood samples were collected and handled following strictly controlled time regimes. Samples used in this study were collected in 3-mL tubes containing the anticoagulant lithium heparin gel and then preprocessed at the study center. Tubes were centrifuged within 2 hours of collection and kept at 21°C until transfer to the Danish National Biobank (*https://www.danishnationalbiobank.com*) the next morning. Within 30 hours of collection, blood samples were analyzed for total and HDL cholesterol using enzymatic colorimetric techniques, for HbA1c using a turbidimetric inhibition immunoassay (TINIA), and for hs-CRP using an immunoturbidimetric assay. Analyses were performed on a CobasR 6000 analyzer by Roche Diagnostics. Blood pressure was measured three times on the left arm after at least 5 minutes of rest before the first measurement and with 1–2 minutes of rest between each measurement. We used the lowest systolic blood pressure and the corresponding diastolic blood pressure value.

At the time blood samples were collected, participants were asked whether they had consumed alcohol within the last 72 hours or smoked within the last 48 hours and, if so, how many hours before had they last smoked. From the questionnaires, we obtained information on environmental tobacco smoking (current exposure to tobacco smoke at home or work, yes/no), physical activity (yes/no and hours/week), and BMI (continuous, $kg/m^{2)}$.

STATISTICAL METHODS AND DATA ANALYSES

LONG-TERM EXPOSURE TO AIR POLLUTION AND RISK OF TYPE 2 DIABETES, MYOCARDIAL INFARCTION, AND STROKE

Overall Approach

In the present study, we addressed four research questions in the investigation of associations between long-term exposure to air pollution and risk of type 2 diabetes, MI, and stroke:

1. What is the association between long-term source-specific air pollution and the three outcomes?
2. What is the effect of adjustment for other environmental exposures, specifically road traffic noise and green space?
3. Are there any interactions with sociodemographic characteristics and comorbidities?
4. What is the potential for residual confounding from lifestyle factors not available from registers?

To answer the first three questions, we conducted the analyses based on the nationwide DK-POP cohort, whereas for the fourth question, we used the questionnaire-based DNHS cohort. We used the Cox model to address all four research questions, and for the third question, we also applied the Aalen model. The models and analyses are described below in detail.

Air Pollution and Type 2 Diabetes, MI, and Stroke

In the DK-POP cohort, we analyzed associations between the endpoints and $PM_{2.5}$, UFPs, EC, and NO_2 as 5-year running averages and expressed associations as hazard ratios (HR) with 95% confidence intervals (CI) per interquartile range (IQR) exposure. We analyzed associations with the contribution to each air pollutant from local road traffic and other sources. The contributions from local road traffic and other sources were included in separate models and were also included in the same model, that is, mutually adjusted. We analyzed associations between outcomes and $PM_{2.5}$, UFPs, EC, and NO_2 in categories according to the following percentiles based on the study base: <10th (reference group), 10th–25th, 25th–50th, 50th–75th, 75th–90th, 90th–95th, and >95th percentile, to explore the shape of the exposure–response relationships.

Cox Models

We used Cox proportional hazards models for all long-term exposure research questions. The Cox models were specified with age as the underlying time scale. To allow for potentially more complicated nonlinear relationships with calendar time we adjusted for calendar year, grouped in 2-year categories. Air pollution was entered time-dependently specified as 5-year running averages updated every third month. The same was true for noise and green space. All registry-based covariates (except country of origin and sex) were similarly entered as time-dependent variables, updated yearly. Participants were followed from baseline until death, emigration, more than 14 consecutive days of unknown address, or the end of follow-up on December 31, 2017, whichever came first. For the type 2 diabetes analyses, censoring also occurred at first type 1 diabetes diagnosis.

Aalen Models

In addition to the Cox model, we used Aalen additive hazards models for the interaction analyses. These models were also specified with age as the time scale and time-dependent exposures and covariates. The Aalen models were sensitive to cells with few observations. To facilitate estimation of risk by Aalen models, we therefore reduced the number of covariates and the age range during which we followed the participants (type 2 diabetes: 50–80 years; MI and stroke: 50–85 years). The interaction analyses based on Cox models followed the same adjustments and age ranges as those applied in the Aalen models to facilitate the comparison of results.

R version 4.2.2 was used for Aalen analyses and for our attempt to develop a random forest-based novel approach (see Additional Materials at the HEI website). All other analysis was performed in SAS version 9.4 (SAS Institute Inc., Cary, NC, USA).

Adjustment Strategy

For the DK-POP cohort, we obtained information on a wide range of registry-based sociodemographic variables at the individual- and area-level. In the DNHS cohort, we had access to the same registry-based variables plus lifestyle information on smoking habits, intake of alcohol and food, physical activity, and BMI. Also in the DNHS, we investigated if adjustment for these lifestyle variables influenced the associations between air pollution and diabetes, MI, and stroke when the models were already adjusted for the registry-based sociodemographic variables. Based on the results (described below in this report), we decided to adjust the analyses based on the DK-POP cohort for all our registry-based sociodemographic variables whenever possible.

Multiexposure Analyses

Air pollution, noise, and lack of green space are correlated in urban environments. In our nationwide DK-POP cohort, we had information about exposures at residential addresses within each of these three environmental domains and we took advantage of this to analyze these exposures simultaneously. To enable investigation of risk associated with lack of surrounding greenness, we redefined our green space variables to express the proportion of nongreen within 1000 m ("NonGreen1000m") and 150 m ("NonGreen150m").

Our multiexposure approach used in analyses of the DK-POP cohort included a preselection of the variables within each of the three environmental domains: air pollution, noise, and (lack of) green space. This preselection was undertaken within each of the domains separately to, if possible, reduce the number of variables to be included in the final multiexposure Cox regression model. For the four air pollutants ($PM_{2.5}$, UFPs, EC, and NO_2), we fitted one-, two-, three-, and four-pollutant models with all combinations of these four air pollution variables. To be included in the final multiexposure model, we required a variable to show a consistent direction of risk in all models, regardless of adjustment for which combination of the other three air pollutants.

In other words, we identified those of the four air pollutants that were consistently associated with elevated risk, both alone and when adjusted for one or more of the other air pollutants. We did the same for noise (LdenMax and LdenMin) and for lack of green space (NonGreen1000m and NonGreen150m). For these two domains, only one- and two-exposure models were relevant, but again we identified exposures consistently associated with risk alone and when adjusted for the other noise and green space metrics.

To quantify the cumulative burden of all investigated environmental exposures in the final multiexposure models, we calculated a cumulative risk index (CRI, per IQR of the exposures) assuming additive effects of the combined exposures on risk, using a method previously described in detail (Crouse et al. 2015).

Effect Modification

We investigated potential effect modification by sociodemographics, comorbidity, financial stress, noise, and green space, using the DK-POP cohort. We used both multiplicative models (Cox) estimating relative risk (HRs) and additive models (Aalen) estimating absolute risk (rate differences). We applied the two models because the baseline risk might differ between the different population strata, which could imply different results when expressing effect modification by relative or absolute risk.

BIOMARKER ANALYSES

For an investigation of the effects of shorter-term exposure to air pollution and changes in biomarkers related to cardiometabolic diseases, we used the DCH-NG cohort. The analyses were based on baseline data, which are cross-sectional in nature, although our design ensured that the air pollution exposure time windows preceded the blood draw. The paragraphs below elaborate on these analyses.

We analyzed associations between air pollution and biomarkers using multivariate linear regression models. We assessed the variance of the residuals visually by plotting them against the predicted values, using histograms and Q-Q plots, and found no deviation from a normal distribution except for CRP. We log-transformed the CRP values to obtain a normal distribution of the residuals.

The included biomarkers are formed by different biological processes and their concentrations in the blood reflect various exposures and conditions during different time periods preceding blood draw. For example, CRP is considered a marker of inflammation for the preceding few days, whereas HbA1c is considered a marker of glucose control for the last few months. We initially analyzed associations with biomarkers for five exposure time windows before blood draw and blood pressure measurement: 24 hours, 72 hours, 7 days, 30 days, and 90 days, to identify a time window for which associations could be detected. We then proceeded with the 30-day window and analyzed associations with total air pollution concentrations and the contributions to each pollutant from local road traffic and other sources.

We adjusted for age and age-squared to allow for nonlinear associations between age and biomarkers. We further adjusted for sex, cohabiting status, educational level, income, smoking before blood draw, hours since last smoke, environmental tobacco smoke, alcohol intake before blood draw, physical activity (yes/no), hours of physical activity per week, BMI, green space at the residence, and percentage of parish population having low income, having only basic education, and living in social housing. Linearity of the association between continuous covariates and biomarkers was evaluated graphically by linear splines. For BMI, we found deviance from linearity, and therefore BMI was included in the models as a linear spline with a cut-point at the value of 30.

RESULTS

POPULATIONS AND AIR POLLUTION LEVELS

DK-POP We included about 2.6 million people living in Denmark in the study population from age 35 years and about 2 million people in the study population from age 50 years. We excluded 3% to 5% as prevalent cases at baseline and about 1% due to missing one or more covariates (**Table 5).**

DNHS cohort From the study population of 324,988 persons, we excluded 78,222 persons with missing address(es) and/or exposure information at any time since 1979. Further, we excluded 12,748 persons with diabetes at baseline in analyses of type 2 diabetes risk, 5710 persons with MI at baseline in analyses of MI risk, and 4778 persons with stroke at baseline in analyses of stroke risk, leaving 234,018 for the analyses of type 2 diabetes risk, and 241,056 and 241,988 for MI risk and stroke risk, respectively.

DCH-NG cohort Of the 41,980 participants with blood samples, we excluded 3443 with incomplete data (address, lifestyle, socioeconomic status [SES], or biomarker); 887 with a previous diagnosis of diabetes, MI, or stroke; 3657 using medications to lower blood pressure or cholesterol or using low-dose aspirin as cardiovascular medication; and 1142 who changed their address within 90 days before blood draw/blood pressure measurement. After these exclusions, we had 32,851 persons for our study.

Table 6 shows the characteristics of the two DK-POP study populations and the DNHS cohort, indicating only relatively small differences. The differences probably relate to differences in age and baseline year. In **Figure 7**, the distribution of air pollution, noise, and green space among people 50 years or older for the period 2005–2017 is shown. **Table 7** shows mean concentrations of 10.0 μg/m^3 $PM_{2.5}$, 10,665 UFPs per cm3, 0.65 μg/m^3 EC, and 15.0 μg/m^3 NO_2. Furthermore, Table 7 shows that the contributions to air pollution from local road traffic were smaller than those from other sources, which is also illustrated in **Figure 8**. **Table 8** shows very high correlations ($R > 0.96$) between the local traffic contributions to the four pollutants, as well as high correlations (R: 0.90–0.97) between the contributions from other sources and total concentrations of $PM_{2.5}$, UFPs, and EC, respectively.

IMPORTANCE OF ADJUSTMENT FOR INDIVIDUAL LIFESTYLE

Table 9 shows individual-level lifestyle characteristics of the DNHS cohort for all and by $PM_{2.5}$ concentration. There were only small differences according to $PM_{2.5}$ concentration, with a slightly higher intake of alcohol and fruit, and a slightly lower intake of red meat among those with high $PM_{2.5}$ concentrations.

Table 10 shows associations between air pollution and the risk of type 2 diabetes, MI, and stroke in the DNHS cohort, based on three different adjustment models. We observed

Table 5. The DK-POP Study Populations for Analyses of Type 2 Diabetes, MI, and Stroke

	People 35 Years and Older	People 50 Years and Older		
	Type 2 Diabetes	Type 2 Diabetes	MI	Stroke
Study base	2,757,813	2,048,286[a]	2,048,282[a]	2,048,282[a]
Exclusions				
Prevalent case at baseline	102,469[b]	104,130[b]	60,967	54,416
Missing covariates	23,856	21,611	22,613	22,620
Analysis data set	2,631,488	1,922,545	1,964,702	1,971,246

[a] After analyses and publication of the diabetes results, we discovered four persons being double counted. Therefore, numbers for the 50+ years populations for type 2 diabetes, MI, and stroke are not identical.

[b] Both type 1 and type 2 diabetes cases before baseline were excluded.

Table 6. Characteristics at Baseline of Two DK-POP Samples and the DNHS Cohort

	Danish People 35 Years and Older[a]	Danish People 50 Years and Older[a]	Danish National Health Survey
Number	2,631,488	1,922,545	246,766
Baseline year(s)	2005	2005	2010, 2013
Cases during follow-up			
Type 2 diabetes	148,020	128,358	6,366
MI	NA	71,285[b]	3,247
Stroke	NA	94,256[b]	4,166
Individual-level sociodemographics, baseline			
Men (%)	48.6	47.5	46.2
Age (mean ± SD)	51.7 ± 14.6	59.9 ± 10.0	52.0 ±19.2
Age (min, max)	35, 84	50, 84	16, 104
Cohabiting status (%)			
Married/cohabiting	74.5	73.6	69.2
Widow/divorced/live alone	25.5	26.5	30.8
Danish origin (%)	98.3	98.1	98.3
Educational level (%)			
Mandatory	31.1	36.0	33.1
Secondary or vocational	47.6	45.3	46.3
Medium or long education	21.3	18.7	20.6
Occupational status (%)			
Blue collar	35.3	30.1	36.9
White collar	29.2	25.5	25.3
Retired/unemployed	35.5	44.4	37.8
Income quintiles, individual (%)			
Q1	20.7	24.8	31.6
Q2–Q4	59.3	54.9	51.8
Q5	20.0	20.3	16.6
Income quintiles, household (%)			
Q1	19.6	20.6	20.4
Q2–Q4	60.8	54.7	60.3
Q5	19.6	24.7	19.3

Continued next page

Table 6. Characteristics at Baseline of Two DK-POP Samples and the DNHS Cohort (*continued*)

	Danish People 35 Years and Older[a]	Danish People 50 Years and Older[a]	Danish National Health Survey
Ever financial stress last 5 years (%)	23.4	17.4	15.9[c]
Comorbidity (%)			
0	89.5	86.0	85.8
1	6.1	7.9	7.0
≥2	4.4	6.1	7.2
Area (parish) level sociodemographics, baseline			
Proportion with (mean ± SD)			
Low income	4.6 ± 2.3	4.5 ± 2.3	4.8 ± 2.1
Only basic education	10.5 ± 3.3	10.4 ± 3.4	8.9 ± 2.8
Unemployment	1.7 ± 0.7	1.7 ± 0.7	1.7 ± 0.6
Manual labor	13.0 ± 3.3	12.9 ± 3.3	12.1 ± 3.0
Non-Western background	5.2 ± 6.0	5.2 ± 6.0	5.5 ± 6.3
Criminal record	0.5 ± 0.3	0.5 ± 0.3	0.5 ± 0.3
Sole providers	5.6 ± 1.8	5.7 ± 1.8	5.9 ± 1.7
In social housing	18.0 ± 16.5	18.2 ± 16.5	17.1 ± 15.8
Population density (%)			
<100 per km^2	26.1	26.5	28.2
100–2000 per km^2	53.8	55.1	55.0
≥ 2000 per km^2	20.1	18.4	16.9
Air pollution, noise, and green space[c]			
$PM_{2.5}$ ($\mu g/m^3$), mean ± SD	10.1 ± 1.3	10.0 ± 1.3	9.9 ± 1.0
UFPs (number/cm^3), mean ± SD	10,741 ± 3,117	10,665 ± 3,111	10,904 ± 2,877
EC ($\mu g/m^3$), mean ± SD	0.66 ± 0.25	0.64 ± 0.25	0.66 ± 0.23
NO_2 ($\mu g/m^3$), mean ± SD	15.2 ± 5.6	15.0 ± 5.5	15.0 ± 5.4
LdenMax (dB), mean ± SD	54.8 ± 8.2	54.5 ± 8.3	54.8 ± 8.3
LdenMin (dB), mean ± SD	44.9 ± 6.5	44.8 ± 6.5	44.5 ± 7.1
Green space 1000m (%), mean ± SD	57.2 ± 18.9	57.1 ± 18.5	57.5 ± 19.3
Green space 150m (%), mean ± SD	15.4 ± 10.5	15.6 ± 10.5	15.2 ± 10.6

[a] Unless otherwise stated, this table is based on the dataset for type 2 diabetes. The data sets for MI and stroke differed slightly because prevalent cases at baseline were excluded from the analyses (i.e., type 2 cases for analyses of type 2 diabetes, MI cases for analyses of MI, and stroke cases for analyses of stroke).

