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RESEARCH REPORT

Birth Cohort Studies of Long-Term Exposure to Ambient Air Pollution in Early Life and Development of Asthma in Children and Adolescents from Denmark

Marie Pedersen, Shuo Liu, Zorana Jovanovic Andersen, Anne-Marie Nybo Andersen, Jørgen Brandt, Esben Budtz-Jørgensen, Klaus Bønnelykke, Lise Marie Frohn, Matthias Ketzel, Jibran Khan, Casper-Emil Tingskov Pedersen, Leslie Thomas Stayner, Jiawei Zhang, Bert Brunekreef, and Steffen Loft

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 and other publications, annual conferences, and presentations to legislative bodies and public agencies.

ABOUT THIS REPORT

Research Report 219, *Birth Cohort Studies of Long-Term Exposure to Ambient Air Pollution in Early Life and Development of Asthma in Children and Adolescents from Denmark,* presents a research project funded by the Health Effects Institute and conducted by Dr. Marie Pedersen, University of Copenhagen, Denmark, and her colleagues. This research was funded under HEI's Walter A. Rosenblith New Investigator Award Program, which provides support to promising scientists in the early stages of their careers. 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 Pedersen 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. This draft report is first examined by outside technical reviewers and a biostatistician. 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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HEI STATEMENT

Synopsis of Research Report 219

Air Pollution and Children's Asthma: Prenatal and Postnatal Assessment of an Array of Air Pollutants

BACKGROUND

Exposure to fine particulate matter and other air pollutants is associated with a myriad of health effects, including increased risk of asthma, a chronic disease that affects 262 million people worldwide and is the most common chronic disease in children. Asthma leads to reduced quality of life, emergency room visits, hospitalizations, and missed school and work days. It is also associated with high health care costs. Asthma prevalence among children and adolescents in high income countries has increased in recent decades. A better understanding of the risk factors that contribute to asthma and how they can be modified is needed. In particular, there is little information about the role of exposure to individual and combined air pollutants in relation to childhood asthma risk and on exposure windows during pregnancy and early childhood that are related to the development of asthma. Additionally, the biological mechanisms of the association between air pollution exposure and asthma are not well understood.

Dr. Pedersen at the University of Copenhagen and colleagues sought to investigate early-life air pollution exposures from multiple sources and in different exposure windows in relation to asthma, lung function, and various biomarkers of inflammation using data from four longitudinal birth cohort studies in Denmark. The team proposed to investigate exposures to an array of air pollutants, including the criteria pollutants — particulate matter, ozone, sulfur dioxide, nitrogen dioxide — and combinations of those pollutants. This study was funded through HEI's Request for Applications 16-1: Walter A. Rosenblith New Investigator Award.

APPROACH

Pedersen and colleagues linked different data sources to create a nationwide cohort and additionally used three existing population-based cohort studies of children born in Denmark between 1998 and 2016 to investigate associations between exposure to ambient air pollution and childhood asthma. They included one large, nationwide administrative cohort of about one million children and three smaller cohorts with detailed individual information on covariates such as maternal smoking during pregnancy, maternal and paternal asthma, presence of indoor sources of air pollutants, and socioeconomic status. The incorporation of smaller and larger cohorts with varying levels of information leveraged the merits of both approaches.

The investigators assessed four outcomes related to childhood asthma: (1) risk of developing asthma based on doctor diagnosis and medical records (asthma incidence), (2) total proportion of children with asthma based on parental-reported asthma and asthma-related symptoms at age seven (asthma prevalence), (3) biomarkers of inflammation that are suspected to be in the biological pathway for asthma development, DNA methylation, and gene expression, and (4) lung function in children at age six by assessing airway obstruction, which is one of the main tests for diagnosing asthma.

The investigators used a sophisticated chemical transport model system that integrates three separate models to estimate regional, urban, and street level ambient air pollution concentrations. Concentrations of

What This Study Adds

- This study investigated children's asthma in four Danish cohorts and focused on exposure to an array of air pollutants, including fine particulate matter, ozone, sulfur dioxide, nitrogen dioxide, and combinations of those pollutants.
- Air pollutant exposures were generally associated with increased risk of developing childhood asthma but were less consistently associated with asthma-related immune mediators and with lung function.
- The study found that both prenatal and postnatal periods are important windows of exposure for asthma development.
- The study underscores the importance of health outcome assessment methods in better understanding asthma risk factors and prevalence.

This Statement, prepared by the Health Effects Institute, summarizes a research project funded by HEI and conducted by Dr. Marie Pedersen at the University of Copenhagen, Denmark, and colleagues. Research Report 219 contains both the detailed Investigators' Report and a Commentary on the study prepared by the Institute's Review Committee.

13 pollutants were estimated, including particulate matter and nitrogen dioxide. They estimated prenatal and postnatal mean exposures during pregnancy and the first year of life for each residential address, while accounting for residential mobility. Additionally, they estimated mean long-term exposure from birth to the age of follow up for analyses that investigated asthma prevalence at age 7 and lung function at age 6.

Pedersen and colleagues used various statistical models to estimate associations between ambient air pollution exposure and the four asthma outcomes. Additionally, they performed analyses using two-pollutant models with fine particulate matter and nitrogen dioxide for asthma incidence and lung function. They adjusted for many individual and area-level covariates and assessed robustness of the associations of air pollution and asthma incidence using various sensitivity analyses.

KEY RESULTS

In the nationwide cohort, 6.1% of about one million children born between 1998 and 2016 were diagnosed with asthma over the course of the study period (asthma incidence). Children in this study were exposed to average concentrations of 10.5 μg/m^3 for fine particulate matter and 17.5 μg/m^3 for nitrogen dioxide during the prenatal period. For most air pollutants, prenatal exposures were moderately to highly correlated with postnatal exposures.

Prenatal exposure to all air pollutants except for ozone and sea salt and postnatal exposure to most air pollutants except for ozone, nitrate, and sea salt were associated with increased risk of developing asthma (**Statement Figure**).

Associations for postnatal exposures were consistent after adjustment for prenatal exposures. In two-pollutant models, Pedersen and colleagues observed that prenatal exposure to fine particulate matter was more consistently associated with asthma incidence than was prenatal exposure to nitrogen dioxide.

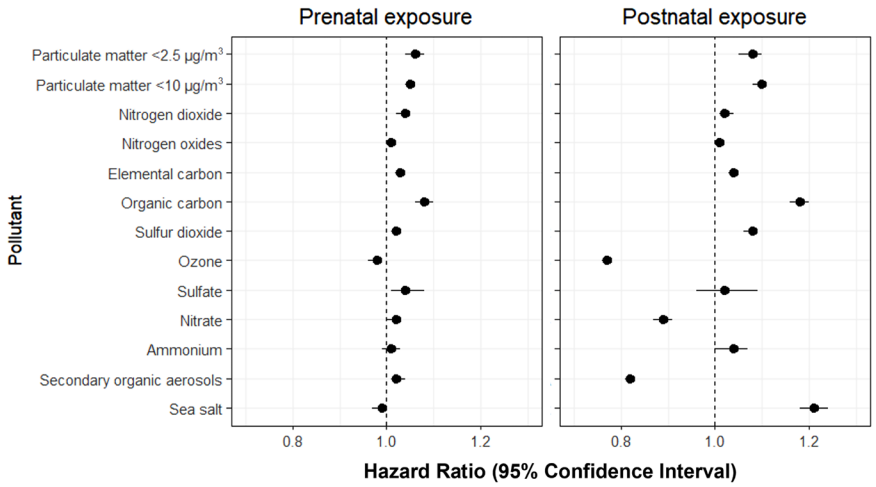
In the smaller cohorts, 4.4% of children had asthma at age 7 (asthma prevalence). Additionally in the smaller cohorts, prenatal and postnatal exposures to some air pollutants were associated with reduced lung function at age 6. For example, a 2%–3% reduction in lung function was associated with prenatal exposure to fine particulate matter and ammonium. Additionally, prenatal exposures to particulate matter and nitrogen dioxide were associated with altered profiles of biomarkers of immune mediators, but not with DNA methylation or gene expression. These altered profiles included biomarkers related to asthma, anti-inflammatory immune responses, and pro-inflammatory immune responses, presenting a unique immune signature.