[b] Numbers of MI and stroke cases derive from the MI and stroke data sets.

[c] Air pollution and noise levels expressed as the mean of all moving 5-year averages for all cohort members over the follow-up period (2005–2017). Green space is given for the address at baseline.

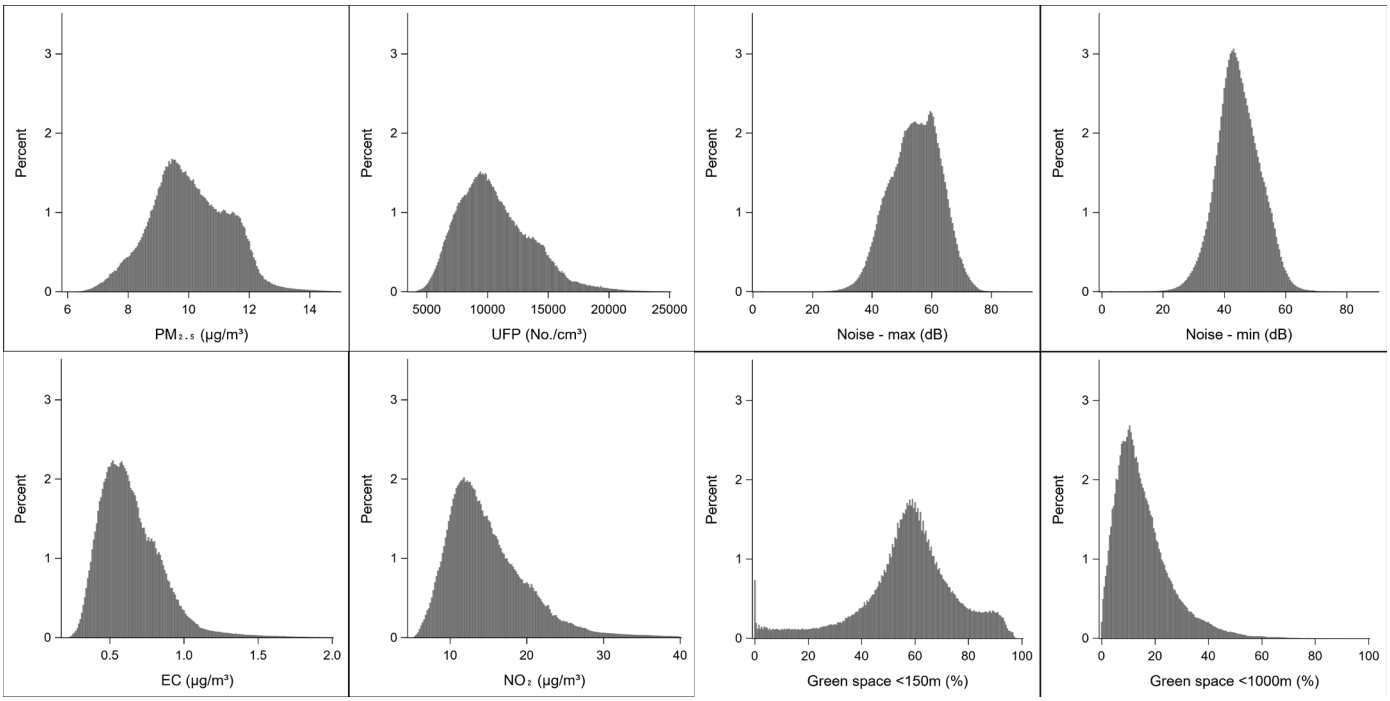

Figure 7. Distribution of residential air pollution, noise, and green space in the Danish population for people ages 50 and older, 2005–2017. Air pollution and noise were based on averages at addresses over the last 5 years. Green space was based on the value at each address.

Table 7. Distribution of Residential 5-Year Average Concentrations of Air Pollution (Total Concentration and Contributions from Local Traffic and Other Sources) Among the Danish Population 50 Years and Older from 2005 to 2017

	Min	5%	25%	50%	75%	95%	Max	Mean
$PM_{2.5}$ (µg/m³)								
Total	5.91	7.96	9.16	9.95	10.97	12.06	31.71	10.04
Other sources	5.89	7.86	8.97	9.66	10.57	11.49	30.48	9.72
Local traffic	0.00	0.04	0.09	0.18	0.39	1.01	9.52	0.32
UFPs (number/cm³)								
Total	3,691	6,454	8,443	10,192	12,502	16,061	93,677	10,665
Other sources	3,649	6,151	7,772	9,080	10,631	12,630	89,299	9,272
Local traffic	7	210	480	962	1,918	3,781	23,005	1,393
EC (µg/m³)								
Total	0.19	0.37	0.49	0.61	0.76	1.02	20.29	0.65
Other sources	0.19	0.35	0.44	0.51	0.57	0.65	19.81	0.51
Local traffic	0.00	0.02	0.04	0.09	0.18	0.39	3.68	0.14
NO_2 (µg/m³)								
Total	4.87	8.36	11.19	13.81	17.61	24.95	69.02	14.97
Other sources	4.68	7.04	8.92	10.24	11.52	13.27	27.08	10.25
Local traffic	0.03	0.83	1.79	3.36	6.26	12.79	55.67	4.73

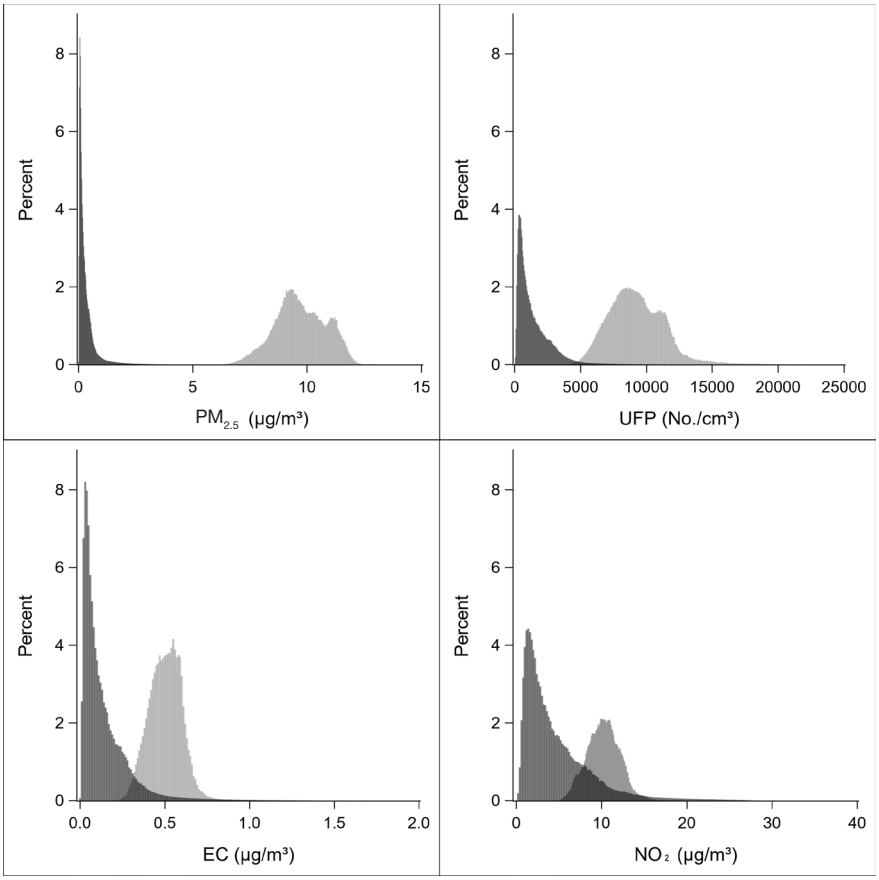

Figure 8. Distribution of 5-year average concentrations of air pollution from local traffic (dark gray) and other sources (light gray) at the residences of Danes ages 50 and older, 2005–2017.
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Table 8. Spearman Correlations Between 5-Year Average Concentrations of Residential Air Pollution (Total Concentration, from Local Traffic and from Other Sources) in the Danish Population 50 Years or Older from 2005 to 2017

	$PM_{2.5}$ Total	UFP Total	EC Total	NO_2 Total	$PM_{2.5}$ Other Sources	UFP Other Sources	EC Other Sources	NO_2 Other Sources	$PM_{2.5}$ Local Traffic	UFP Local Traffic	EC Local Traffic
$PM_{2.5}$ total	-	-	-	-	-	-	-	-	-	-	-
UFP total	0.80	-	-	-	-	-	-	-	-	-	-
EC total	0.74	0.92	-	-	-	-	-	-	-	-	-
NO_2 total	0.76	0.91	0.92	-	-	-	-	-	-	-	-
$PM_{2.5}$ other sources	0.97	0.72	0.61	0.63	-	-	-	-	-	-	-
UFP other sources	0.80	0.96	0.82	0.80	0.77	-	-	-	-	-	-
EC other sources	0.74	0.88	0.91	0.77	0.69	0.87	-	-	-	-	-
NO_2 other sources	0.79	0.83	0.71	0.83	0.77	0.85	0.72	-	-	-	-
$PM_{2.5}$ local traffic	0.58	0.78	0.89	0.90	0.42	0.62	0.67	0.56	-	-	-
UFP local traffic	0.62	0.84	0.93	0.92	0.47	0.69	0.74	0.61	0.97	-	-
EC local traffic	0.62	0.83	0.92	0.92	0.49	0.67	0.72	0.60	0.99	0.99	-
NO_2 local traffic	0.60	0.80	0.91	0.91	0.44	0.64	0.70	0.56	0.99	0.98	0.99

Table 9. Baseline Characteristics of the DNHS Study Population for Total Population and Tertiles of 5-Year Average Concentrations of $PM_{2.5}$ at Baseline[a]

Baseline Characteristics	Total Study Population[b] (*N* = 246,766)	Population[b] in Tertiles of $PM_{2.5}$		
		<9.5 µg/m³ (*N* = 82,155)	9.5–10.4 µg/m³ (*N* = 82,419)	≥10.4 µg/m³ (*N* = 82,192)
Individual-Level Questionnaire Information				
Smoking status (%)				
Never	47.6	49.2	47.4	46.1
Occasional	3.6	3.1	3.5	4.3
Former	31.3	30.6	32.1	31.3
Present	17.5	17.1	17.0	18.4
Smoking intensity among present smokers (g tobacco/day)[c]	15.2 ± 8.6	15.3 ± 8.9	15.2 ± 8.6	15.1 ± 8.3
Intake of alcohol (drinks/week)[c]	7.6 ± 11.0	6.9 ± 10.5	7.6 ± 11.1	8.3 ± 11.3
Intake of salad (%)				
Never/rarely	18.6	19.0	18.3	18.5
1–2 times/week	34.0	34.5	34.0	33.6
3–4 times/week	24.3	24.3	24.4	24.3
≥5 times/week	23.0	22.2	23.3	23.7
Intake of red meat (%)				
Never/rarely	4.0	3.0	4.2	4.8
1–2 times/week	28.7	25.0	29.5	31.5
3–4 times/week	42.4	42.1	42.6	42.4
≥5 times/week	25.0	29.8	23.8	21.3
Intake of fruit (%)				
0–2 times/week	14.4	15.0	14.9	13.2
3–6 times/week	20.0	20.7	20.4	19.1
1–4 times/day	59.0	58.4	58.3	60.2
≥5 times/day	6.6	5.9	6.4	7.6
Physical activity in leisure time (%)				
Highly physically active	26.8	26.2	26.9	27.2
Medium physically active	58.0	57.8	57.5	58.7
Mainly inactive	15.2	16.0	15.6	14.1
BMI (kg/m²)[c]	25.5 ± 4.6	25.8 ± 4.6	25.6 ± 4.6	25.2 ± 4.4

[a] All numbers calculated based on the 25 imputed datasets (using PROC MIANALYZE in SAS).

[b] Study population before exclusion of prevalent cases of the three outcomes investigated.

[c] Values given as mean ± standard deviation.

Table 10. Associations (Hazard Ratios with 95% Confidence Intervals) Between Air Pollution and Type–2 Diabetes, MI, and Stroke in the DNHS Cohort[a]

		Per Fixed Unit $PM_{2.5}$: 5 µg/m³ NO_2: 10 µg/m³			Per IQR $PM_{2.5}$: 1.85 µg/m³ NO_2: 7.15 µg/m³
	***N* Cases**	**Model 1** Age, sex, calendar year	**Model 2** Model 1 + registry-based sociodemographic variables[b]	**Model 3** Model 2 + lifestyle variables[c]	**Model 3** Model 2 + lifestyle variables[c]
Type 2 diabetes	6,366				
$PM_{2.5}$		1.00 (0.85–1.16)	1.27 (1.06–1.52)	1.24 (1.03–1.50)	1.08 (1.01–1.16)
NO_2		1.02 (0.96–1.07)	1.16 (1.07–1.24)	1.14 (1.06–1.23)	1.10 (1.04–1.16)
MI	3,247				
$PM_{2.5}$		1.02 (0.82–1.27)	1.16 (0.90–1.49)	1.18 (0.91–1.52)	1.06 (0.97–1.17)
NO_2		0.98 (0.91–1.06)	1.05 (0.94–1.16)	1.03 (0.92–1.14)	1.02 (0.94–1.10)
Stroke	4,166				
$PM_{2.5}$		1.08 (0.89–1.31)	1.09 (0.87–1.37)	1.11 (0.88–1.40)	1.04 (0.95–1.13)
NO_2		1.05 (0.98–1.13)	1.11 (1.01–1.22)	1.10 (1.00–1.20)	1.07 (1.00–1.14)

[a] Number of included cohort members differed slightly for the three endpoints, because previous and prevalent cases of the endpoint under study were excluded. Type 2 diabetes: *N* = 234,018; MI: *N* = 241,056; stroke: *N* = 241,988.

[b] Registry-based variables adjusted for age, sex, calendar year, marital status, individual income, household income, country of origin, occupational status, education, and area-level percentage of population with low income, with only basic educational level, who is unemployed, who does manual labor, with a non-Western background, who has a criminal record, who is the sole provider, and who lives in social housing.

[c] Lifestyle variables adjusted for smoking status, smoking intensity, intake of alcohol, intake of salad, intake of fruit, intake of red meat, physical activity, and BMI.

higher HRs for all three endpoints in models adjusted for all the registry-based variables compared to HRs from the crude models adjusted for only age, sex, and calendar year. However, further adjustment for the individual lifestyle variables (smoking status; smoking intensity; intake of alcohol, salad, fruit, and red meat; physical activity; and BMI) only resulted in minor changes in HRs for all three endpoints. Further details concerning these analyses and results can be found in a report by **S**ørensen and colleagues (2022a).

ASSOCIATIONS BETWEEN AIR POLLUTION AND TYPE 2 DIABETES, MI, AND STROKE

We found that higher total concentrations of each of the four air pollutants was associated with higher risk of type 2 diabetes, MI, and stroke, with HRs per IQR of 1.043 (95% CI: 1.031–1.056), 1.053 (95% CI: 1.035–1.071), and 1.077 (95% CI: 1.061–1.094) per 1.85 µg/m³ $PM_{2.5}$, for type 2 diabetes, MI and stroke, respectively (**Table 11a**). For type 2 diabetes, the contribution to UFPs and EC from local traffic was associated with higher HRs than contributions from other sources, whereas contributions to $PM_{2.5}$ and NO_2 from local traffic and other sources were associated with similar HRs. For MI and stroke, the contribution to $PM_{2.5}$, UFPs, and NO_2 from other sources was associated with higher HRs than contributions from local traffic. The picture was less clear for EC. Appendix Tables A1–A3 (see Additional Materials on the HEI website) show results based on different adjustment models. **Table 11b** resembles Table 11a, however HRs are expressed per fixed exposure increment instead of per IQR. For type 2 diabetes, contributions to $PM_{2.5}$, UFPs, and EC from local traffic were associated with higher HRs than were contributions from other sources. For MI and stroke, HRs were higher in association with contributions to $PM_{2.5}$, UFPs, and NO_2 from other sources than the corresponding HRs in association with local traffic contributions. **Table 12** shows associations between air pollution from local traffic and other sources when based on single-source models (as in Tables 11a and 11b) and when based on two-source models, that is when mutually adjusted for each other. The mutually adjusted results support the general patterns observed in Tables 11a and 11b that air pollution from local traffic is more strongly associated with type 2 diabetes than air pollution from other sources, whereas air pollution from other sources seems to be most important for the risk of MI and stroke. **Figure 9** shows results for the total concentrations of the four air pollutants and each of the three endpoints, based on categories of air pollution. There is a general picture of increasing HRs with increasing exposure, however, with a leveling off in the upper end of the exposure distributions. Further details concerning these analyses and

Table 11a. Associations Between Air Pollution (per IQR) and Type 2 Diabetes, MI, and Stroke in the Danish Population[a] from 2005 to 2017

		HR[b] (95% CI) per IQR		
Air Pollutant	**IQR[c]**	**Type 2 Diabetes (148,020 cases)**	**MI (71,285 cases)**	**Stroke (94,256 cases)**
$PM_{2.5}$ (μg/m³)				
Total	1.85	1.043 (1.031–1.056)	1.053 (1.035–1.071)	1.077 (1.061–1.094)
Other sources	1.63	1.020 (1.007–1.032)	1.051 (1.032–1.069)	1.091 (1.074–1.108)
Local traffic	0.37	1.026 (1.020–1.031)	1.011 (1.003–1.018)	1.004 (0.998–1.011)
UFPs (number/cm³)				
Total	4,248	1.052 (1.042–1.063)	1.040 (1.025–1.055)	1.039 (1.026–1.052)
Other sources	2,769	1.027 (1.019–1.036)	1.034 (1.022–1.046)	1.038 (1.028–1.049)
Local traffic	1,698	1.049 (1.040–1.058)	1.011 (0.999–1.024)	1.003 (0.992–1.014)
EC (μg/m³)				
Total	0.28	1.022 (1.016–1.027)	1.009 (1.000–1.019)	1.009 (1.001–1.018)
Other sources	0.12	1.003 (0.999–1.007)	1.001 (0.996–1.007)	1.005 (1.000–1.009)
Local traffic	0.17	1.037 (1.030–1.043)	1.013 (1.003–1.023)	1.005 (0.996–1.013)
NO_2 (μg/m³)				
Total	7.15	1.056 (1.046–1.065)	1.027 (1.013–1.040)	1.028 (1.017–1.040)
Other sources	2.68	1.043 (1.034–1.053)	1.048 (1.034–1.062)	1.077 (1.065–1.089)
Local traffic	5.17	1.039 (1.031–1.047)	1.009 (0.998–1.020)	1.001 (0.991–1.010)

[a] Type 2 diabetes: population 35 years and older (N = 2,631,488). MI: population 50 years and older N = 1,964,702). Stroke: population 50 years and older (N = 1,971,246).

[b] Adjusted for age, sex, calendar year, civil status, individual and family income, country of origin, occupational status, educational level, and area-level percentage of the population with low income, with only basic education, who is unemployed, who does manual labor, with a non-Western background, who has a criminal record, who is the sole provider, and who lives in social housing.

[c] IQRs based on the Danish population from 2005 to 2017.

results can be found in Sørensen and colleagues (2022c) and Poulsen and colleagues (2023a and 2023d).

All results are based on models adjusted for age, sex, calendar year, civil status, individual and family income, country of origin, occupational status, educational level, and area-level percentage of the population with low income, with only basic education, being unemployed, with manual labor, with non-Western background, with criminal record, being the sole provider, and living in social housing.

The exposure categories were based on the following percentiles: <10th (reference), 10th–<25th, 25th–<50th, 50th–<75th, 75th–<90th, 90th–<95th, and 95th–100th. The HR with 95% CI of each category is located on the *x*-axis at the median value of the category. The exact numbers upon which the figure is based can be found in Sørensen and colleagues (2022c) and Poulsen and colleagues (2023a and 2023d).

INTERACTIONS BY SOCIODEMOGRAPHICS, COMORBIDITY, FINANCIAL STRESS, NOISE, AND GREEN SPACE

Figures 10 and **11** illustrate modification of associations between air pollutants and type 2 diabetes, MI, and stroke, when investigated using both Cox models (relative risk) and Aalen models (absolute risk). The figures show results for $PM_{2.5}$ and UFPs. The exact numbers behind the figures and corresponding results for EC and NO_2 can be found in Sørensen and colleagues (2023) and Poulsen and colleagues (2023b and 2023e).

For type 2 diabetes, effect modifications were consistent across all four air pollutants, and we observed similar results in the Cox and Aalen models. We found higher risk estimates among men than for women, those without financial stress, and those with comorbidities (Figures 10 and 11).

Table 11b. Associations Between Air Pollution (per Fixed Unit) and Type 2 Diabetes, MI, and Stroke in the Danish Population[a] from 2005 to 2017

		HR[b] (95% CI) per Fixed Unit		
Air Pollutant	**Unit**	**Type 2 Diabetes (148,020 cases)**	**MI (71,285 cases)**	**Stroke (94,256 cases)**
$PM_{2.5}$ (μg/m³)				
Total	5	1.121 (1.086–1.159)	1.150 (1.097–1.204)	1.222 (1.174–1.275)
Other sources	5	1.063 (1.022–1.101)	1.165 (1.101–1.227)	1.306 (1.245–1.370)
Local traffic	5	1.415 (1.307–1.511)	1.159 (1.041–1.273)	1.055 (0.973–1.159)
UFPs (number/cm³)				
Total	10,000	1.127 (1.102–1.155)	1.097 (1.06–1.134)	1.094 (1.062–1.127)
Other sources	10,000	1.101 (1.070–1.136)	1.128 (1.082–1.176)	1.144 (1.105–1.189)
Local traffic	10,000	1.325 (1.260–1.394)	1.067 (0.994–1.150)	1.018 (0.954–1.085)
Elemental carbon (μg/m³)				
Total	1	1.081 (1.058–1.100)	1.033 (1.000–1.070)	1.033 (1.004–1.066)
Other sources	1	1.025 (0.992–1.060)	1.008 (0.967–1.060)	1.042 (1.000–1.078)
Local traffic	1	1.238 (1.190–1.281)	1.079 (1.018–1.143)	1.03 (0.977–1.079)
NO_2 (μg/m³)				
Total	10	1.079 (1.065–1.092)	1.038 (1.018–1.056)	1.039 (1.024–1.056)
Other sources	10	1.170 (1.133–1.213)	1.191 (1.133–1.252)	1.319 (1.265–1.375)
Local traffic	10	1.077 (1.061–1.093)	1.017 (0.996–1.039)	1.002 (0.983–1.019)

[a] Type 2 diabetes: population 35 years and older (N = 2,631,488). MI: population 50 years and older (N = 1,964,702). Stroke: population 50 years and older (N = 1,971,246).

[b] Adjusted for age, sex, calendar year, civil status, individual and family income, country of origin, occupational status, educational level, and area-level percentage of population with low income, with only basic education, who is unemployed, who does manual labor, with a non-Western background, who has a criminal record, who is the sole provider, and who lives in social housing.

For MI, the risk estimates were higher among those with comorbidity, which was consistent across all four pollutants and on the relative and additive scale. Furthermore, consistently across all four pollutants, absolute risks estimated by Aalen models were higher for men, those with lower education, those with lower income, and those without financial stress. These effect modifications were not apparent for relative risk estimated by Cox models.

For stroke, the risk estimates were higher among those with comorbidity, which was consistent across all four pollutants in both the Cox and Aalen models. Furthermore, consistently across all four pollutants, absolute risks were higher for those with lower education, those with lower income, and those without financial stress. These effect modifications were not apparent for relative risk. Also, there was a tendency toward higher risk estimates (both relative and absolute risks) in association with indicators for rural living (lower population density, low noise, and high levels of green space).

MULTIEXPOSURE ANALYSES OF AIR POLLUTION, NOISE, AND GREEN SPACE

Table 13 shows Spearman correlation coefficients between variables of three domains of environmental exposures (air pollution, noise, and lack of green space) that we included in the multiexposure analyses. The correlations were relatively high between the four air pollutants ($R > 0.73$) and low to moderate between the variables of noise and green space ($R < 0.54$). Based on the preselection procedure, described in the statistical methods, we excluded $PM_{2.5}$ and EC from the multiexposure analyses of type 2 diabetes; EC and NO_2 from the multiexposure analyses of MI; and UFPs, EC, NO_2, and noise at the least-exposed façade from the multiexposure analyses of stroke. Thus, the preselection procedure reduced the number of environmental exposure variables by excluding those that did not show a consistent direction of risk in all two-, three-, and four-pollution models within a domain. More details on the preselection procedure can be found in Sørensen and colleagues (2022b) and Poulsen and colleagues (2023c and 2023f).

Table 12. Associations[a] Between Air Pollution Contributions from Local Traffic and Other Sources, and Type 2 Diabetes, MI, and Stroke, Based on Single- and Two-Source Models

Pollutant Source	IQR[b]	Single-Source Model HR (95% CI) per IQR	Two-Source Model HR (95% CI) per IQR
Type 2 diabetes			
$PM_{2.5}$			
Other sources	1.63 μg/m³	1.020 (1.007–1.032)	1.013 (1.000–1.026)
Local traffic	0.37 μg/m³	1.026 (1.020–1.031)	1.025 (1.020–1.030)
UFPs			
Other sources	2769 number/m³	1.027 (1.019–1.036)	1.018 (1.009–1.026)
Local traffic	1698 number/m³	1.049 (1.040–1.058)	1.045 (1.036–1.054)
EC			
Other sources	0.12 μg/m³	1.003 (0.999–1.007)	1.001 (0.997–1.005)
Local traffic	0.17 μg/m³	1.037 (1.030–1.043)	1.036 (1.030–1.043)
NO_2			
Other sources	2.68 μg/m³	1.043 (1.034–1.053)	1.035 (1.025–1.045)
Local traffic	5.17 μg/m³	1.039 (1.031–1.047)	1.033 (1.025–1.041)
MI			
$PM_{2.5}$			
Other sources	1.63 μg/m³	1.051 (1.032–1.069)	1.048 (1.030–1.067)
Local traffic	0.37 μg/m³	1.011 (1.003–1.018)	1.009 (1.001–1.016)
UFPs			
Other sources	2769 number/m³	1.034 (1.022–1.046)	1.033 (1.021–1.046)
Local traffic	1698 number/m³	1.011 (0.999–1.024)	1.004 (0.991–1.017)
EC			
Other sources	0.12 μg/m³	1.001 (0.996–1.007)	1.001 (0.995–1.007)
Local traffic	0.17 μg/m³	1.013 (1.003–1.023)	1.013 (1.003–1.023)
NO_2			
Other sources	2.68 μg/m³	1.048 (1.034–1.062)	1.048 (1.034–1.062)
Local traffic	5.17 μg/m³	1.009 (0.998–1.020)	1.001 (0.990–1.012)
Stroke			
$PM_{2.5}$			
Other sources	1.63 μg/m³	1.091 (1.074–1.108)	1.091 (1.074–1.108)
Local traffic	0.37 μg/m³	1.004 (0.998–1.011)	1.000 (0.994–1.007)
UFPs			
Other sources	2769 number/m³	1.038 (1.028–1.049)	1.040 (1.029–1.050)
Local traffic	1698 number/m³	1.003 (0.992–1.014)	0.994 (0.983–1.006)
EC			
Other sources	0.12 μg/m³	1.005 (1.000–1.009)	1.005 (1.000–1.009)
Local traffic	0.17 μg/m³	1.005 (0.996–1.013)	1.004 (0.995–1.012)
NO_2			
Other sources	2.68 μg/m³	1.077 (1.065–1.089)	1.079 (1.067–1.092)
Local traffic	5.17 μg/m³	1.001 (0.991–1.010)	0.989 (0.979–0.999)

[a] Based on the Danish population 2005–2017: Type 2 diabetes: 35 years and older (N = 2,631,488); MI: 50 years and older (N = 1,964,702); Stroke: 50 years and older (N = 1,971,246). Adjusted for age, sex, calendar year, civil status, individual and family income, country of origin, occupational status, educational level, and area-level percentage of the population with low income, with only basic education, who is unemployed, who does manual labor, with a non-Western background, who has a criminal record, who is the sole provider, and who lives in social housing.

[b] IQRs based on the Danish population, 2005–2017.

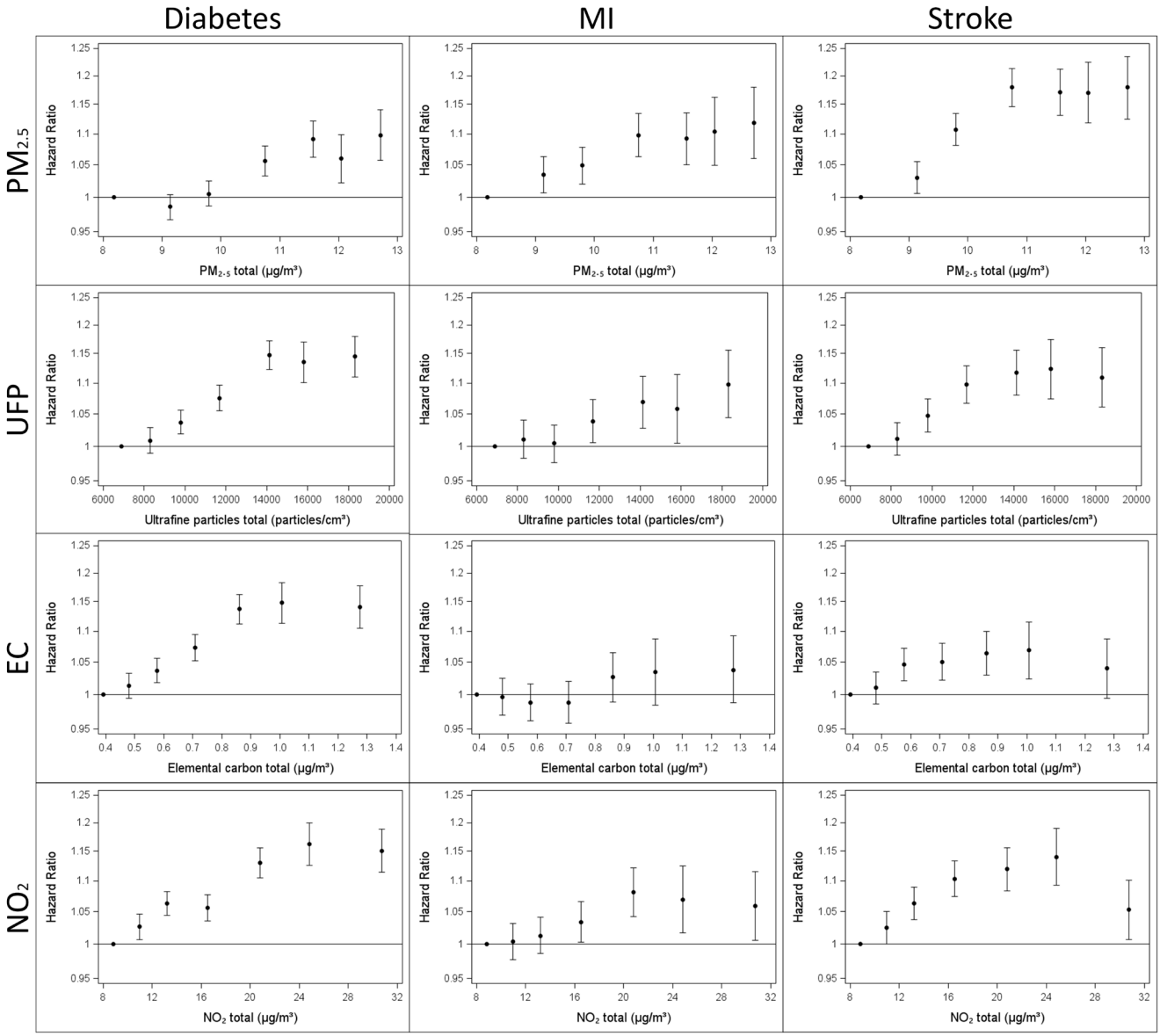


Figure 9. Associations between categories of 5-year total concentrations of air pollutants and risk of type 2 diabetes, MI, and stroke in the Danish population for people 35 years and older for diabetes and 50 years and older for MI and stroke, 2005–2017.
Diabetes data plots reproduced from Sørensen et al. 2022c; stroke plots from Poulsen et al. 2023d. Used by permission of Oxford University Press on behalf of the International Epidemiological Association.