INTERPRETATION AND CONCLUSIONS

This study represents an important contribution to our knowledge about exposure to ambient air pollutants in relation to childhood asthma and immune mediators. The study's findings suggest that both prenatal and postnatal ambient air pollution exposures affect asthma development. These findings were observed at fine particulate matter and nitrogen dioxide levels below the current (25 and 40 μg/m^3) and even the proposed (10 and 20 μg/m^3) annual European Union air quality standards. Additionally, the study found that asthma outcome assessment methods are critical in better understanding asthma risk factors and prevalence.

The study observed less consistent results for associations of air pollution exposures with asthma-related immune mediators and with lung function. However, the report presents an important step toward the better understanding of air pollution exposure in relation to asthma development, including specific risk factors and critical windows of exposure.

Continued development of two-pollutant and multipollutant models would further advance our understanding of asthma risk and development. Ultimately, this study has documented that prenatal and postnatal exposures to ambient air pollutants, such as particulate matter and nitrogen dioxide, are associated with increased risk of childhood asthma in Denmark.



Statement Figure. Associations between prenatal and postnatal exposure to ambient air pollutants and risk of asthma development among children in the Danish Nationwide Cohort.

INVESTIGATORS' REPORT

Birth Cohort Studies of Long-Term Exposure to Ambient Air Pollution in Early Life and Development of Asthma in Children and Adolescents from Denmark

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ABSTRACT

Introduction Exposure to ambient air pollution from combustion-source emissions contributes to the prevalence of asthma, but the role of early-life exposure in asthma development is not well understood. The objective was to examine the effects of early-life exposure to multiple specific ambient air pollutants on incidence and prevalence of asthma and to determine the mechanistic basis for these effects.

Methods The study included all live-born singletons in Denmark during 1998–2016 (N = 1,060,154), participants in the Danish National Birth Cohort (DNBC*, N = 22,084), and participants in the Copenhagen Prospective Studies on Asthma in Childhood (COPSAC, N = 803). We modeled the concentrations of particulate matter ≤2.5 and ≤10 µm in aerodynamic diameter ($PM_{2.5}$ and PM_{10}), PM-related elemental carbon (EC), organic carbon (OC), sulfate (SO_4^{2-}), nitrate (NO_3^-), ammonium (NH_4^+), secondary organic aerosols (SOA), and sea salt as well as nitrogen dioxide (NO_2), nitrogen oxides (NO_x), sulfur dioxide (SO_2), and ozone (O_3) — from all sources. Prenatal and postnatal time-weighted mean exposures were calculated for all residential addresses.

We defined *asthma incidence* as the first registered asthma diagnosis for all and used parental recall at child age 7 to determine the *prevalence* of doctor-diagnosed *asthma ever* and *active asthma* for the DNBC participants. For the COPSAC participants, we analyzed inflammatory markers in blood collected at 6 months of age; at 6 years of age we analyzed nasal epithelial deoxyribonucleic acid (DNA) methylation, gene expression, immune mediators, and forced expiratory volume in 1 second (FEV_1).

Cox proportional hazard models were fitted with fixed prenatal means and time-varying running annual means of a year before the event for the postnatal follow-up period for asthma incidence. Logistic regression models with cluster-robust standard errors and generalized estimating equations for dependence between women being included more than once were used for asthma prevalence. Mixed-effect linear regression models with random intercept for cohort were used to examine changes in lung function, and linear regression models were used to examine changes in biomarkers.

Results The prenatal mean and interquartile range (IQR) concentrations of $PM_{2.5}$ and NO_2 were 10.5 (2.4) and 17.5 (8.7) µg/m^3. In the nationwide study the risk of asthma incidence increased with increasing prenatal exposure to all pollutants except for O_3 and sea salt. An IQR increase in prenatal exposure was associated with an adjusted hazard ratio (HR) and 95% confidence interval (CI) of 1.06 (95% CI: 1.04–1.08) for $PM_{2.5}$ and 1.04 (1.02–1.05) for NO_2. The corresponding estimates for postnatal exposures were 1.08 (1.05–1.10) and 1.02 (1.01–1.04), respectively.

In the DNBC participants, the asthma incidence results from models further adjusted with cohort-specific covariates were similar to models adjusted for register-based covariates only. Prenatal exposure to $PM_{2.5}$, PM_{10}, NO_2, NO_x, EC, SO_4^{2-}, and sea salt were weakly associated with elevated risk for asthma incidence. There was no evidence of associations with asthma prevalence.

For the COPSAC children, an IQR of $PM_{2.5}$ and of NH_4^+ was each associated with a 2%–3% (95% CI: 1%–5%) reduction in mean FEV_1, consistently for prenatal and postnatal exposures. Prenatal exposure to PM and NO_2 was associated with immunological changes in blood and the airways but not with DNA methylation or gene expression changes.

This Investigators' Report is one part of Health Effects Institute Research Report 219, 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. Marie Pedersen, University of Copenhagen, Department of Public Health, Section of Epidemiology, Nørregade 10, 1172 København, Denmark; email: *mp@sund.ku.dk*. No potential conflict of interest was reported by the authors.

This report summarizes the research conducted as per the HEI Research Agreement, Walter A. Rosenblith New Investigator Award, No. 4957-RFA16-1/17-3. The contents of this document have not been reviewed by private party institutions, including those that support the Health Effects Institute; therefore, it may not reflect the views or policies of these parties, and no endorsement by them should be inferred.

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

Conclusions The results of these studies strengthen the evidence that long-term exposure to ambient air pollution contributes to the development of asthma in early life through an altered immune profile, even at these relatively low concentrations.

INTRODUCTION

Asthma is the most common chronic disease in children; it affected 262 million individuals worldwide in 2019 (GBD 2019 Diseases and Injuries Collaborators 2020). A large variation in the global prevalence of asthma has been reported in the International Study of Asthma and Allergies in Childhood (ISAAC) (Asher et al. 2021). Recent decades have witnessed an approximate doubling of the prevalence of asthma in children and adolescents in developed countries (Eder et al. 2006), which cannot be solely explained by changes in diagnosis or in genes, thereby suggesting an important role of environmental exposures in disease development. Asthma severity ranges from intermittent to severe life-threatening disease. Asthma leads to reduced life quality, emergency room visits, hospitalizations, and missed school or work days, and the health care costs are high (Bosquet 2007). Asthma has a complex multifactorial etiology, which is not fully understood. Many factors that start during prenatal development and growth may be involved and interact with each other (Beasley et al. 2015; Korten et al. 2017; Peat and Mellis 2002). Asthma is largely a developmental disease (Sly and Holt 2011) and most childhood asthma cases begin during the first six years of life (Yunginger et al. 1992). Children with asthma have an increased risk of developing chronic obstructive pulmonary disease (COPD) in adulthood (Hayden et al. 2018), and many adults with asthma have a childhood-onset disease that has persisted into adulthood (Trivedi and Denton 2019). Thus, better knowledge of modifiable risk factors of early life is needed to prevent asthma.