Results from the multiexposure analyses with mutual adjustment for air pollutants, noise, and lack of green space are shown in **Figure 12**. We observed a consistent pattern of higher HRs in basically all single-pollutant analyses. However, in analyses with mutual adjustment for the other environmental exposures, the HRs were generally lower compared to the HRs in single-pollutant models or for some pollutants, the association with disease was no longer present in the multiexposure analyses. For type 2 diabetes, the multiexposure analyses showed statistically significant increased HRs in association with UFPs, noise at both the most- and least-exposed facades, and lack of green space, with the highest HR per IQR for lack of green space within 150 m (HR = 1.038; 95% CI: 1.031–1.044). Results for MI showed statistically significant associations with $PM_{2.5}$, noise at the most exposed façade, and lack of green space within 150, with the highest HR per IQR for $PM_{2.5}$ (HR = 1.026; 95% CI: 1.002–1.050). Results for stroke showed statistically significant associations with $PM_{2.5}$ and noise at the most exposed façade, with the highest HR per IQR for $PM_{2.5}$ (HR = 1.058; 95% CI: 1.042–1.075).

In **Table 14**, we have summarized which variables contributed to the risk of type 2 diabetes, MI, and stroke in the multiexposure models. Air pollution, noise, and green space

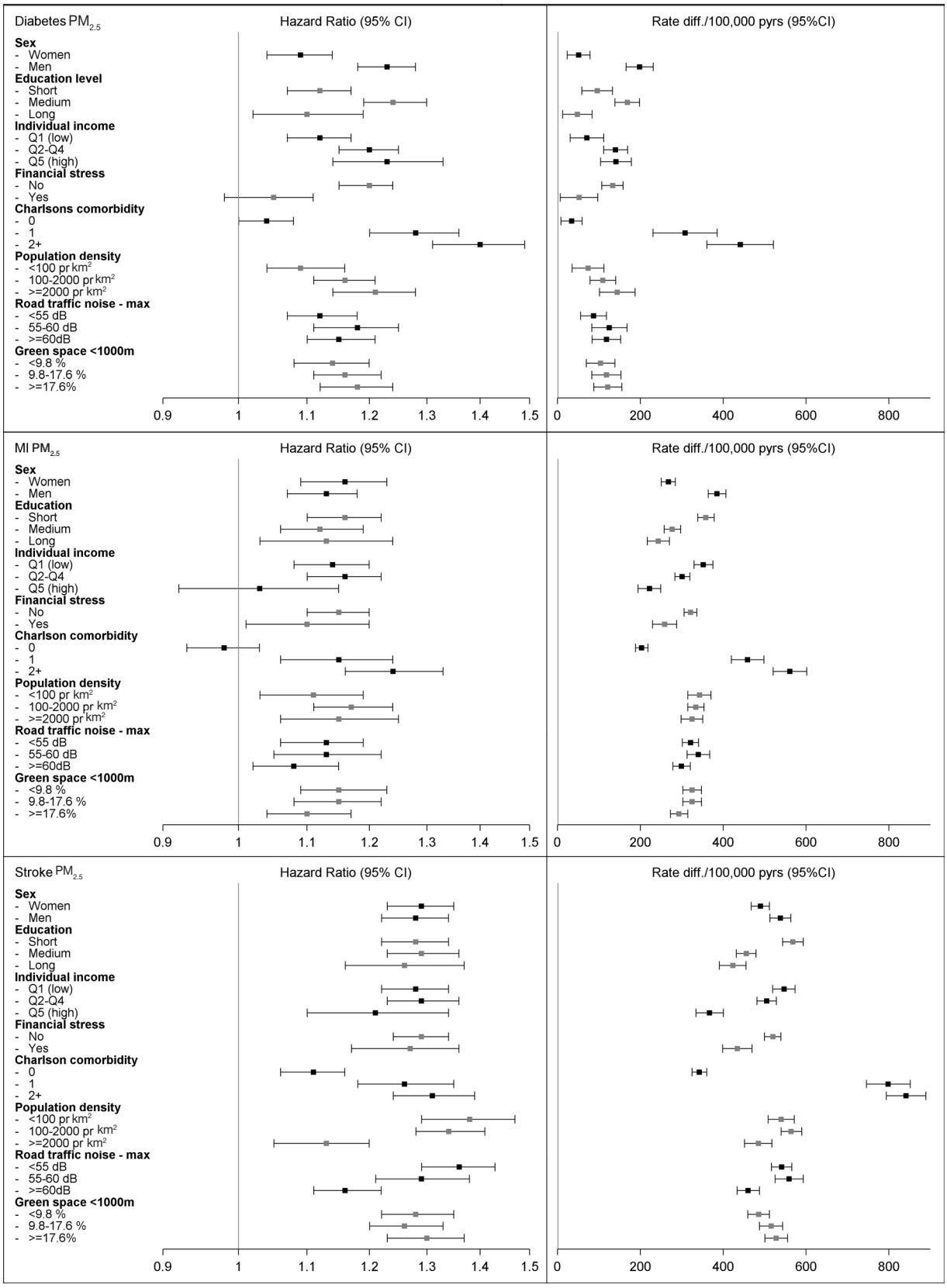


Figure 10. Modification of associations between 5-year average $PM_{2.5}$ and type 2 diabetes, MI, and stroke, by sociodemographic variables, comorbidity, noise, and green space, in the Danish population for people ages 50 and older, 2005–2017. (Note: pyrs = person-years.) In analyses of type 2 diabetes, we followed participants from age 50 to 80 years. The analyses were based on 1,843,597 participants and 113,985 incident cases, and adjusted for age, sex, calendar year, educational level, cohabiting status, personal income, country of origin, and percentage of parish population with only mandatory education, non-Western background, and a criminal record. In analyses of MI and stroke, we followed participants from age 50 to 85 years. The analysis data set for MI included 1,964,702 participants and 65,311 incident MI cases, and for stroke, the dataset included 1,971,246 participants and 83,211 incident cases. The analyses were adjusted for age, sex, calendar year, educational level, cohabiting status, personal income, household income, country of origin, occupational status, and percentage of parish population with only mandatory education. HRs are given per 5 $\mu g/m^3$ $PM_{2.5}$ and 10 $\mu g/m^3$ NO_2.

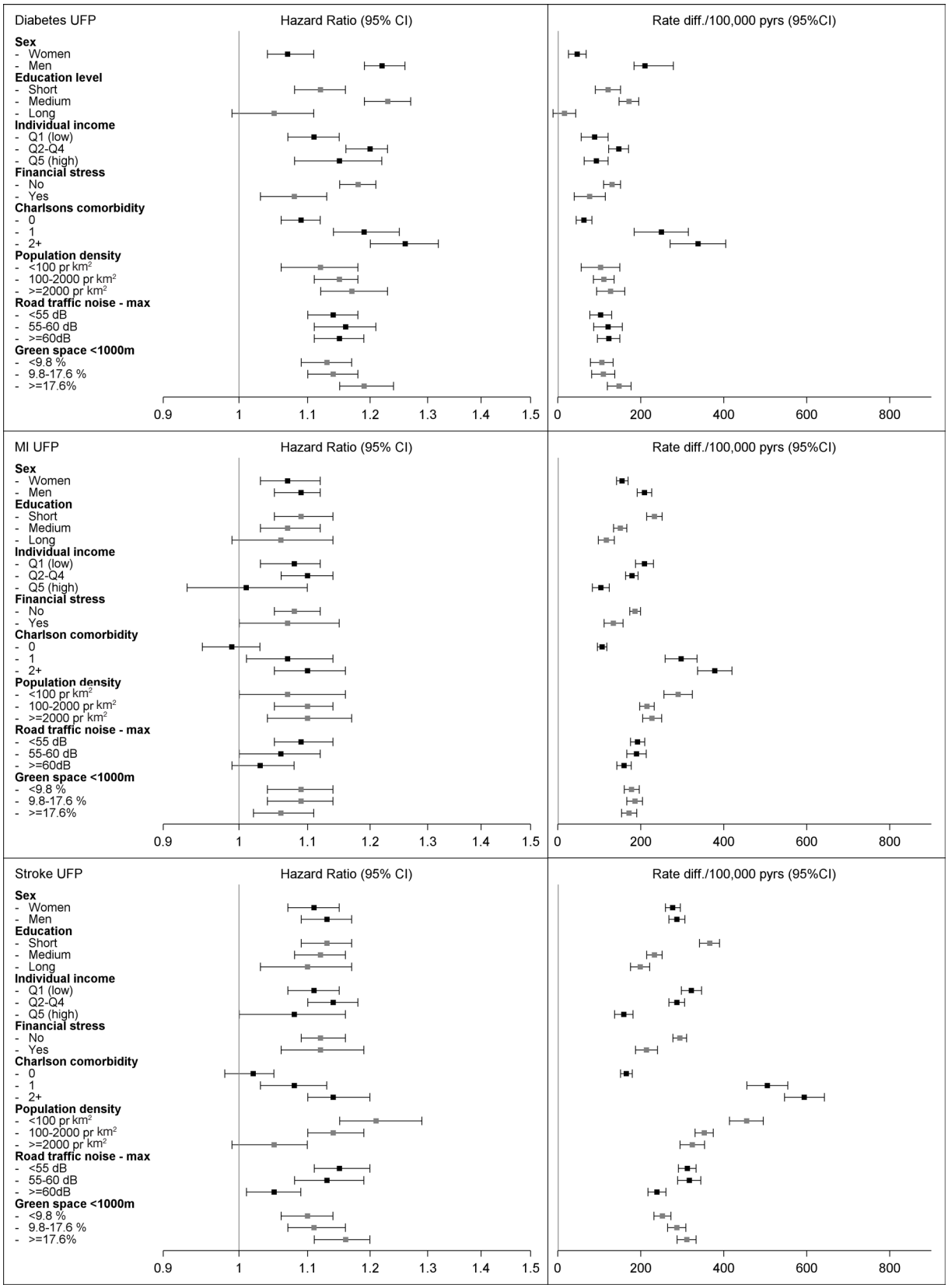


Figure 11. Modification of associations between 5-year average UFPs and type 2 diabetes, MI, and stroke, by sociodemographic variables, comorbidity, noise, and green space, in the Danish population for people ages 50 and older, 2005–2017. (Note: pyrs = person-years.) In analyses of type 2 diabetes, we followed participants from age 50 to 80 years. The analyses were based on 1,843,597 participants and 113,985 incident cases, and adjusted for age, sex, calendar year, educational level, cohabiting status, personal income, country of origin, and percentage of parish population with only mandatory education, non-Western background, and a criminal record. In analyses of MI and stroke, we followed participants from age 50 to 85 years. The analysis data set for MI included 1,964,702 participants and 65,311 incident MI cases, and for stroke, the dataset included 1,971,246 participants and 83,211 incident cases. The analyses were adjusted for age, sex, calendar year, educational level, cohabiting status, personal income, household income, country of origin, occupational status, and percentage of parish population with only mandatory education. HRs are given per 5 μg/m³ $PM_{2.5}$ and 10 μg/m³ NO_2.

Table 13. Spearman Correlations Between 5-Year Averages of Air Pollution, Noise, and Lack of Green Space at Addresses of Danes 50 Years and Older, 2005–2017[a]

	$PM_{2.5}$	UFPs	EC	NO_2	Noise Max	Noise Min	NonGreen 150m	NonGreen 1000m
$PM_{2.5}$	1.00	-	-	-	-	-	-	-
UFPs	0.80	1.00	-	-	-	-	-	-
EC	0.74	0.92	1.00	-	-	-	-	-
NO_2	0.76	0.91	0.92	1.00	-	-	-	-
LdenMax	0.19	0.23	0.31	0.38	1.00	-	-	-
LdenMin	0.25	0.42	0.49	0.53	0.48	1.00	-	-
NonGreen150m	0.22	0.35	0.38	0.40	0.19	0.33	1.00	-
NonGreen1000m	0.02	–0.06	–0.07	–0.04	0.05	–0.08	0.01	1.00

[a] This table is based on the data set used for the multiexposure analyses of type 2 diabetes (N = 1,922,545). Only marginal differences were seen when based on data used for the analyses of MI (N = 1,964,702) or stroke (N = 1,971,246).

Table 14. Summary of the Multiexposure Results[a]

	Type 2 Diabetes	MI	Stroke
$PM_{2.5}$		+	+
UFPs	+	–	
EC			
NO_2	–		
Noise at the most exposed facade	+	+	+
Noise at the least exposed facade	+	–	
Lack of green space within 150 m	+	+	–
Lack of green space within 1000 m	+	–	–

[a] Blank space *means* eliminated in the preselection procedure; **—** *means* not statistically significant in the multiexposure model; + *means* statistically significant in the multiexposure model.

all influenced risk of type 2 diabetes and MI, whereas only air pollution and noise showed statistically significant associations with stroke. Details about the multiexposure analyses and results are available (Sørensen and colleagues (2022b) and Poulsen and colleagues (2023c and 2023f).

AIR POLLUTION, NOISE, AND BIOMARKERS

In this part of the HERMES study, we investigated possible associations of air pollution and noise with biomarkers and blood pressure, which might be on the pathway between the environmental exposures and the endpoints investigated in the HERMES study (**Figure 13**). Although the overall idea that the biomarkers might be intermediates between air pollution and noise and cardiometabolic diseases is the connection between this biomarker study and the study of the long-term effect of exposures on cardiometabolic diseases, the biomarker study is based on a cohort established between 2015 and 2019 and thus with very short follow-up time for cardiometabolic diseases. This prevented us from undertaking formal mediation analyses. The biomarker analyses thus addressed associations between exposures and biomarkers, as indicated by the red frame in Figure 13. We refer to Roswall and colleagues (2023) for details about these analyses.

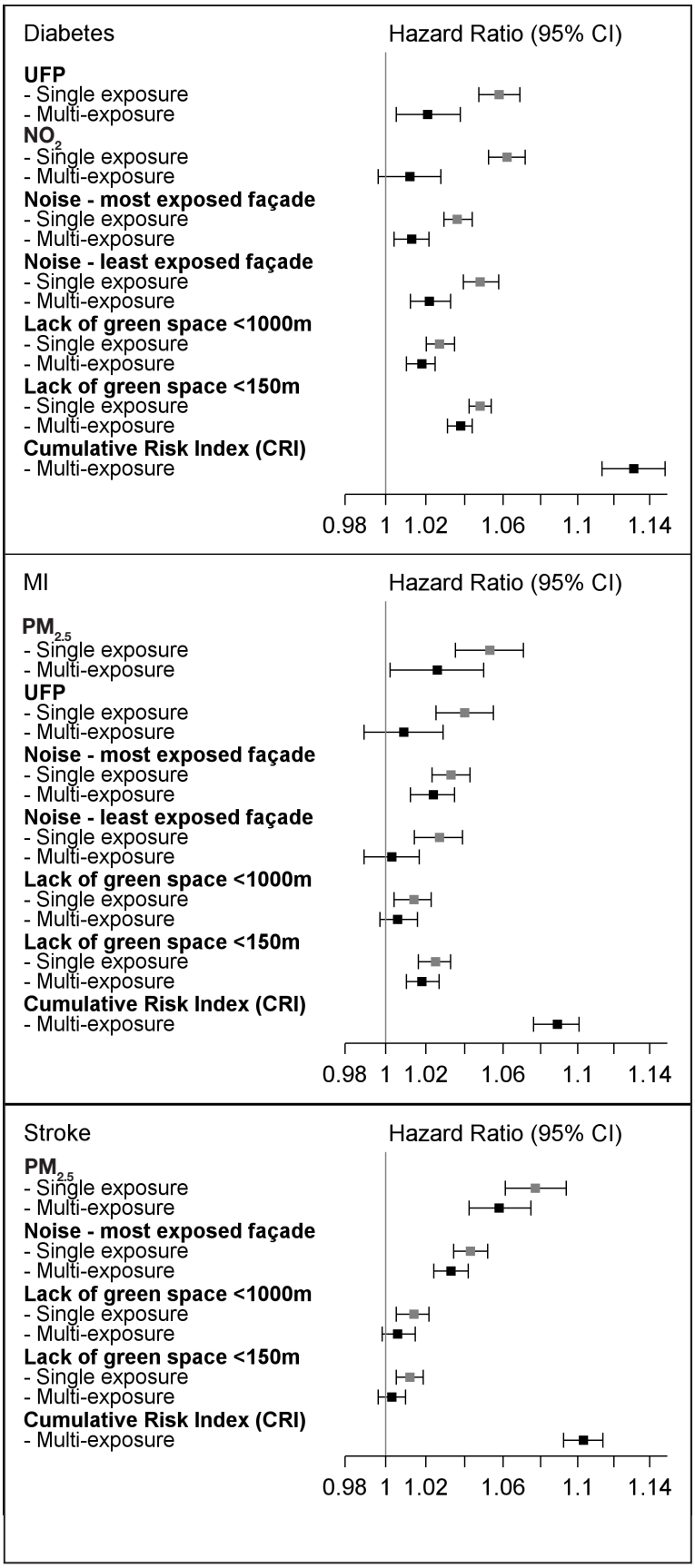
We used the DCH-NG cohort for the biomarker study. Characteristics of the study population are shown in **Table 15** for all participants and by UFP concentration. Most sociodemographic characteristics, lifestyle variables, and biomarkers were similarly below and above the median of UFPs. The season of blood draw, population density, green space, and the other air pollutants differed between those above and below the median of UFPs. There were only very small differences between the biomarkers and blood pressure values in the different seasons (see Additional Materials on the HEI Website, Appendix Table A4).

Table 16 shows the distribution of air pollutants when averaged over the last 24 hours, 72 hours, 7 days, 30 days, and 90 days before blood draw/blood pressure measurement of 32,851 participants. We observed that the variation in air pollution was much lower for the longer time windows. We found higher correlations between air pollution averaged over "similar" time windows — for example, means for 24 hours and 72 hours showed higher correlations than those for 24 hours and 90 days (**Table 17**).

Figure 14 shows associations between air pollution at different time periods and blood concentrations of non-HDL

Figure 12. Associations (HR per IQR) between type 2 diabetes, MI, and stroke and 5-year averages of air pollution, noise, and lack of green space at the residence, analyzed in single- (gray symbols) and multiexposure (black symbols) models, based on people ages 50 and older, 2005–2017. Type 2 diabetes: N = 1,922,545; MI: N = 1,964,702; and stroke: N = 1,971,246. All results adjusted for age, sex, calendar year, cohabiting status, individual and family income, country of origin, occupational status, educational level, and area-level percentage of the population with low income, with only basic education, who is unemployed, who does manual labor, with a non-Western background, who has a criminal record, who is the sole provider, and who lives in social housing. Multiexposure models add mutual adjustment for air pollutants, noise, and lack of green space.

Diabetes panel: reproduced from Sørensen et al. 2022b by permission of Elsevier; Creative Commons CC BY-NC-ND license. MI panel: reproduced from Poulsen et al. 2023c by permission of Oxford University Press.



lipoprotein. We observed a consistent picture for all four air pollutants of higher non-HDL concentrations in association with means during the last 30 days before blood draw. In Additional Materials on the HEI Website, Appendix Figure A1 shows a consistent picture across all four air pollutants of lower concentrations of HDL with higher air pollution concentrations during the last 7 and 30 days before blood draw. Appendix Figure A2 shows a consistent picture of higher systolic and diastolic blood pressure in association with higher air pollution concentrations during the last 30 and 90 days before blood pressure measurement, and Appendix Figures A3 and A4 show that air pollution concentrations were associated with lower CRP and HbA1c concentrations regardless of the air pollution exposure time window.

Table 18a shows that in general, the adverse associations between the IQR of 30-day air pollution means and the cardiovascular biomarkers (HDL, non-HDL, as well as systolic and diastolic blood pressure) were most pronounced or only present for the contributions to the air pollutants from sources other than local traffic. There was no systematic difference between associations with CRP and HbA1c for the air pollution contributions from local traffic and other sources (Table 18a). Table 18b resembles Table 18a, but associations are expressed per fixed exposure difference instead of per IQR. The general picture of adverse associations with the cardiovascular biomarkers and mostly contributions from sources other than local traffic was also evident when expressing

Figure 13. Concept of the biomarker study.

Table 15. Characteristics at Blood Draw (Baseline) of the DCH-NG Cohort Participants, Total and by Level of UFPs

	All Included Participants	UFPs, 30 Days ≤ Median (8173 #/cm^3)	UFPs, 30 Days > Median (8173 #/cm^3)
Number	32,851	16,425	16,426
Baseline year(s)	2015–2018	2015–2018	2015–2018
Individual-level sociodemographics, baseline			
Men (%)	40.9	40.8	41.0
Age (mean ± SD)	42.5 ± 12.8	43.3 ± 12.6	41.8 ± 13.0
Age (min, max)	18, 78	18, 78	18, 77
Cohabiting status (%)			
Married/cohabiting	65.7	68.1	63.3
Widow/divorced/live alone	34.3	31.9	36.7
Educational level (%)			
Mandatory	12.1	12.6	11.6
Secondary or vocational	44.8	45.0	44.7
Medium or long education	43.1	42.4	43.7
Income, individual (%)			
Q1	20.4	18.6	22.2
Q2–Q4	41.1	42.6	40.1
Q5	38.5	38.8	37.7
Area (parish) level sociodemographics, baseline			
Proportion with (mean ± SD):			
Low income	5.3 ± 2.8	4.9 ± 2.6	5.6 ± 2.9
Only basic education	5.9 ± 2.5	6.2 ± 2.5	5.5 ± 2.4
In social housing	20.3 ± 16.7	19.0 ± 16.3	21.7 ± 17.0
Population density (%)			
<2000 per km^2	51.6	62.3	40.8
≥2000 per km^2	48.4	37.7	59.2
Individual lifestyle			
Smoking, last 72 hours (%)	14.6	14.3	15.0
Hours since last smoke[a] (mean ± SD)	4.2 ± 3.5	4.1 ± 3.5	4.3 ± 3.6
Environmental tobacco smoke (%)	16.3	16.3	16.4
Alcohol intake, last 48 hours (%)	43.7	45.8	41.6
Physical activity, hours/week (mean ± SD)	3.2 ± 3.5	3.2 ± 3.6	3.2 ± 3.5
BMI, kg/m^2 (mean ± SD)	24.8 ± 4.0	24.9 ± 4.1	24.7 ± 4.0
Season of blood sampling (%)			
March–May	22.5	17.7	27.4
June–August	26.2	47.7	4.8
September–November	27.4	26.2	28.6
December–February	23.9	8.5	39.3
Biomarkers			
HDL, mmol/L (mean ± SD)	1.58 ± 0.44	1.59 ± 0.44	1.58 ± 0.44
Non-HDL, mmol/L (mean ± SD)	3.43 ± 1.02	3.44 ± 1.02	3.41 ± 1.01
% outside cholesterol recommendations[b]	7.14	7.37	6.92
Systolic blood pressure, mm Hg	116.0 ± 15.8	116.0 ± 16.0	115.9 ± 15.6
Diastolic blood pressure, mm Hg	80.4 ± 10.9	80.5 ± 11.1	80.3 ± 10.7
% above blood pressure recommendations[c]	6.7	7.11	6.21
CRP, mg/L	1.6 ± 3.5	1.6 ± 3.6	1.5 ± 3.4
HbA1c, mmol/mol	34 ± 4	32.8 ± 4.0	32.3 ± 3.7

Continued next page

Table 15. Characteristics at Blood Draw (Baseline) of the DCH-NG Cohort Participants, Total and by Level of UFPs (*continued*)

	All Included Participants	UFPs, 30 Days ≤ Median (8173 #/cm³)	UFPs, 30 Days > Median (8173 #/cm³)
Air pollution[d], noise, and green space			
$PM_{2.5}$ (μg/m³), mean ± SD	8.3 ± 2.3	7.0 ± 3.9	9.7 ± 5.8
UFPs (number/cm³), mean ± SD	8,539 ± 2,354	6,631 ± 1,015	10,446 ± 1,665
EC (μg/m³), mean ± SD	0.54 ± 0.27	0.34 ± 0.13	0.74 ± 0.24
NO_2 (μg/m³), mean ± SD	14.7 ± 4.9	12.0 ± 3.7	17.3 ± 4.5
LdenMax (dB), mean ± SD	56.5 ± 7.8	55.5 ± 7.8	57.5 ± 7.7
LdenMin (dB), mean ± SD	47.3 ± 6.1	46.5 ± 6.3	48.1 ± 5.8
Green space 1000m (%), mean ± SD	52.0 ± 19.4	51.4 ± 21.5	43.2 ± 22.1

[a] Among those who smoked the last 72 hours.
[b] Recommendations by the Danish Society of Cardiology: HDL, men: >1.0 mmol/L; HDL, women: >1.2 mmol/L; non-HDL, both sexes: <3.4 mmol/L. We count "outside recommendations" if outside the limit for both HDL and non-HDL.
[c] Recommendations by World Health Organization: Systolic blood pressure: <140 mm Hg; diastolic blood pressure: <90 mm Hg. We count "outside recommendations" if above the limit for both blood pressure measurements.
[d] Mean of the last 30 days before blood draw.

Table 16. Distribution of Air Pollution in Different Time Windows Before Blood Draw and Blood Pressure Measurements Among the 32,851 Cohort Participants

	Min	P1	P5	P25	P50	P75	P95	P99	Max
$PM_{2.5}$ (μg/m³)									
24 hours	1.3	2.2	2.9	4.8	7.1	10.8	19.1	26.2	41.1
72 hours	1.6	2.7	3.4	5.4	7.4	10.4	16.7	22.5	31.7
7 days	2.2	3.2	4.3	6.0	7.7	10.0	15.7	19.4	25.7
30 days	4.0	4.8	5.5	6.6	7.8	9.5	12.8	15.2	18.7
90 days	4.6	5.5	6.0	6.8	7.7	9.5	11.5	12.4	15.4
UFPs (number/cm³)									
24 hours	931	1,994	2,855	4,967	7,239	10,986	20,095	29,333	62,777
72 hours	1,459	2,564	3,530	5,621	7,499	10,518	16,918	22,768	36,062
7 days	1,886	3,396	4,432	6,261	7,993	10,425	15,232	18,931	28,605
30 days	2,931	4,241	5,164	6,773	8,173	10,167	12,687	14,531	18,783
90 days	3,148	4,567	5,478	6,967	8,197	9820	11,955	13,399	15,926
EC (μg/m³)									
24 hours	0.02	0.06	0.10	0.25	0.42	0.73	1.51	2.27	4.33
72 hours	0.03	0.08	0.14	0.27	0.44	0.72	1.33	1.80	3.06
7 days	0.06	0.12	0.18	0.30	0.46	0.74	1.23	1.56	2.41
30 days	0.08	0.15	0.20	0.32	0.47	0.74	1.05	1.24	1.65
90 days	0.11	0.17	0.23	0.33	0.49	0.72	0.95	1.10	1.51
NO_2 (μg/m³)									
24 hours	0.8	2.1	3.3	7.7	12.8	20.0	33.6	44.6	77.0
72 hours	1.1	2.8	4.7	9.1	13.2	18.8	28.4	36.8	56.2
7 days	2.1	4.5	6.4	10.4	14.0	18.3	26.4	33.9	50.4
30 days	3.6	5.9	8.0	11.4	14.0	17.1	23.9	30.2	44.2
90 days	4.3	6.5	8.2	11.6	14.0	16.6	23.2	29.4	41.1

P1 = 1st percentile; P5 = 5th percentile; P25 = 25th percentile; P50 = 50th percentile (median); P75 = 75th percentile; P95 = 95th percentile; P99 = 99th percentile.

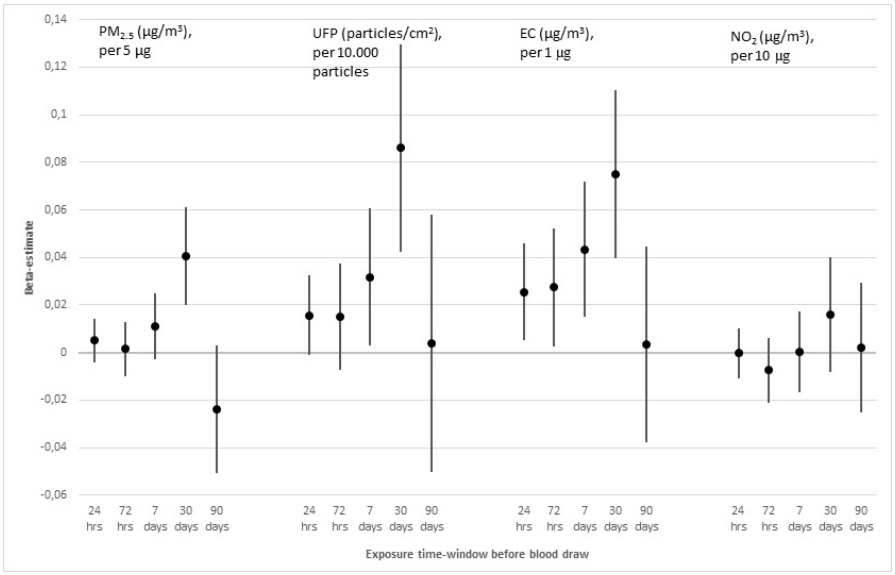


Figure 14. Associations (beta-estimates with 95% CI) between air pollution means of five time windows, and non-HDL ("bad cholesterol"). Associations adjusted for age, age-squared, sex, marital status, educational level, income, smoking before blood draw (yes/no), hours since last smoke, environmental tobacco smoke, alcohol before blood draw, physical activity (yes/no), hours of physical activity/week, body mass index, percentage of parish population having low income, having only basic education, living in social housing, and green space at the residence.