Exposure during early life may be more critical than exposure occurring later in life. Epidemiological studies of early-life exposure to air pollution are important for the identification of harmful exposure, because these studies can identify opportunities for lifelong disease prevention. Starting prevention in early life is a particularly efficient approach for improving human health and quality of life (Godfrey et al. 2010).

The effect of exposure in early life differs from exposure during later life. During pregnancy, which in humans averages 266 days counted from the day of fertilization, the fetus develops and grows from a single cell to a complex living being. Throughout prenatal development the cell proliferation, differentiation, and mitigation are more complex and intense than later in life (Blackburn 2007). Development of the airways starts in the embryonic period at 3–7 weeks of gestation, passing through several distinct stages of maturation and growth (Pinkerton and Joad 2000). Lung structures and cells are differentiated so that extrauterine life can be supported from around 24 weeks of gestation; however, alveolarization and growth continues until adolescence or even early adulthood. Approximately 80% of alveoli in the adult lung arise postnatally. Children of all ages are still developing; increased vulnerability of exposure toward environmental toxicants, such as those in the air during early life, has been suggested to be related to the intensive development and growth, unique routes of exposure, different levels of exposure, immaturity of the respiratory system, metabolism, endocrine, cell damage repair mechanisms, and immunological systems (Scheuplein et al. 2002). Hence, both prenatal and postnatal exposure in early life are recognized as critical windows of exposure with heightened vulnerability, but our understanding of critical specific time windows for exposure effects, for example, the timing of lung development in utero and of immune system differentiation in early life, is still limited.

Children may experience higher exposures to air pollution than do adults, as they inhale more air per kilogram of body mass. They may also spend more time outside, where concentrations of combustion-generated air pollution are generally higher; be more physically active; and be closer to the sources of ambient air pollution (Bateson and Schwartz 2008). Nasal breathing in adults reduces some exposure to larger fractions of PM, but children typically breathe through the mouth, which suggests that the composition of the exposure mixture at the alveolar level in children may differ from that of adults. The higher ventilation rates and mouth breathing may pull air pollutants deeper into children's lungs, thereby making clearance slower and more difficult. Children also have immature immune systems, which plays a significant role in asthma (Sly and Holt 2011). The observed consequences of early-life exposure to air pollutants, such as NO_2 and $PM_{2.5}$, in ambient air include diminished lung function and increased susceptibility to acute respiratory illness and asthma. Those exposures can deliver higher doses of varying composition that may remain in the lung for a longer duration as compared with adults. The undeveloped lung is more vulnerable to assault and less able to fully repair itself when injury disrupts morphogenesis (Bateson and Schwartz 2008). Finally, exposure during fetal and early-life development and growth may contribute not only to adverse effects with onset in early life, but also to irreversible effects that persist throughout life or that predispose children to adverse health and lower quality of life later in life (Barker 2004). Growing experimental and epidemiological evidence supports the developmental origin of health and disease, which links early-life environmental exposure, such as ambient air pollution, to adverse prenatal development of metabolic, cardiovascular, and respiratory morbidity in children and adults (Garcia et al. 2021; Gheissari et al. 2022; Grandjean et al. 2008). For these reasons, studies of health effects of exposure to air pollution in early life are very important and can provide new knowledge needed for cost-effective preventive actions.

There is also growing experimental and epidemiological evidence that exposure to ambient air pollution from combustion, such as motor vehicle emissions, not only exacerbates existing asthma (Orellano et al. 2017), but also contributes to

the development of asthma in children, although substantial inconsistencies exist among studies (as reviewed by Bettiol et al. 2021; Bowatte et al. 2015; Bråbäck and Forsberg 2009; Gasana et al. 2012; Han et al. 2021; HEI 2010, 2022; Khreis et al. 2017). Most recently, a comprehensive systematic review and meta-analyses has been made by an expert Panel appointed by HEI to systematically evaluate the epidemiological evidence regarding the associations between long-term exposure to traffic-related air pollution (TRAP) and selected adverse health outcomes, including respiratory outcomes in children (HEI 2022). The HEI Panel included 118 epidemiological studies with respiratory outcomes assessed in children, 80 of which considered at least one air pollutant and 38 included indirect measures of traffic exposures in the review. The Panel concluded that the certainty of the evidence for an association between TRAP exposure and respiratory outcomes in children was moderate to high (HEI 2022). The respiratory outcomes evaluated in children included asthma onset (incidence), asthma ever (asthma prevalence at any point in time), active asthma (asthma prevalence of ongoing symptoms), exacerbation of asthma symptoms, prevalence of wheeze (a symptom of asthma), as well as the incidence of acute lower respiratory infections. Different pollutants, traffic-exposure indicators, and exposure periods have been studied in relation to respiratory outcomes in children.

Out of the reviewed studies, 12 studies that evaluated associations between long-term perinatal exposure to NO_2 and asthma onset in children were included in a meta-analysis (HEI 2022). The pooled effect estimate of the meta-analyses was 1.05 (95% CI: 0.99–1.12) per 10-μg/m^3 increase. For NO_2 and prevalence of asthma in childhood, a total of 21 and 12 studies on asthma ever and active asthma, respectively, were included in the main meta-analyses resulting in pooled effect estimates of 1.09 (1.01–1.18) and 1.12 (1.02–1.23) per 10-μg/m^3 increase, respectively. For perinatal exposure to $PM_{2.5}$, a total of five studies on asthma onset and three on asthma ever were included in a meta-analysis. The pooled effect estimates were 1.33 (0.90–1.98) and 1.23 (0.58–2.87) per 5-μg/m^3 increase, respectively. Although most of the effect estimates from the individual studies included in these meta-analyses were elevated, these were often not statistically significant; a few studies reported inverse associations resulting in significant heterogeneity.

The observed heterogeneity among the studies on TRAP and asthma in children may be partly explained by differences in exposure assessment and other methodological differences, such as the asthma definition used, age at follow up, adjustment for potential confounders, differences in the air quality of the study areas, and differences among the study populations.

Most of the existing evidence comes from well-characterized North American and European studies of urban TRAP-exposed populations with advanced exposure assessment of individual pollutants (HEI 2022), but there is supportive evidence from studies based on proxies of TRAP and studies from various locations. For example, higher exposure to self-reported truck traffic on the street of residence has been associated with increased reports of wheeze in children of 13–14 and 6–7 years of age in a large study with children from different areas of the world (Brunekreef et al. 2009). Most of the previous studies on TRAP and child asthma were based on children participating in birth cohort studies that relied on parental recall of child asthma and asthma-related outcomes (HEI 2022). Fewer studies are based on administrative cohorts. Such data are only available from areas with medical records of asthma diagnosis or prescribed asthma medicine. Since there is no gold standard of asthma and because asthma can be difficult to diagnose in children, especially in the first three years, the definition and diagnosis of asthma are subject to controversy (Moral et al. 2019). Asthma definitions vary widely among studies that evaluate the associations between exposure to air pollution and asthma in children.

Studies on various parameters of lung function that are measured with spirometry provide evidence for adverse effects of long-term exposure to ambient air pollution on lung function in children from Europe and elsewhere; although the reduction is small, and most evidence originates from studies of children living in urban areas. Diversity among the study designs limits the comparability of the studies on long-term exposure to air pollution and reduced lung function in children (Garcia et al. 2021; Götschi et al. 2008; Schultz et al. 2017). The heterogeneity of these study findings might also be partly explained by unmeasured confounding, misclassification of exposures, the use of different lung function measures, assessment at different stages of lung development in early life, and differences in the composition of air pollution and study populations.