Table 17. Spearman's Correlation Coefficients Between Different Exposure Time Windows for Each of Four Air Pollutants (N = 32,851)

$PM_{2.5}$	**72 hours**	**7 days**	**30 days**	**90 days**
24 hours	0.77	0.63	0.41	0.33
72 hours		0.82	0.52	0.41
7 days			0.67	0.50
30 days				0.80
UFPs	**72 hours**	**7 days**	**30 days**	**90 days**
24 hours	0.75	0.62	0.43	0.36
72 hours		0.81	0.56	0.46
7 days			0.72	0.59
30 days				0.85
EC	**72 hours**	**7 days**	**30 days**	**90 days**
24 hours	0.85	0.77	0.66	0.52
72 hours		0.90	0.77	0.61
7 days			0.87	0.69
30 days				0.80
NO_2	**72 hours**	**7 days**	**30 days**	**90 days**
24 hours	0.78	0.65	0.48	0.46
72 hours		0.83	0.59	0.56
7 days			0.75	0.69
30 days				0.91

exposure differences in fixed concentrations, although that picture was less clear for associations with UFPs and systolic blood pressure.

We found that higher noise levels at both the most- and the least-exposed façades were associated with higher systolic blood pressure and lower HbA1c concentrations (**Table 19**). Furthermore, noise at the least-exposed façade was associated with lower diastolic blood pressure and higher CRP levels.

DISCUSSION

SUMMARY OF MAIN FINDINGS

The HERMES study was based on a nationwide Danish study population of two million people who were 50 years and older, the questionnaire-based DNHS cohort of 246,766 people, and the DCH-NG cohort of 32,851 people from whom information on biomarkers was available. We developed a CTM for assessing UFPs at all Danish addresses. Comparison between modeled and measured UFPs showed correlations at a level similar to the other three pollutants, $PM_{2.5}$, EC, and NO_2. Based on the DNHS cohort, we found that when analyses of associations between air pollution and type 2 diabetes, MI, and stroke were adjusted for registry-based individual- and area-level sociodemographic variables, additional adjustment for individual lifestyle hardly affected the estimated associations.

In analyses of the nationwide cohort, we observed that all four air pollutants were associated with a higher risk of each of the three endpoints in single-pollutant models. The local traffic contribution to air pollution seemed more important for risk of type 2 diabetes than the contribution from other sources, whereas for MI and stroke, the contribution from other sources seemed most important. The most consistent interaction, across the four air pollutants, three endpoints, and two analytical models, was a stronger association between air pollution and type 2 diabetes, MI, and stroke among those with comorbidity. Further, for MI and stroke, we found several interactions on the absolute scale, which could not be detected based on relative measures. In multiexposure analyses, air pollution with $PM_{2.5}$ (stroke and MI) and UFPs (diabetes) were the most important of the four air pollutants, and residential noise and lack of green space were associated with a higher risk of cardiometabolic eases. Analyses of the DCH-NG cohort showed associations between exposure to air pollution and higher concentrations of non-HDL, lower concentrations of HDL, and higher blood pressure. We observed that the contributions to air pollution from sources other than local traffic seemed mainly responsible for these associations.

Table 18a. Associations[a] Between IQR Higher Air Pollution (Total, Local Traffic, Other Sources) Averages over 30 Days Before Blood Draw and Biomarkers

		Beta-Estimates (95% CI)					% Change (95% CI)
	IQR Increment	HDL (mmol/L)	Non-HDL (mmol/L)	Systolic BP (mm Hg)	Diastolic BP (mm Hg)	HbA1c (mmol/mol)	CRP
$PM_{2.5}$ (μg/m³)							
Total	2.95	–0.003	0.024	0.62	0.31	–0.35	–0.04
		(–0.008, 0.002)	(0.012, 0.036)	(0.44, 0.80)	(0.17, 0.44)	(–0.39, –0.30)	(–0.05, –0.03)
Other sources	2.78	–0.003	0.024	0.58	0.30	–0.43	–0.05
		(–0.008, 0.002)	(0.012, 0.036)	(0.40, 0.76)	(0.17, 0.43)	(–0.49, –0.36)	(–0.06, –0.03)
Local traffic	0.29	0.001	–0.001	0.16	0.05	–0.09	–0.01
		(–0.003, 0.004)	(–0.008, 0.007)	(0.05, 0.28)	(–0.04, 0.13)	(–0,13, –0.06)	(–0.02, 0.001)
UFPs (number/cm³)							
Total	3394	–0.008	0.029	0.83	0.53	–0.35	–0.05
		(–0.015, –0.002)	(0.014, 0.044)	(0.61, 1.06)	(0.37, 0.69)	(–0,41, –0.29)	(–0.07, –0.04)
Other sources	2544	–0.010	0.027	0.80	0.59	–0.39	–0.05
		(–0.016, –0.004)	(0.013, 0.041)	(0.59, 1.02)	(0.43, 0.74)	(–0.46, –0.32)	(–0.07, –0.03)
Local traffic	1169	–0.002	0.027	0.67	0.20	–0.62	–0.06
		(–0.009, 0.006)	(0.010, 0.044)	(0.41, 0.92)	(0.01, 0.38)	(–0,70, –0.55)	(–0.08, –0.04)
EC (μg/m³)							
Total	0.42	–0.002	0.032	1.21	0.64	–0.52	–0.06
		(–0.008, 0.004)	(0.017, 0.046)	(0.99, 1.44)	(0.48, 0.81)	(–0.58, –0.46)	(–0.08, –0.04)
Other sources	0.09	–0.003	0.033	1.23	0.58	–0.55	–0.05
		(–0.009, 0.003)	(0.018, 0.078)	(1.00, 1.46)	(0.52, 0.85)	(–0,62, –0.48)	(–0.07, –0.03)
Local traffic	0.38	0.002	0.007	0.38	0.10	–0.34	–0.03
		(–0.003, 0.008)	(–0.007, 0.020)	(0.18, 0.58)	(–0.05, 0.24)	(–0.40, –0.28)	(–0.04, –0.01)
NO_2 (μg/m³)							
Total	5.71	–0.004	0.009	0.26	0.13	–0.23	–0.03
		(–0.010, 0.002)	(–0.005, 0.023)	(0.05, 0.47)	(–0.02, 0.28)	(–0.28, –0.17)	(–0.04, –0.01)
Other sources	2.43	–0.009	0.013	0.33	0.30	–0.31	–0.04
		(–0.014, –0.004)	(0.001, 0.025)	(0.15, 0.50)	(0.18, 0.43)	(–0.37, –0.25)	(–0.05, –0.02)
Local traffic	4.60	0.003	0.002	0.08	–0.06	–0.26	–0.01
		(–0.003, 0.008)	(–0.013, 0.015)	(–0.13, 0.29)	(–0.22, 0.08)	(–0.31, –0.20)	(–0.03, 0.01)

Air pollution was associated with lower CRP and HbA1c levels and noise was associated with higher systolic blood pressure.

LOCAL TRAFFIC VERSUS OTHER CONTRIBUTIONS TO AIR POLLUTION

Previous HEI reports have summarized the epidemiological evidence for long-term exposure to traffic-related air pollution and risk of various health outcomes (HEI 2010, 2022), including type 2 diabetes, coronary events (including MI), and stroke. The most recent of these literature reviews showed that there was sufficient evidence to conclude that an association is likely to exist between air pollution from traffic and type 2 diabetes, whereas the evidence was weaker for coronary events and stroke (HEI 2022). The results from our nationwide cohort are in line with these conclusions, we found associations between traffic-related air pollution and risk of type 2 diabetes but our results pointed at associations between mainly air pollution from sources other than local traffic and risk of MI and stroke. Furthermore, our results from the biomarker study also pointed toward the importance of air pollution from sources other than local traffic for HDL, non-HDL, and blood pressure, which are on the biological pathway to MI and stroke.

Table 18b. Associations[a] Between Fixed Unit Higher Air Pollution (Total, Local Traffic, Other Sources) Averages over 30 Days Before Blood Draw and Biomarkers

		Beta-Estimates (95% CI)					% Change (95% CI)
	Fixed Unit Increment	**HDL** (mmol/L)	**Non-HDL** (mmol/L)	**Systolic BP** (mmHg)	**Diastolic BP** (mmHg)	**HbA1c** (mmol/mol)	**CRP**
$PM_{2.5}$ (µg/m³)							
Total	5	–0.005	0.041	1.05	0.53	–0.59	–0.07
		(–0.014, 0.003)	(0.02, 0.061)	(0.75, 1.36)	(0.29, 0.75)	(–0.66, –0.51)	(–0.08, –0.05)
Other sources	5	–0.005	0.043	1.04	0.54	–0.77	–0.09
		(–0.014, 0.004)	(0.022, 0.065)	(0.72, 1.37)	(0.31, 0.77)	(–0.88, –0.65)	(–0.11, –0.05)
Local traffic	5	0.017	–0.017	2.76	0.86	–1.55	–0.17
		(–0.052, 0.069)	(–0.138, 0.121)	(0.86, 4.83)	(–0.69, 2.24)	(–2.24, –1.03)	(–0.34, 0.02)
UFPs (number/cm³)							
Total	10,000	–0.024	0.085	2.45	1.56	–1.03	–0.15
		(–0.044, –0.006)	(0.041, 0.130)	(1.80, 3.12)	(1.09, 2.03)	(–1.21, –0.85)	(–0.21, –0.12)
Other sources	10,000	–0.039	0.106	3.14	2.32	–1.53	–0.20
		(–0.063, –0.016)	(0.051, 0.161)	(2.32, 4.01)	(1.69, 2.91)	(–1.81, –1.26)	(–0.28, –0.12)
Local traffic	10,000	–0.017	0.231	5.73	1.71	–5.30	–0.51
		(–0.077, 0.051)	(0.086, 0.376)	(3.51, 7.87)	(0.09, 3.25)	(–5.99, –4.70)	(–0.68, –0.34)
EC (µg/m³)							
Total	1	–0.005	0.076	2.88	1.52	–1.24	–0.14
		(–0.019, 0.010)	(0.040, 0.11)	(2.36, 3.43)	(1.14, 1.93)	(–1.38, –1.10)	(–0.19, –0.10)
Other sources	1	–0.033	0.367	13.67	6.44	–6.11	–0.56
		(–0.100, 0.033)	(0.200, 0.867)	(11.11, 16.22)	(5.78, 9.44)	(–6.89, –5.33)	(–0.78, –0.33)
Local traffic	1	0.005	0.018	1.00	0.26	–0.89	–0.08
		(–0.008, 0.021)	(–0.018, 0.053)	(0.47, 1.53)	(–0.13, 0.63)	(–1.05, –0.74)	(–0.11, –0.03)
NO_2 (µg/m³)							
Total	10	–0.007	0.016	0.46	0.23	–0.40	–0.05
		(–0.018, 0.004)	(–0.009, 0.040)	(0.09, 0.82)	(–0.04, 0.49)	(–0.49, –0.30)	(–0.07, –0.02)
Other sources	10	–0.037	0.053	1.36	1.23	–1.28	–0.16
		(–0.058, –0.016)	(0.004, 0.103)	(0.62, 2.06)	(0.74, 1.77)	(–1.52, –1.03)	(–0.21, –0.08)
Local traffic	10	0.007	0.004	0.17	–0.13	–0.57	–0.02
		(–0.007, 0.017)	(–0.028, 0.033)	(–0.28, 0.63)	(–0.48, 0.17)	(–0.67, –0.43)	(–0.07, 0.02)

[a] Adjusted for age, age-squared, sex, marital status, educational level, income, smoking before blood draw (yes/no), hours since last smoke, environmental tobacco smoke, alcohol before blood draw, physical activity (yes/no), hours of physical activity/week, BMI, percentage of parish population having low income, having only basic education, living in social housing, and green space at the residence.

In the HERMES study, air pollution from local traffic was defined as contributions from road traffic within 25 km of the receptor point, thus reflecting local sources and approximating a contribution to air pollution, which could be influenced by local abatement strategies. The contribution denoted as from "other sources" includes air pollution from all sources other than road traffic within 25 km. Thus, air pollution from "other sources," for which we found associations with risk of MI and stroke, included contributions from road traffic beyond 25 km from the receptor point, which could include, for example, secondary nitrate particles formed in the atmosphere from NO_x emissions from road traffic abroad.

We report HRs both per IQR and by fixed increment (Tables 10, 11a, 11b, 18a, and 18b). The comparison between HRs for the local traffic and other sources' contribution to a pollutant can provide different pictures dependent on the choice of either IQR or fixed increment. The overall picture from our nationwide study — associations between mainly local traffic-related air pollution and risk of type 2 diabetes, but associations between other sources of air pollution and the risk of MI and stroke — persisted regardless of the chosen exposure contrast. HRs expressed per IQR would be appropriate for comparisons between exposures within the same population if the focus is primarily on the health effects of the

Table 19. Associations[a] Between Road Traffic Noise at the Most- (L_{den}max) and Least- (L_{den}min) Exposed Facade in Relation to Biomarkers

	Beta-Estimates (95% CI)					% Change (95% CI)
	HDL (mmol/L)	**Non-HDL** (mmol/L)	**Systolic BP** (mm Hg)	**Diastolic BP** (mm Hg)	**HbA1c** (mmol/mol)	**CRP** (mg/L)
Ldenmax, per 10 dB	0.002 (–0.004, 0.007)	0.009 (–0.005, 0.022)	0.30 (0.10, 0.50)	–0.03 (–0.18, 0.12)	–0.10 (–0.16, –0.05)	1.2 (–0.5, 2.7)
Ldenmin, per 10 dB	–0.007 (–0.014, 0.0003)	0.008 (–0.009, 0.025)	0.27 (0.02, 0.53)	–0.24 (–0.43, –0.06)	–0.29 (–0.36, –0.23)	3.1 (1.1, 5.1)

[a] Adjusted for age, age-squared, sex, marital status, educational level, income, smoking before blood draw (yes/no), hours since last smoke, environmental tobacco smoke, alcohol before blood draw, physical activity (yes/no), hours of physical activity/week, percentage of parish population having low income, having only basic education, living in social housing, and green space at the residence.

emission sources and exposure mixture of that population. Such focus could include interest in what could be gained if removing a similar proportion of two pollutants, for example, half of the emission sources of local traffic and other sources, respectively. However, IQRs differ between study populations and HRs per IQR would, therefore, not be appropriate for comparison of results across study populations. HRs per fixed increment is more relevant for such comparisons.

Overall, the HERMES study showed that the air pollution source being associated with health depended on the health outcome: local traffic-related air pollution was associated with type 2 diabetes, and air pollution from other sources was associated with MI and stroke. This difference might relate to differences in the composition of the air pollution mixture from local traffic compared with air pollution from other sources and/or to different biological mechanisms that lead to type 2 diabetes, MI, and stroke. The result indicates the need for future studies to assess risk estimates in association with source-specific contributions to air pollution. For example, the association between air pollution from sources other than local traffic and MI and stroke could be further investigated by distinguishing the major contributors other than local traffic.