TRAP is most commonly studied, as motorized road vehicles are a main source of ambient air pollution in urban areas worldwide, but multiple additional sources — including human and natural sources — contribute to ambient air pollution (e.g., power production, industries, residential wood burning, agriculture, and shipping). In Denmark and Europe, emissions from motorized road vehicles contribute to approximately 20% of the background concentrations of NO_2 and $PM_{2.5}$ when all emissions are considered (Brandt et al. 2013). Road traffic, biomass burning, ships, and industrial and agricultural activities contribute to both local and regional background levels. For Copenhagen, the capital and most populous city of Denmark, local sources contribute to approximately 24% and 8% of the background concentration of NO_2 and $PM_{2.5}$, respectively (Jensen et al. 2020). In areas with heavy traffic, the contribution from motorized road vehicles can be as high as 80% of NO_2 and NO_x. Sources outside Copenhagen, including those in other countries, contribute the most to the background concentrations. For the urban background concentration of NO_2 in Copenhagen the major sources are road traffic and power plant emissions, but all other combustion processes also contribute. For the urban background concentration of $PM_{2.5}$ in Copenhagen, wood burning for household heating is the dominating local source

after motorized road vehicles. Many of the human activities that contribute to emissions of ambient air pollution with NO_2, NO_x, SO_2, $PM_{2.5}$, and PM_{10} in high-income countries — including energy production, transport and industry — have decreased over the last years. However, it is of concern that air pollution with PM from biomass burning is increasing in many areas of the world; for instance, it has been reported that the increase in biomass use from 2005 to 2017 has contributed to an increase of 13% and 8% in European Union-wide emissions of $PM_{2.5}$ and PM_{10}, respectively (European Environment Agency 2019).

Although the majority of children are born and continue to live in urban areas, where air pollution concentrations are in general the highest, children from nonurban areas are also exposed. It has been estimated that 99% of the world's population lives in places where air pollution concentrations exceed the guideline limits recommended by the World Health Organization (WHO 2021).

Most of the previous studies have assigned exposure to the maternal home address at birth and have not taken into account residential changes in early life. The associations with air pollutants have most often been evaluated only in single-exposure models, while results of two-pollutant models and the shape of the exposure–response relationship have less commonly been reported.

Multiple combinations of risk factors, including a wide range of inhalable airborne gases and particles, may lead to asthma and symptoms of asthma (Bowatte et al. 2015; Bråbäck and Forsberg 2009; Han et al. 2021; HEI 2010, 2022; Khreis et al. 2017). Indoor sources of air pollutants may also be associated with the location of the home and thereby with exposure to ambient air pollution (e.g., smoking, home and neighborhood characteristics, and other individual factors associated with respiratory health such as mold, dampness, pets, gas and wood stoves, socioeconomic status [SES] and breastfeeding) (Beasley et al. 2015). Thus, the potential for confounding the air pollution effects on asthma is high.

The current project was motivated by uncertainty of the role long-term exposure to ambient air pollution from multiple sources in early life plays in the asthma epidemic. We addressed this issue using several large longitudinal birth cohort studies of children and adolescents in Denmark. We assessed early-life exposure to ambient air pollution from multiple sources, asthma and asthma-related outcomes, and risk factors that were measured at individual levels by the best available methods.

In the first stage of the project, we prepared data from registries and cohorts, we modeled the air pollution exposure concentrations at the individual home residences, and then post-processed the air pollution data so we could link all the data. In the second stage, we initiated the epidemiological studies on asthma, lung function, and asthma-related biomarkers. Several studies are still ongoing, and some of the planned epidemiological analyses have not yet started. The project began January 1, 2018 and ended June 30, 2022.

OBJECTIVES

The main hypothesis was that long-term exposure to multiple specific ambient air pollutants in early life increases the risk of asthma development in children and adolescents. We assessed the associations in well-characterized cohorts from Denmark using different definitions of asthma in single- and two-pollutant models for time-weighted mean concentrations during prenatal and postnatal time periods, fitted separately and jointly. We did not evaluate multiple-pollutant models nor effect modification between the various pollutant exposures on asthma in the first studies. We are reporting multiple-pollutant effects on asthma incidence including effects of explorative analysis without a priori hypotheses testing interactions among multiple specific air pollutants in an ongoing study. We assessed the shape of the exposure–response functions and the effect estimates in models with increasing degrees of adjustment for potential confounders.

In addition, we aimed to determine the mechanistic basis for these effects by studying changes in lung function as well as in nasal epithelial DNA methylation, gene expression, immune mediators, and systemic inflammation measured in children.

The specific aims were to examine associations between prenatal and postnatal exposure to ambient air pollution components and

- Incidence of asthma in a nationwide cohort of all live-born singletons born in Denmark between 1998 and 2016
- Incidence and prevalence of asthma at age 7 in the children of the DNBC
- Lung function at age 6 in the children of the $COPSAC_{2000}$ and $COPSAC_{2010}$
- Asthma prevalence and asthma-related biomarkers measured from birth to age 6 in blood and nasal epithelial cells of the $COPSAC_{2010}$ children.

The project evaluated associations for multiple main pollutants from all sources: $PM_{2.5}$, PM_{10}, PM-related components; EC, OC, NO_3^-, NH_4^+, SO_4^{2-}, SOA, and sea salt, as well as gases; NO_2, NO_x, SO_2, and O_3. To minimize multiple testing, the COPSAC biomarker study focused on $PM_{2.5}$, PM_{10}, and NO_2.

METHODS AND STUDY DESIGN

STUDY DESIGN

We evaluated the associations between early-life exposure and ambient air pollution and between asthma and asthma-related outcomes by performing prospective cohort studies based on a large nationwide study population and two smaller-sized study populations of participants of longitudinal birth cohorts using data from Denmark (**Figure 1**).

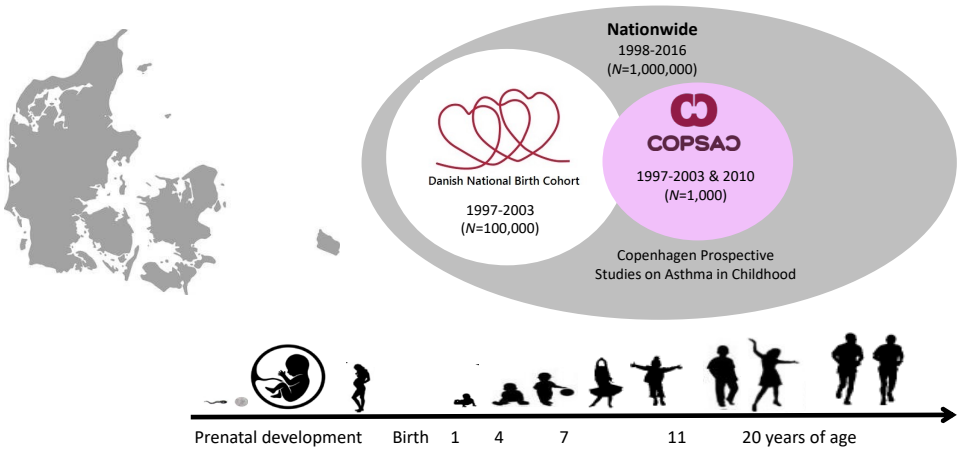

Figure 1. Study design.

We obtained data on home address(es), asthma, and smoking, as well as other personal, home, and neighborhood characteristics from national registries for the nationwide register-based study at the individual level from the women giving birth in Denmark during 1998–2016 and their live-born singletons from birth to end of follow up in 2017. The children were 0–19 years old.

We estimated long-term exposure at individual levels using the best available modeling methods for all addresses (Figure 1). Next, we linked this data with more comprehensive data obtained from cohort-specific data collections through interviews, questionnaires, clinical examinations, and biomarker measurements as part of the DNBC and COPSAC cohorts, which include children born in the same period as the nationwide cohort.