INTERACTIONS

We found stronger associations between air pollution and risk for all three endpoints among individuals with one or more comorbidities, which was consistent across all pollutants and the two statistical models (Cox and Aalen). Previous studies have shown similar results, although not consistently (Amini et al. 2020; Andersen et al. 2012; Chen et al. 2013; Hart et al. 2015; Hystad et al. 2020; Olaniyan et al. 2022). Several diseases, including type 2 diabetes, cardiovascular diseases, chronic obstructive pulmonary disease, and asthma, are characterized by systemic inflammation and/or oxidative stress and it seems intuitively correct that individuals already challenged by other diseases are more susceptible to detrimental effects of air pollution on diseases involving the same biological pathways. Thus, individuals with morbidities should be the focus of prevention strategies. We used the Charlson comorbidity index as measure for comorbidity, which is based on scores for many different diseases. The next research step could be to investigate if the stronger associations between air pollution and our three endpoints are most pronounced among individuals with specific disease(s), which could facilitate a further focus of prevention strategies on the most susceptible individuals.

For type 2 diabetes and MI, we found higher absolute risk estimates among men compared with women. Previous studies on sex differences in risk of type 2 diabetes and cardiovascular diseases in relation to air pollution have shown inconsistent results (Chen et al. 2013; Danesh Yazdi et al. 2021; Voss et al. 2021; Weinmayr et al. 2015; Yuan et al. 2019; Zhang et al. 2022). Our higher risk estimates for MI among men are, however, in line with a previous study showing higher mortality due to cardiovascular diseases in association with air pollution among Danish men (Raaschou-Nielsen et al. 2020). Such differences between sexes might relate to different biological responses to air pollution as suggested by a study showing associations between $PM_{2.5}$ and inflammation markers in men, but not in women (Hoffmann et al. 2009). Gender differences in activity patterns leading to different exposure to air pollution might also play a role, for example, in some countries women spend more time at home than men (Clougherty 2010).

We found a general pattern for MI and stroke of higher absolute risk estimates among those with low SES, which we could not detect when considering relative risk estimates. Many previous studies have similarly found that relative risk of MI and stroke in relation to air pollution did not differ by socioeconomic factors (Beelen et al. 2014; Hayes et al. 2020; Hystad et al. 2020; Ljungman et al. 2019; Stafoggia et al. 2014; Yang et al. 2021), although the pattern is not consistent (Bai et al. 2019; Hystad et al. 2020; Olaniyan et al. 2022; Shin et al. 2019). We are aware of only one previous study using absolute risk when analyzing SES as a potential effect modifier and they found higher absolute risk of MI and stroke in association with air pollution among those with lower SES, which is similar to our findings (Danesh Yazdi et al. 2021).

These results indicate that using both relative and absolute risk can provide a better understanding of interactions. If the basic rate of the endpoint is similar for the population groups compared, we would expect the two approaches to provide similar pictures of interaction. However, if the basic disease rate differs between the population groups (which is often the case for subpopulations defined by SES), the two approaches can provide different results, as demonstrated in the HERMES study. It is important to add that estimation of absolute risk is not more correct than relative risk or vice versa, but for understanding the public health implications, we believe that absolute risk estimates are preferable.

The results showed higher absolute risk estimates among individuals without financial stress consistently for all endpoints and air pollutants, which might seem counterintuitive. However, it might relate to undiagnosed cases, which exist for both type 2 diabetes (Jørgensen et al. 2020), MI (Pride et al. 2013) and stroke (Saini et al. 2012). Among the individuals who experience mild or transient symptoms, those with financial stress might be less prone to approach the healthcare system and receive a diagnosis, which could result in a lower risk in this group. Such a mechanism would not relate to the economic situation of the individual per se because healthcare is free of charge in Denmark but could relate to a less active health-seeking behavior when being in a state of financial stress.

MULTIEXPOSURE ANALYSES

Air pollution, noise, and lack of green space at the residence are three correlated aspects of urban living, and each of these exposures has been associated with a risk of type 2 diabetes, MI, and stroke. Several studies have analyzed concomitant exposure from two of these environmental domains, but we are aware of only one previous study that included exposures from all of these domains in cross-sectional analyses of associations with self-reported diagnoses of cardiometabolic diseases (Klompmaker et al. 2019).

There is a need for statistical methods that can address the simultaneous exposures to multiple environmental factors, as this reflects real-life conditions; it is important to identify the effect of individual exposures in the presence of other factors. One promising approach is Bayesian Kernel Machine Regression (BKMR), a nonparametric method that can handle nonlinear functions and complex relationships between exposures. We considered the BKMR method but decided against it because it was relatively new when our project began, and the computational demands made it impossible to run our adjusted models even on a 1% sample of our data. Instead, we intended to develop a new method for such multiexposure analyses in large cohorts, based on machine learning and the principles of causal inference. However, we were not able to make this method work on our data set and we have not identified the source(s) of error, except that it occurred during the machine learning phase. The Additional Materials on HEI's website have a more comprehensive description of this work.

For future work on the development of similar methods, we would recommend starting the development with a small, easily managed computer-generated data set such that all correlations and structures in the data are understood and under control, and only gradually expanding this to reflect real-world data in a late stage of development. A part of our problem might have been that we relied too early in the development phase on a huge real-world data set. We also suggest that the underlying methods — whether that be random forest or other machine learning methods — need to be redesigned to more efficiently accommodate survival-type data and to handle the situation of extremely rare outcomes. In our data, the outcomes are rare because we have high temporal resolution, which implies that for any specific person at a specific time, the probability of, for example, diabetes is minimal. The usual "tricks" of rebalancing data to get a more even distribution of case and noncase records would likely not work as we also need the absolute risk estimates to be correct. Headway could be made by exploring different loss functions (describing the difference between actual and predicted outcomes) for the fit; again, the loss functions should reflect the survival nature of the problem.

Our development of the machine-learning approach failed, so we based our analyses on traditional Cox models, including a preselection procedure. In this procedure, we identified exposures within each environmental domain (air pollution, noise, and green space) that showed consistent associations with the endpoint regardless of which other exposures within the same domain we adjusted for. We used these preselected exposures in the final multiexposure model for mutual adjustment. Overall, the results pointed to particulate matter air pollution, noise, and lack of green space as independent risk factors for type 2 diabetes, MI, and stroke. We also found a consistent pattern of stronger associations based on single-exposure models compared with associations based on multiexposure models, especially for air pollution and noise, which indicates that studies without mutual adjustment for exposures within these three environmental domains will overestimate the strength of the association with the exposure studied. Interestingly, we found noise at the most-exposed façade to be more strongly associated with cardiovascular diseases than noise at the least-exposed façades, whereas for type 2 diabetes the opposite was observed. This suggests that inclusion of more proxies for noise than the standard noise (Lden) at the most-exposed facade could prove important in the disentangling of effects of noise and air pollution. We found no consistent effect modification by noise when investigating the effects of air pollution on the three health outcomes.

We used input data of similar high quality for the assessment of air pollution, noise, and green space and with similar levels of spatial and temporal resolution. This is of major importance because otherwise, better-estimated exposure is likely to dominate in multiexposure analyses. To the best of our knowledge, no previous large-scale epidemiological study has used such detailed multiexposure information about air

pollution, noise, and green space as we did in the HERMES study.

BIOMARKERS AND BLOOD PRESSURE

We found associations between exposure to air pollution and higher concentrations of non-HDL, lower concentrations of HDL, and higher blood pressure, all of which have been associated with a higher risk of cardiovascular diseases. Our results are in line with previous results (McGuinn et al. 2019; Wu et al. 2019; Yang et al. 2018; Zhao et al. 2022) and in accordance with the notion that influence of air pollution on blood lipids and blood pressure is on the biological pathway between air pollution and cardiovascular diseases. Furthermore, the observation that the associations between air pollution and blood lipids and blood pressure are mainly observed for the air pollution contribution from sources other than local traffic is in accordance with our observation that the contribution from such other sources was most important for the risk of MI and stroke in the nationwide cohort study.

Air pollution was associated with lower CRP and HbA1c levels. The direction of these associations was opposite to our expectations, which we cannot explain. It is possible that these biomarkers are not good indicators for the biological pathways from air pollution to cardiovascular disease and type 2 diabetes.

Noise was associated with higher systolic blood pressure, indicating that increased blood pressure might be on the biological pathway between noise and cardiovascular diseases. This is in accordance with the few previous studies investigating this (Kupcikova et al. 2021; Lee et al. 2019).

We analyzed associations between the biomarkers and air pollution in five different time windows before blood draw/blood pressure measurement. At least three factors influence which time windows showed the strongest associations: (1) the uncertainty of the exposure assessment, which seems lower for long-term than for short-term averages (Tables 1–4), (2) the variation in the air pollution data, which is lower for long-term than for short-term averages (Table 16), and (3) the time needed for biological processes to translate air pollution exposure into changes of the biomarker level. Thus, our choice of the 30-day period for the main analyses should not be taken as identification of the most relevant biological time window, but rather as a practical choice of a time window for which we were able to observe associations for all the biomarkers, given our exposure and biomarker data. Our results do not permit general conclusions about the most relevant air pollution–exposure time window for each biomarker.

MODELING UFP CONCENTRATIONS

The development of a model for assessing UFP concentrations, as part of the HERMES study, was the first implementation of PNC in our modeling system. Although the modeled concentrations correlated well with measurements (see Methods section of this report), several aspects of the complex PNC modeling can be improved. We found that correlations with measurements were highest for the street location and annual averages, while correlations were lower for daily and monthly means at the rural and urban background locations. This finding indicates that the processes related to local traffic emissions are better reproduced by the modeling system than the processes related to emissions from sources other than local traffic at background locations. Thus, further model development is needed to better reproduce the observed seasonal variation at the background locations (e.g., revisiting the seasonal variations in the emissions from various sources). Also, a wider geographic spread of the measuring locations would be helpful to assess the spatial performance of the model. Emissions are crucial input for deterministic models and our approaches to building PNC emission inventories for Denmark and Europe can be refined to include size-fraction-specific emissions for all relevant source sectors and implement these in the UBM and OSPM models and to better describe how emission factors vary in time (e.g., due to changing engine technology, fuel composition, and after treatment, as well as changes in season and weather). Improvement of our model also can be related to modeling particle dynamics at each scale of the DEHM/UBM/AirGIS framework to cover the full-size range of UFPs at all scales. This includes the treatment of VOCs based on natural emissions during summertime as precursors for the formation of new particles by nucleation, coagulation processes, condensational growth, evaporation, and deposition.

METHODOLOGICAL ISSUES, STRENGTHS, AND LIMITATIONS

It was a major strength of the HERMES study that we combined several rich data sources, including three cohorts and a wealth of reliable, high-quality, nationwide Danish registry data. We identified our outcomes in high-quality nationwide patient (Lynge et al. 2011), mortality (Helweg-Larsen 2011), and prescription (Kildemoes et al. 2011) registries with high degrees of completeness and validity. The data on sociodemographic variables at the individual and small-area (parish) level were updated yearly, and changes in residential addresses were updated in the Danish Civil Registration System (C.B. Pedersen 2011) within days after moving to a new address. The follow-up of participants in the Danish registries also prevented loss of follow-up. We further enriched the cohort data with state-of-the-art modeling of air pollution and noise as well as an assessment of green space at the residences using a detailed land use map (Levin et al. 2017).

We used results from the DNHS (Christensen et al. 2022) and the DCH-NG (Petersen et al. 2022) cohorts to qualify the interpretation of the results from the nationwide cohort study. We used the DNHS cohort to examine the consequence of lack of adjustment for lifestyle in analyses already adjusted for registry-based variables, thereby qualifying the conclusions drawn from the nationwide cohort for which

registry-based variables, but not lifestyle data, were available. In the biomarker study, our finding of associations between air pollution from sources other than local traffic and blood lipids and blood pressure strengthened our confidence that the results for air pollution from such other sources and cardiovascular diseases in the nationwide cohort were not due to chance. Thus, the ability of the HERMES study to provide results from different cohorts with different types of data, but related to the same research questions, was a major strength.

One limitation in the comparison of results between the nationwide cohort study and the biomarker study is that the exposure time windows differ. The associations found in the nationwide study were based on 5-year-average air pollution concentrations whereas associations found in the biomarker study were for shorter averaging periods (e.g., 30 days), reflecting that exposures and conditions over days, weeks, and months would influence the biomarkers and blood pressure. Nevertheless, the biomarkers are known risk factors for the cardiometabolic diseases under study and demonstrated associations between air pollution and the biomarkers would support the notion that the biomarkers could be on the biological pathway between air pollution and development of the diseases. Furthermore, we would expect a correlation between short- and long-term concentrations of air pollution, such that locations with high 5-year-average concentrations would also experience higher 30-day-average concentrations and more 30-day periods exceeding a certain air pollution concentration.

The analyses of associations between air pollution and biomarkers were not adjusted for season of blood draw for two reasons, First, such adjustment would "adjust away" exposure contrast because air pollution is associated with season (Table 15), thus limiting the possibilities of detecting associations between air pollution and biomarkers. The second reason is that we found very little seasonal variation in biomarkers (Appendix Table A4 in Additional Materials on the HEI Website), which implies limited potential for confounding from season of blood draw.

Also, our development of a nationwide cohort with a high-quality assessment of exposure to four air pollutants, two noise measures, and two measures of green space with the same temporal resolution and at the exact residential level over an 18-year period is unique and facilitated analyses of concomitant exposures in relation to type 2 diabetes, MI, and stroke.

We used the DEHM/UBM/AirGIS modeling system to assess exposure to air pollution, which belongs to the CTM class of models, which model the physical and chemical processes from emissions over atmospheric transport, dispersion, and atmospheric chemistry to the concentration at the receptor point. We took advantage of the option to switch on or off local traffic emissions in the calculations to specify contributions to air pollution from local traffic and other sources. Future studies could use a similar approach to assess the health effects of air pollution from different sources. CTMs also offer the opportunity to define specific future scenarios (e.g., 50% or 100% electrification of the transport sector) and to calculate the population exposure under such scenarios. The validity of such exercises will strongly depend on the quality of information about emissions from the sources under study and specific scenarios.

We found high correlations between air pollution concentrations ($PM_{2.5}$, UFPs, EC, and NO_2) that were modeled with DEHM/UBM/AirGIS and that were measured — with correlation coefficients between 0.87 and 0.99 for annual means, between 0.73 and 0.93 for monthly means, and between 0.68 and 0.87 for daily means — when considering the combined spatial and temporal performance for all available measurements (Table 2). When considering only the temporal performance at single stations for different averaging intervals, we found the highest correlation coefficients for annual averages at the street station (between 0.86 and 0.95) (Table 1). We found a tendency toward lower correlation coefficients for urban background and rural stations, indicating that our models perform best for local traffic emission sources, while some emissions and processes at the urban and regional scales (e.g., residential wood combustion, natural emissions, and secondary formed particles) are connected with higher uncertainties.

Even the best model (or measurement) used for exposure assessment will inevitably imply some degree of exposure misclassification. We would expect our misclassification to stem from a combination of classical and Berkson error (Sheppard et al. 2012) and to be nondifferential with respect to the case status of the cohort participants. Such misclassification can affect both the risk estimate and its precision (Sheppard et al. 2012). Our noise model has similarly shown excellent agreement with measurements (Ström 1997) and used input data of similarly high quality as the input data for the air pollution model. Our assessment of green space at the residences was based on high-resolution maps (10 m × 10 m) of Denmark with 36 classes of land use (Levin et al. 2017). Thus, our exposure measures for air pollution, noise, and green space were all of high quality and at a similar high spatial resolution. It is a limitation that we had no information about nonresidential exposures, and we cannot rule out that our results were influenced by such exposures.

Air pollutants, noise, and green space are correlated aspects of modern urban living, and the interpretation of associations with each of the correlated exposures should be made with caution. We used a multiexposure approach with preselection of variables within each of the three exposure domains and included only exposures being consistently associated with the outcome in all two-, three-, and four-exposure models within their domain. Nevertheless, in the final multiexposure model correlation between variables and possible differences in the precision with which each variable was determined could have influenced the results.

The results of the HERMES are based on multiple analyses, and we would expect to detect some associations simply by chance. Therefore, patterns of results — for example, associations observed consistently for several pollutants and/or endpoints rather than single observations — seem most reliable and have been given weight in this HEI report.

The comprehensive registry-based variables provided a very detailed description of the sociodemographic characteristics of each individual and of the parish where the individual lived. We adjusted for these variables and have demonstrated that after such adjustment, we would not expect the estimated risk to change much by further adjustment for individual lifestyle (Sørensen et al. 2022a). However, we cannot exclude that some residual confounding would have occurred. If our results were affected by such residual confounding from socioeconomic factors, our risk estimates could be underestimated because high socioeconomic status is associated with lower incidence of type 2 diabetes (Kyrou et al. 2020) and cardiovascular disease (Powell-Wiley et al. 2022), and with higher concentrations of air pollution at the residence (Raaschou-Nielsen et al. 2022). In the DNHS and DCH-NG cohorts, error in self-reporting of health behaviors could also have resulted in residual confounding.

Lastly, although the HERMES study was based on the entire Danish population and we therefore believe that our results can be generalized to other Western populations, differences in ethnicity, genetics, and air pollution sources and concentrations must be considered when generalizing the results.

CONCLUSIONS

In this nationwide Danish study, air pollutants $PM_{2.5,}$ UFPs, EC, and NO_2 were all associated with type 2 diabetes, MI, and stroke in single-pollutant models.

In multiexposure analyses, particulate matter air pollution (UFPs for type 2 diabetes and $PM_{2.5}$ for MI and stroke), noise, and lack of green space were all associated with higher risk of type 2 diabetes, MI, and stroke. The results showed higher risk estimates in single-exposure analyses compared with risk estimates in a multiexposure approach, indicating that estimating the effect of only one of these environmental exposures might result in an overestimation of the effect of that exposure.

The results showed that air pollution from local traffic was the most important for risk of type 2 diabetes, whereas air pollution from sources other than local traffic was most important for the risk of MI and stroke.

In a subsample of the Danish population (DNHS cohort) we showed that when associations between air pollution and type 2 diabetes, MI, and stroke were adjusted for individual and small-area sociodemographic variables (as done in the nationwide study), further adjustment for individual lifestyle hardly affected the risk estimates.

Associations between air pollution and type 2 diabetes, MI, and stroke were consistently stronger among individuals with comorbidity, indicating susceptibility to negative air pollution effects in this subpopulation.

The results of the interaction analyses showed that higher risk estimates among those of low socioeconomic status could be detected when estimating absolute risk but not when estimating relative risk.

The biomarker study showed expected associations between exposure to air pollution and blood lipids and blood pressure, adding evidence that these markers are on pathways between air pollution and cardiovascular diseases.

IMPLICATIONS OF THE FINDINGS

The demonstration of negative health effects of air pollution at the relatively low Danish air pollution concentrations shows that reduction of air pollution has potential for public health benefits, even at relatively low levels.

The HERMES study demonstrated that CTMs hold the potential for air pollution source-specific assessment of risk, given access to high-quality emission inventories. Future studies should take advantage of that and the closely related potential of the CTMs to study exposure and health effects for different scenarios for reduced emissions from, for example, the transport or energy sector. The results of such studies could guide development of the most efficient prevention strategies.

The results of our study showed that the air pollution contributions from sources other than local traffic were most important for the risk of MI and stroke. This result indicates a need for studies disentangling the contributions of air pollution from these sources and relating them to the risk for MI and stroke. Our demonstration of the importance of different air pollution sources for different health endpoints also indicates a general need for studies of source-specific contributions to air pollution regardless of the health endpoint.

The results of the HERMES study show that a multiexposure analyses approach, with an estimation of exposures using state-of-the-art models of comparable high quality across exposure domains, is needed to provide an accurate picture of which of the many correlated pollutants (specific air pollutants, noise, lack of green space, and potentially others) related to urban living are most harmful to human health. Also, this could guide development of the most efficient prevention strategies.

The stronger associations between air pollution and health effects among those with comorbidities identify a group of individuals with a special need for protection.

The results showed that conclusions about potential effect modification by socioeconomic status may depend on whether the risk is estimated at the relative or absolute scale. When basic disease or mortality rates differ between the pop-

ulation strata studied, the use of both relative and absolute risk would provide the best understanding of potential effect modification.

DATA AVAILABILITY STATEMENT

Data for the HERMES project was built and analyzed within the secure IT environment at Statistics Denmark, from where no individual-level data can be transferred. Access to individual-level Danish data at Statistics Denmark is governed by Danish authorities. These include the Danish Data Protection Agency, the Danish Health Data Authority, the Ethical Committee, and Statistics Denmark. An application for access to individual-level data at Statistics Denmark requires a scientific project, which has been approved before initiation, and approval is granted to a specific Danish research institution. Researchers at Danish research institutions may obtain approval and access to the relevant data. International researchers may gain data access if governed by a Danish research institution having the needed approval and data access.

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HEI QUALITY ASSURANCE STATEMENT

The conduct of this study was subjected to an independent audit by Westat staff members Dr. Joseph Abraham, Dr. David Wright, Mr. Michael Giangrande, and Ms. Rebecca Birch. These staff members are experienced in quality assurance (QA) oversight for air quality modeling and exposure assessment, geographic information systems, epidemiological methods, and statistical modeling.

The QA oversight program consisted of a remote audit of the final report and the data processing steps. Key details of the dates of the audit and the reviews performed are listed below.

Final Remote Audit

Date: February 2024 – April 2024; review of revisions June 2024

Remarks: The Raaschou-Nielsen et al. study underwent an independent quality assurance (QA) audit by a Westat team consisting of three auditors with quality assurance oversight experience and expertise relevant to exposure assessment, air quality monitoring and modeling, epidemiological methods, geospatial analysis, and statistical analysis.

The planned QA oversight program was to consist of an initial on-site audit to evaluate adherence to the study protocol and standard operating procedures and a final remote audit to evaluate data processing, analyses, and the final report. However, due to the COVID-19 pandemic, the planned on-site audit of the research study for conformance to study protocols and standard operating procedures was not conducted. The remote QA audit of data processing, analysis procedures, the presentation and interpretation of results, and appropriateness of study conclusions in the final report was performed by Dr. Abraham, Mr. Giangrande, and Dr. Wright of Westat. Ms. Birch, also of Westat, provided project management and oversight, including reviewing of audit plans and draft QA documents.

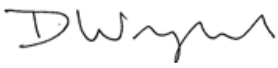
The Westat QA review of the final Raaschou-Nielsen et al. report focused on adherence to the study protocol, appropriateness of the documentation of the study methods, whether study assumptions and limitations were adequately addressed, and whether the investigators' conclusions were reasonable given the study findings and in consideration of the limitations of the investigation. The QA team also evaluated whether the report was generally easy to follow and understand.

The QA auditors provided HEI and the investigators with specific recommendations for improvement of the report. Overall, the QA auditors were satisfied both with the quality of the work conducted by Raaschou-Nielsen et al. and with the quality of their final report. QA feedback included a suggestion to elaborate on the evidence base and provide

additional evidence of the open areas of research noted by the investigators in the report's introduction, expansion of the characterization of the geocoding methods used, including commenting on the accuracy of the registry-based address information, an apparent discrepancy between the proposed air pollutants to be evaluated and the results presented in the final report, which focused on a subset of these pollutants. The QA auditors recommended additional discussion of the potential for, and magnitude of, measurement errors (e.g., in noise exposure estimates and in potential confounders), and the potential effects of these errors on study findings. The auditors suggested the potential to improve the quality of the report by expanding the discussion of the steps taken to verify assumptions underlying statistical models had been met. Finally, the auditors noted that some of the report's conclusions read merely as restatements of study findings. The Westat QA auditors concluded that the study was well conducted in accordance with the study protocol and that the report was well-written, well-organized, and of high quality.

Raaschou-Nielsen et al. responded to the QA recommendations and appropriately incorporated the feedback from the QA auditors in a revised final draft of the report that HEI provided to Westat. The Westat QA audit team attests that the final report appears to be representative of the study conducted.

Joseph Abraham, ScD, Epidemiologist, Quality Assurance auditor



David Wright, PhD, Statistician, Quality Assurance auditor

Michael Giangrande, MGIS, Geographic Information System Analyst, Quality Assurance auditor

Rebecca Jeffries Birch, MPH, Epidemiologist, Quality Assurance auditor

Date: July 15, 2024

ADDITIONAL MATERIALS ON THE HEI WEBSITE

Appendix Tables A1–A4, Appendix Figures A1–A4, and the Method for Multiexposure Analyses are supplemental material not included in the main report. They are available on the HEI website at *https://www.healtheffects.org/publications*.

Appendix Table A1. Associations between air pollution and type 2 diabetes in the Danish population, 2005–2017, in three adjustment models.

Appendix Table A2. Associations between air pollution and myocardial infarction in the Danish population, 2005–2017, in three adjustment models.

Appendix Table A3. Associations between air pollution and stroke in the Danish population, 2005–2017, in three adjustment models.

Appendix Table A4. Seasonal variation in lipid levels and blood pressure (mean ± SD).

Appendix Figure A1. Associations (beta-estimates with 95% CI) between air pollution means of five time windows, and HDL ("good cholesterol").

Appendix Figure A2. Associations (beta-estimates with 95% CI) between air pollution means of five time windows, and systolic and diastolic blood pressure.

Appendix Figure A3. Associations (percentage with 95% CI) between air pollution means of five time windows, and CRP.

Appendix Figure A4. Associations (beta-estimates with 95% CI) between air pollution means of five time windows, and HbA1c.

Method for Multiexposure Analyses

ABOUT THE AUTHORS

Ole Raaschou-Nielsen, MSc, PhD, is head of the Work, Environment and Cancer research group at the Danish Cancer Institute and is a professor at Aarhus University. His research focuses on environmental exposures such as air pollution, radon, noise, cadmium, and persistent organic pollutants in relation to risk for cancer and other health endpoints.

Aslak H. Poulsen, MSc, PhD, is a staff scientist in the Work, Environment and Cancer research group at the Danish Cancer Institute. His main research area is on the health effects of environmental exposures such as air pollution and noise with a particular focus on management, analysis, and general application of huge datasets.

Matthias Ketzel, PhD, is a professor at the Department of Environmental Science, Aarhus University, Roskilde, Denmark, and a visiting professor at the Global Centre for Clean Air Research, University of Surrey, UK. He received his PhD from Lund University, Sweden. His main research topics are atmospheric dispersion, aerosol dynamics modeling, and human exposure estimation at regional, urban, and street scale.

Lise M. Frohn, PhD, is a senior scientist at the Department of Environmental Science, Aarhus University, Roskilde, Denmark. She received her PhD from Copenhagen University, Denmark. Her main research topics are three-dimensional atmospheric chemistry-transport modeling from hemispheric to local scale and assessment of health effects and socioeconomic costs of air pollution.

Nina Roswall, MSc, PhD, is a senior scientist in the Work, Environment and Cancer research group at the Danish Cancer Institute. Her main research areas are epidemiological studies of traffic noise and air pollution exposure, mainly in relation to noncommunicable diseases, such as cardiovascular disease and cancer, as well as related biomarkers.

Jesper H. Christensen, PhD, is a senior scientist at the Department of Environmental Science, Aarhus University, Denmark. He has a PhD from the University of Copenhagen, Denmark. He is an expert in multiscale atmospheric modeling especially in the development of chemical atmospheric transport models and weather forecast models and application of models for air quality assessment. He is the main developer of the three-dimensional air pollution model system, Danish Eulerian Hemispheric Model (DEHM).

Jørgen Brandt, PhD, is a professor of atmospheric modeling at the Department of Environmental Science, Aarhus University, Denmark. He has a PhD from the University of Copenhagen, Denmark. He is an expert in multiscale atmospheric modeling and health impact assessment from air pollution.

Ulla A. Hvidtfeldt, PhD, is a senior scientist in the Work, Environment and Cancer research group at the Danish Cancer Institute. She has several years of research experience within the field of air pollution and health and vast experience within social epidemiology with a focus on SES and health.

Mette Sørensen, PhD, is a senior scientist in the Work, Environment and Cancer research group at the Danish Cancer Institute, and a professor at the Department of Natural Science and Environment, Roskilde University. She has many years of experience in environmental epidemiology and during the last decade has focused on investigating the health effects of environmental noise.

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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/m³ to 9 µg/m³, and the European Union recently lowered the air quality standard for $PM_{2.5}$ from 25 µg/m³ to 10 µg/m³ (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/m³ (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/m³ in the European Union (recently lowered from 40 µg/m³) (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/m³ (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.

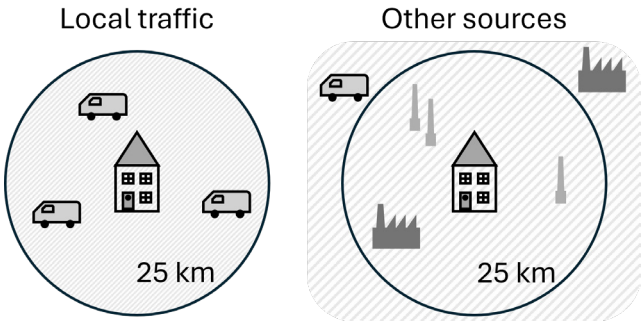
EXPOSURE ASSESSMENT

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.

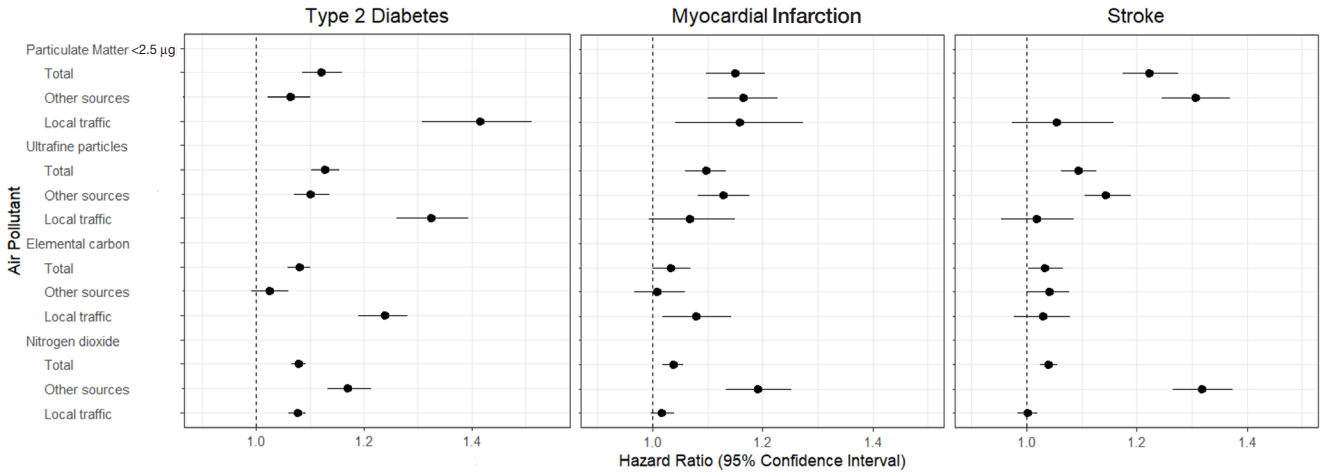
Overall, the investigators found that all four examined traffic-related air pollutants were associated with a higher risk of type 2 diabetes, MI, and stroke. Exposure to air pollution from local traffic sources was generally more strongly associated with a higher risk of type 2 diabetes compared to exposure 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



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.

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 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.

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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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