The incorporation of both the very large nationwide cohort with limited individual covariate data and the two birth cohorts with detailed individual covariate and outcome information in one project gave us new insights into the merits of both approaches. **Table 1** summarizes the included study population in the different studies.

STUDY POPULATIONS

Nationwide Cohort

First we identified all singletons live-born in Denmark during 1998–2016, and we estimated prenatal exposure to air pollution for a total of 1,139,767 children from whom the complete maternal address history was available before birth. We excluded 79,613 (7.0%) children from the project because of missing information in the national registries on maternal smoking, education, and/or income, resulting in the inclusion of 1,060,154 children in the nationwide cohort. The nationwide register-based cohort contributed to asthma incidence analyses, and the findings have been published (Pedersen et al. 2023). This cohort was based on linkage between data obtained from national registries and air pollution data at the individual level. We restricted data to this period to ensure the highest quality of the ambient air pollution exposure assessment and because information on maternal tobacco smoking during pregnancy (yes/no) was available from the Danish medical birth registry for this period (Knudsen and Olsen 1998). We noted that the percentage of children with asthma was similar among the included and excluded population (6.1% vs. 6.0%) while the mean prenatal exposure to $PM_{2.5}$ was slightly lower among the included population as compared with the excluded population (10.5 vs. 10.8 μg/m^3, Pedersen et al. 2023).

This large register-based study has very strong statistical power and no bias related to selection or loss to follow up, but it lacked information on a few factors (e.g., breast-feeding, postnatal exposure to tobacco smoke and to mold or dampness in the home) that could potentially confound the findings. Next, in order to address these potential sources of biases, we performed similarly focused studies on asthma incidence and prevalence with a large subset of these live-born singletons from whom more detailed data were obtained as part of their participating in the DNBC (Olsen et al. 2001).

DNBC Cohort

All general practitioners in Denmark were invited to recruit pregnant women for participation in the DNBC. About 50% of the general practitioners participated, and 60% of the women invited agreed to participate. Enrollment occurred in gestational weeks 6 to 10 from 1996 to 2003, and computer-assisted telephone interviews with follow-up interviews started at about the 12th week of gestation. Women were ineligible if they did not speak sufficient Danish or if they did not intend to carry their pregnancy to term or to give birth in Denmark. For the first interview, 91,748 women participated, including more than 100,000 pregnancies, corresponding to 35% of all pregnancies in the study period. Comprehensive follow-up questionnaires about health, behavior, and lifestyle were mailed to the mothers when the children were 1.5 and 7 years old. Answers were available for 53,637 (57%) children at age 7 (Hansen et al. 2012). When the children reached 11, the parents and the children were invited to answer questionnaires online about the children's health and a wide range of home indoor characteristics; answers at the 11-year follow up are available for 55% of the invited children (Groot et al. 2022). Although attrition in the DNBC is associated

Table 1. Study Populations of Children Born in Denmark, 1998–2016

Study Population	Study Area	Years of Birth	Population Size	Inclusion/Exclusion Criteria	Outcomes
Nationwide Cohort Pedersen et al. 2023	Entire Denmark	1998–2016	1,060,154	Live-born singletons with exposure and data on maternal education, income, smoking, asthma, and parity	Asthma Incidence (ICD-10 codes)
DNBC Pedersen et al. 2022	Entire Denmark	1998–2003	22,084	Live-born singletons with exposure and data on the covariates listed above participating in the DNBC interview 1 and with info on breastfeeding, 7 years asthma and 11 years	Asthma incidence (ICD-10 codes) Asthma prevalence at age 7 (parental recall of doctor-diagnosed asthma)
$COPSAC_{2010}$ Tingskov Pedersen et al. 2023	Zealand	2008–2010	700	Live-born with exposure, the outcomes listed to the right and data on covariates	Cytokines in blood from 6 m of age Nasal epithelial DNA methylation and gene expression at age 6 Asthma prevalence at age 6 (parental recall and clinical judgement) Allergic sensitization prevalence at age 6 (skin prick test) Allergic rhinitis at age 6 (parental recall and clinical judgement)
$COPSAC_{2010}$ $COPSAC_{2000}$ Pedersen et al., unpublished data	Zealand and Greater Copenhagen	1998–2001 2008–2010	803	Live-born singletons with exposure, the outcomes listed to the right and data on covariates	Lung function at age 6 (forced expiratory volume in 1 second, FEV_1)

ICD = International Classification of Diseases.

with lower socioeconomic position, few effects of selection bias have been found for association studies in the DNBC (Nohr and Liew 2018). For instance, we previously reported effect estimates of maternal exposure to NO_2 during the first trimester for preeclampsia that were similar to those reported elsewhere (Pedersen et al. 2017b).

Like for the nationwide study population, we restricted the study population to live-born singletons for whom information was available on exposure to ambient air pollution, maternal smoking, and education and/or income. We further excluded children with incomplete information on a priori selected covariates, which were collected as part of the pregnancy and postnatal questionnaires, resulting in the inclusion of 22,084 children in the multivariate models with the most comprehensive adjustment in the DNBC study (Pedersen et al. 2022).

Finally, we restricted the study population to children who had the same home address from birth to age 11, for whom complete data on home environment had been obtained in sensitivity analyses. This resulted in a study population of 9,507 children.

The data used for the DNBC study in this project was based on linkage among data obtained from national registries, air pollution data, and cohort-specific data at the individual level.

The DNBC study population contributed to studies of the effects of ambient air pollution on asthma incidence and prevalence, as well as to a number of related studies conducted as part of collaborations with other research projects. These include ongoing studies on indoor environment and asthma (Keller et al. 2023), a completed study on indoor home

characteristics (Groot et al. 2022), and another one on pet ownership, asthma, and allergy (Pinot de Moira et al. 2022, 2023), which we conducted as part of a large European birth cohort collaboration (Pinot de Moira et al. 2021).

COPSAC Cohort

We also analyzed data from COPSAC in the studies on changes in asthma-related biomarkers (Tingskov Pedersen et al. 2023) and lung function (Pedersen et al., unpublished data). COPSAC is a prospective clinical pregnancy cohort that follows the respiratory health of children longitudinally, together with genotyping and a comprehensive assessment of the early-life exposome (Bisgaard et al. 2013). The first COPSAC cohort is a high-risk cohort of children of mothers with a history of asthma established around year 2000 ($COPSAC_{2000}$) (Bisgaard 2004). Pregnant women from the Greater Copenhagen area were recruited through the DNBC and the prenatal clinics during 1998–2001. Women fluent in Danish with a history of doctor-diagnosed asthma after the age of 7 years and a history of daily treatment with inhaled inhaled β_2 agonists or glucocorticoids (minimum of 2 weeks during two seasons or continuously for 1 year) were invited to participate in the $COPSAC_{2000}$ cohort (Bisgaard 2004). Women were excluded from the cohort if they failed to show up at the first prenatal visit or if the delivery occurred before 36 weeks of gestation. Children with major congenital malformation and a need for mechanical ventilation, or with a lower respiratory tract infection prior to enrollment were excluded. At one month of age, 411 children participated in the $COPSAC_{2000}$ cohort.

The second birth cohort ($COPSAC_{2010}$) aimed to replicate and explore the key findings of the $COPSAC_{2000}$ cohort in an unselected cohort of pregnant women with a home residence on Zealand, Denmark. They were recruited between 2008 and 2010 at the Gentofte and Naestved hospitals using the same standardized operating procedures, infrastructure, and skilled personnel as in $COPSAC_{2000}$ (Bisgaard et al. 2013, 2016; Chawes et al. 2016). Pregnant women were recruited through surveillance of pregnancy visits at their general practitioners. They received an invitation by mail to participate (Bisgaard et al. 2013). Exclusion criteria were gestational age above week 26 at the time of enrollment, a daily intake of more than 600 IU vitamin D during pregnancy, or having any endocrine, heart, or kidney disorders. A total of 736 pregnant women and 700 children were enrolled, and the participating families were monitored closely from gestational week 24. Randomized controlled trials of high-dose vitamin D and fish oil supplements were conducted during pregnancy, and a trial of azithromycin for acute lung symptoms was conducted in the children with early asthma symptoms. Apart from the maternal asthma status, the two COPSAC cohorts are quite similar, except for a remarkable reduction in maternal smoking (8% vs. 24%) and intake of alcohol during pregnancy (14% vs. 26%), as well as a higher level of education in the recent $COPSAC_{2010}$ cohort (28% vs. 13%) (Bisgaard et al. 2013). This cohort has been followed intensely with several scheduled and acute visits to the research unit, where the pediatricians were solely responsible for the diagnosis and treatment of respiratory, allergic, and skin-related symptoms (Bisgaard et al. 2013, 2016, Chawes et al. 2016).

The $COPSAC_{2010}$ cohort contributed to our study on established asthma-related biomarkers of inflammatory and immunological markers and novel biomarkers measured in blood and airway epithelial cells (Tingskov Pedersen et al. 2023).

We restricted the analyses to live-born children for whom information on air pollution and biomarkers was available ($n = 700$). Children were excluded because of missing outcome and covariate data or due to quality control issues, resulting in approximately 500 children. To maximize the power, we included three pairs of twins and allowed the number of children to vary slightly among the selected outcomes and combinations of outcomes considered in this mechanistic study.

For the studies on lung function measured at age 6 we pooled the data from both COPSAC cohorts available at this age (Pedersen et al., unpublished data). Like for the nationwide and the DNBC study population, we restricted this COPSAC study population to include live-born singletons with available information on exposure to ambient air pollution, maternal smoking, and education or income. We further excluded the children with incomplete information on sex-, age- or height-calibrated lung function measurement at age 6, or missing information on a priori selected covariates, which was collected as part of the pregnancy and postnatal questionnaires. This resulted in the inclusion of 803 children — 272 children from $COPSAC_{2000}$ and 531 children from $COPSAC_{2010}$.

Ethics and Data Safety

According to the Danish Act on Processing of Personal Data, register-based studies based on data from Danish registers do not require informed consent, involvement by the study population, or ethical approval by the Danish National Committee on Health Research Ethics. Personal data obtained from national registries may be processed without consent from the data subject where the processing takes place for the sole purpose of carrying out statistical or scientific studies of significant public importance, and where such processing is necessary to carry out these studies (Thygesen et al. 2011). Prior to initiation, permission for the access and use of the address data was obtained, and all studies were registered at the local Danish Data Protection Agency at the University of Copenhagen. All data linkage and statistical analyses were performed under the highest data safety procedure at secure servers provided by the Public Health Database provided by Statistic Denmark at the Department of Public Health, University of Copenhagen, with the exception of the biomarker study, which was performed at the secure servers at the COPSAC clinic at Gentofte Hospital.

We solely used data already obtained from the cohort participants. No further contact with the cohort members was needed. The cohort studies were conducted in accordance

with the Declaration of Helsinki. All birth cohort participants had provided written informed consent, and the cohort studies were approved by the relevant Danish Ethics Committees (Bisgaard et al. 2004, 2013, Olsen et al. 2001). For the COPSAC studies, both parents gave verbal and written informed consent for the participation of the children before enrollment.

Our rationale for choosing study populations living in Denmark in this specific time period relates to our unique opportunities to access and enrich existing data at very high quality to conduct environmental epidemiological research. We used the unique personal identification number system (Pedersen 2011), which permits tracking of the entire Danish population over time and accurate linkage of individual-level information across the many, valuable registers with information on the entire Danish population and society. In Denmark, it is also possible to obtain life-long, detailed information on individual health, family history of asthma, prescriptions of drug, SES, and complete residential history from our rich national registries at the individual levels (Kildemoes et al. 2011; Lynge et al. 2011; Pedersen 2011; Schmidt et al. 2015). Finally, we benefitted from accurate registration of residential buildings, wood stoves, and road traffic and from standardized ambient air monitoring and state-of-the-art air pollution modeling in Denmark. This made it possible to accurately assess individual lifelong exposure to air pollution for the entire Danish population at high temporal and spatial resolution for a very wide range of air pollutants starting from before birth.

In contrast to the United States, in Denmark the personal data protection laws allow register-based research without informed consent, and comprehensive health care data are available from the national registries. Importantly, access to health care is less affected by ethnic, racial, cultural, and/or socioeconomic differences in Denmark than in the United States, making confounding by these factors less likely. Furthermore, residential buildings are low, road traffic is well characterized, and the landscape is flat. Denmark has a long tradition of ambient air pollution monitoring and world-class modeling, which makes it possible to accurately assess individual exposure to a wide range of air pollutants from multiple sources — including often ignored sources such as wood burning — for the entire population many years back in time. Finally, in Denmark linkage with extensive data from the DNBC (Olsen et al. 2001), which is one of the largest birth cohorts with almost 20 years of follow up, and the COPSAC birth cohort (Bisgaard et al. 2013) provided us these unique possibilities for addressing the current gaps in the epidemiological literature on the role of early-life exposure to ambient air pollution in the development of asthma. Furthermore, our studies add to the growing evidence of studies being conducted in areas with relatively low levels of air pollution exposure.

EXPOSURE ASSESSMENT

Detailed information on individual residential address(es) was collected from the Danish Civil Registration System (Pedersen 2011) for the mothers starting from a year prior to the delivery date of the index child and for the children from their date of birth until the latest day of follow up including: the street, house number, level of the floor if a multiple-level building, and location of the home if multiple at the same house number, postal code, city and zone for each address, the dates of moving, emigration, immigration, and death as well as population density (persons/km^2) within 1-km buffers of each address. For estimation of the air pollution exposure for each child, we constructed their full home address history with corresponding time periods for each address, and we geocoded these locations.

In Denmark all residential address records (both present and former addresses) of the whole population are stored in the central population registry of the Danish Civil Registration System (Pedersen 2011). All Danish addresses have a number code consisting of unique codes for municipality, street, and house number. We received these address codes records for each woman giving birth in this study period and for their children, including start and end dates for each address in the record. These records are free of errors as they are coming from a quality-controlled register; no spelling mistakes in street names or city names are possible. The number codes for each address are linked with the geographic coordinates (i.e., X and Y in the Universal Transverse Mercator coordinate projection) using the Danish Civil Registration System (Pedersen 2011). The whole geocoding process is therefore very precise (98% match) and is completely based on central well-maintained data. To minimize possible inaccuracies, we obtained information on all addresses during pregnancy for the women and during the entire early-life period for the offspring. We restricted the study population to those giving birth in Denmark and censored the study population in case of emigration outside Denmark or moving to a 'protected' address for which we did not have information on the municipality, street, and house number.

We modeled ambient air pollution concentrations of $PM_{2.5}$, PM_{10}, NO_2, NO_x, EC, OC, SO_2, O_3, SO_4^{2-}, NO_3^-, NH_4^+, SOA, and sea salt at each address and each time period on an hourly basis for the entire study population from the 1st of January 1997 to the 31st of December 2017 using the DEHM-UBM-AirGIS air pollution modeling system (*https://envs.au.dk/en/research-areas/air-pollution-emissions-and-effects/the-monitoring-program/air-pollution-models/airgis/about-airgis)* with the Operational Street Pollution Model (OSPM) (Brandt et al. 2001, 2012; Jensen et al. 2017; Hvidtfeldt et al. 2018; Khan et al. 2019). DEHM-UBM-AirGIS is an extensively validated air pollution modeling system that is based on detailed data and knowledge about emission sources, meteorology, chemical reactions in the atmosphere, atmospheric dispersion, and transformations (Hvidtfeldt et al. 2018; Ketzel et al. 2011, 2012; Khan et al. 2019). One key feature of the DEHM-UBM-AirGIS modeling system is that, unlike in land use regression (LUR) approaches, the modeling system is diagnostic. By solving the governing equations of the atmosphere, the physical fate of each pollutant can be determined. The models include detailed data and knowledge required to

capture a broad range of emission sources, the atmospheric dispersion, and physical and chemical transformation processes, all of which are fundamental to an accurate estimation of the concentration of ambient air pollution in street canyons and urban areas, including small and relatively homogeneous areas (**Figure 2**).

The DEHM-UBM-AirGIS system is state-of-the-art; for example, DEHM (Danish Eulerian hemispheric model) is part of the Copernicus Atmosphere Monitoring Service (CAMS) and performs similarly to the other CAMS2 40 models (*https://atmosphere.copernicus.eu/.).*The Danish emission inventory used in this modeling system is of exceptionally high quality; DEHM is based on some of the best available gridded emission databases and provides operational air pollution forecasts on a daily basis. The DEHM has been extensively validated and used in many studies (Brandt et al. 2012; Geels et al. 2021). Comparisons of trends of DEHM-estimated concentrations with measured concentrations in countries with a long time series of monitoring data like Denmark generally showed good agreement. The urban background model (UBM) local scale model has recently been evaluated with measurements for the continental Nordic countries for the 1990–2018 time period (Frohn et al. 2022).

The applied DEHM-UBM-AirGIS modeling system has been evaluated against long-term measurements from Danish monitoring stations and performs very well. For example, in Khan and colleagues (2019), the most recent AirGIS (a Geographical Information Systems-based air pollution and human exposure modeling system) development and performance was evaluated for ambient air pollution with $PM_{2.5}$, PM_{10}, NO_x, and NO_2 for many years. In terms of reproducing the temporal variation of observed air pollution levels, the validation correlations varied in the range, but correlations were high for the long-term exposure windows of relevance for our study (Hvidtfeldt et al. 2018; Ketzel et al. 2011; Khan et al. 2019). In terms of reproducing the temporal variation of observed air pollution levels, the validation correlations varied in the 0.45–0.96 range. Whereas, for reproducing spatial variation, the correlation was in the 0.32–0.92 range. Correlations of monthly modeled vs. measured concentrations at fixed-site monitoring stations and measuring campaigns in Copenhagen of NO_x, $PM_{2.5}$, and PM_{10} were in the 0.54–0.89 range (Hvidtfeldt et al. 2018; Ketzel et al. 2011). Briefly, Hvitfeldt and colleagues compared the modeled concentrations with measured concentrations of PM_{10} and $PM_{2.5}$ from two fixed-site monitoring stations (background and street) and from two measurement campaigns in Copenhagen, Denmark. Modeled concentrations of black carbon (BC) were also compared with measured $PM_{2.5}$ absorbance and PM_{10} absorbance. The model underestimated by 7%–13% in comparison with the fixed-site monitoring stations. High Pearson correlation coefficients of 0.82 were observed for monthly averages of measured and modeled $PM_{2.5}$ at the background site and, correspondingly, 0.85 at the street site. For PM_{10}, correlation coefficients of 0.70 were observed for monthly averages of measured and modeled PM_{10} at the background site and, correspondingly, 0.74 at the street site. The spatial variation, as evaluated from the two measurement campaigns, was also well reproduced. In summary, the results of the studies imply that the AirGIS modeling system performs well in regard to both spatial and temporal variation, with minor absolute differences between measured and modeled concentrations and high correlation coefficients. More relevant details of the DEHM-UBM-AirGIS system have been described by Khan and colleagues (2019). We used the same approach and data for the modeling of the above listed pollutants as for the Health Effects of Air Pollution Components, Noise and Socioeconomic Status project (Sørensen et al. 2022a,b).

The DEHM-UBM-AirGIS system is regularly being compared with available measurements. These ongoing routine validations ensure the high performance of the air pollution models; however, they are not published for every model run

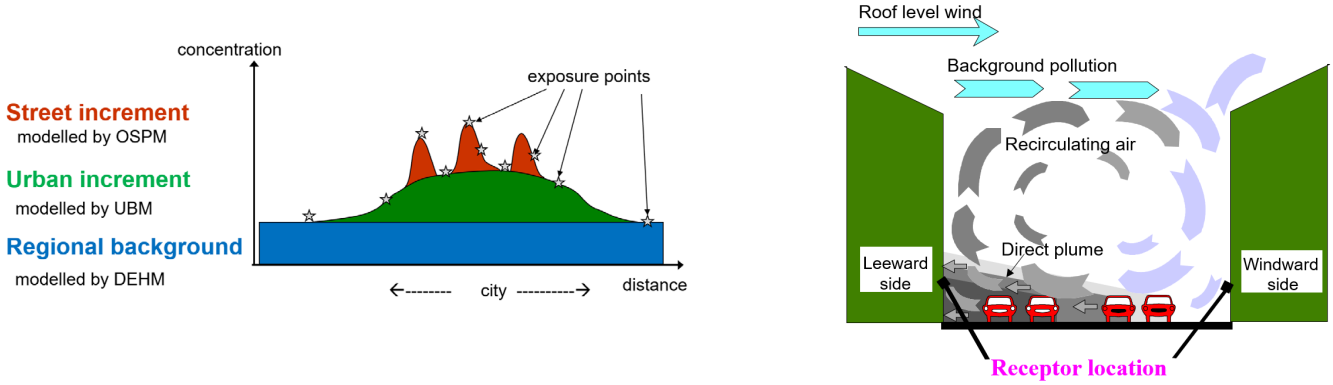

Figure 2. Ambient air pollution modeling. Spatial variation in the three air pollution levels considered by the Danish DEHM-UBM-AirGIS system (left). The direct street contributions (red on the left) from traffic hotspots were estimated at the exact address level with the OSPM (right). The urban background concentration (green on the left) is calculated by the UBM and the regional background by the DEHM (blue on the left). AirGIS = A geographical information systems-based air pollution and human exposure modeling system; DEHM = Danish Eulerian Hemispheric Model; OSPM = Operational Street Pollution Model; UBM = urban background model.

(but are part of the standard national monitoring reporting on an annual basis). We have examined the validation plots for the applied models for the selected pollutants and are convinced that our models reproduce both the spatial and temporal variation in the exposure of our study population well.

The correlation coefficients of model vs. measured comparisons depend on the pollutant, the number of available measurements, and the averaging time (year, month, week, day, hour); they often approach 0.9 and higher; see Appendix Table A1 (available on the HEI website).

As illustrated in Figure 2, we calculated the local contribution from traffic at the street level with the OSPM from street traffic data such as intensity, speed, and vehicle types and street and building geometry data at the exact address level (Jensen et al. 2017). The local contribution from sources of primary anthropogenic pollutants was calculated from a detailed emission database with a 1 km × 1 km spatial resolution using the UBM (Brandt et al. 2001; Frohn et al. 2022). Finally, the contribution from long-range transport and regional background due to nonlocal natural and anthropogenic sources was calculated using the DEHM with a 5.6 km × 5.6 km resolution (Brandt et al. 2012; Christensen 1997). The final pollution estimate (address-level) is produced by the spatial aggregation of these pollution levels. All three models are operated on an hourly basis, taking the variation in emissions and meteorology into account, and double counting of emissions is avoided. In case of low traffic flow (less than 500 vehicles per day) at the nearby streets, the local traffic contribution (modeled by OSPM) is omitted and only DEHM-UBM results are applied for exposure estimates. More details on the spatial resolution and the main sources of each pollutant are provided elsewhere (Pedersen et al. 2023).

Monthly mean concentrations were calculated as basis and later we post-processed into time-weighted monthly means for everyone for each address and time period, taking into account the exact number of days at each address for individuals with multiple addresses before transferring the air pollution exposure data to the secure servers provided by Statistic Denmark where the linkage and data analyses were made using unidentifiable identifiers.

Prenatal and postnatal time-weighted mean exposures were calculated taking all residential addresses into account. We defined prenatal exposure from the date of birth and the gestational age as recorded in the Danish Medical Birth registry (Knudsen and Olsen 1998).

OUTCOME DEFINITION

Asthma Incidence (Asthma Onset Based on ICD-Codes)

First, we evaluated asthma incidence from birth to end of follow up, defined as the first registered diagnosis according to the International Classification of Diseases (ICD), 10th revision; J45-J46 from hospital inpatient admission, emergency room, and outpatient visit records in the Danish National Patient Register (DNPR) (Lynge et al. 2011; Schmidt et al. 2015). For children with four or more years of follow up, we also defined asthma incidence after four years of age since the diagnosis is more certain at this age than at earlier ages (Moral et al. 2019). Since we were able to follow the children from birth to the end of follow up, asthma incidence reflects the onset of asthma. It is an important outcome for identification of modifiable risk factors that contribute to asthma development.

Asthma Prevalence (Asthma Ever and Active Asthma Based on Parental Recall)

Next, we evaluated additional measures of parental-reported asthma. Parental recall of asthma and asthma-related symptoms was obtained from questionnaires given when the child was 7 years old. The reports were used to define prevalence of asthma ever from birth to age 7 and current active asthma at 7 years of age, according to the definition developed during the Mechanisms of the Development of Allergy (MeDALL) collaboration (Pinart et al. 2014).

Asthma ever was defined as having a positive answer to the following question at age seven: *Has a doctor ever said that your child has asthma?* Asthma ever reflects the childhood prevalence of asthma from birth to the follow up around age 7.

Active asthma was defined as having a positive answer to at least two of the following questions at age seven: (1) *Has a doctor ever said that your child has asthma?* (2) *Has your child taken asthma medicine during the past 12 months?* (3) *Has your child had wheezing or whistling in the chest in the past 12 months?* Active asthma reflects the subset of children with asthma ever who have current asthma.

Immune Mediators, DNA Methylation, and Gene Expression

Nasal mucosal lining fluid samples were collected from the $COPSAC_{2010}$ children at age 4 weeks and analyzed for cytokines using a synthetic absorptive matrix (Chawes et al. 2010). Blood was collected from the children at 6 months of age and analyzed for inflammatory markers using immunoassays based on electrochemiluminescence (Chawes et al. 2015).

Detailed results of these analyses together with the results of analyses of changes in nasal epithelium DNA methylation and gene expression are reported by Tingskov Pedersen and colleagues (2023).

Lung Function

Lung function was measured in the $COPSAC_{2000\ \&\ 2010}$ children by spirometry in the child's sixth year of life using a pneumotachograph Masterscope Pneumoscreen, system 754,916 spirometer (Erich Jäeger, Würzburg, Germany) (Bisgaard et al. 2012). The measurements were performed by trained personnel according to the American Thoracic Society (ATS) guidelines (ATS 1995). The children were tested

sitting and wearing nose clips. The FEV_1 was calibrated by age, height, weight, and sex (Bisgaard et al. 2007). Children's body weight and height were measured during the medical examination by trained personnel using calibrated equipment. We also recorded the exact age of the child at the lung function measurement.

COVARIATES

For each analysis, we defined a priori which potential confounders to adjust for. We used a directed acyclic graph to guide the selection of covariates (Appendix Figure A1). Based on this graph, the minimum set of covariates that should be controlled for are those marked red. However, since some of the variables available may not have perfectly captured the underlying factors that we aimed to control, we tested different levels of adjustment and, as far as possible, tried to match those used in a similar study that had been conducted as part of the European Study of Air Pollution Effects (ESCAPE) (Gehring et al. 2015b).

We obtained information about the children's status of birth (singletons or not, live-born or not), date of birth, sex (boy, girl), gestational age calculated from last menstrual period, and the date of birth, taking into account ultrasonic scans from 2004 onward, birth order, and maternal smoking during pregnancy on an individual level from the Danish Medical Birth Registry (Knudsen and Olsen 1998). We used the status of the birth as well as the completeness of the data to define the study population. We restricted the analyses to complete cases to avoid differences in study population selection when comparing results of models with different degrees of adjustment. We used the date of birth to calculate the season of birth (four seasons). We obtained information on the maternal highest attained education from the Population Education Register (Jensen and Rasmussen 2011) and categorized it into low, middle, high. We used household equivalized disposable income (after taxation and interest per person, adjusted for number of household persons and divided into tertiles based on Danish background population) from the Income Statistics Register (Baadsgaard and Quitzau 2011). Income and education data from a year prior to the birth were used. We obtained parish codes corresponding to 2,158 geographically defined areas of differing size, in terms of land and water cover, from the Danish Geodata Agency. We linked these to parish-level proportion of inhabitants with low, middle, and high degrees of education and disposable income in 2001 from Statistic Denmark. We combined these indicators to adjust for residential area-level SES, which reflects area material deprivation, in sensitivity analyses.

Denmark is comprised of 98 municipalities, which are geographically defined areas of differing size in terms of land and water cover ranging from 8 to 1,470 km^2 as well as in terms of population size, which varied from 1,897 to 549,050 persons in 2012 (Wikipedia 2022), and population and land-use characteristics. We linked the home address of each child with the corresponding municipality. Municipality used as a confounder could account for variation across study areas as it is the unit of administration for schooling, primary care, and other public services in Denmark. The municipality approach was used in similar studies conducted in Sweden (Gruzieva et al. 2013; Olsson et al. 2021). We used municipality rather than zip code or parish, which are geographically smaller units, or region, which are much larger, as this would be very coarse with only five units in Denmark.

We obtained information about maternal asthma diagnosis from the DNPR (ICD-8 code 493; ICD-10 codes J45-J46) and about maternal asthma medicine prescriptions (a minimum of two) from the Danish National Prescription Register (Kildemoes et al. 2011).

From the DNBC participants we also obtained self-reported information on maternal and paternal asthma (yes, no), maternal smoking during pregnancy (yes, no) as well as maternal exposure to pets with fur or feathers during pregnancy (yes, no) from the telephone interviews conducted at approximately 16- and 31-weeks of gestation. We obtained information of the home size at birth from the Danish building and residential registry through Statistic Denmark and categorized these according to the median size ($< P50$, $\geq P50$ m^2). Information on breast feeding (yes, no) and daycare attendance of the child (yes, no) was obtained from the questionnaires administrated approximately 6 and 18 months after birth. Finally, information on the presence of visible mold and dampness in the home (yes, no), child exposure to environmental tobacco smoke (ETS) in the home (yes, no), presence of gas stove for cooking (yes, no), presence of wood stove in the home (yes, no), as well as burning of candle lights during winter and summer ($<$ once a week, $\geq$ once a week) was retrieved from the parental questionnaire at follow up around 11 years age of the child. We used the exact age of the child at the 7 years of age follow up for calculation of the postnatal exposure means.

From the COPSAC participants we also retrieved information on self-reported maternal smoking during pregnancy (yes, no), maternal exposure to ETS during pregnancy (yes, no), child exposure to ETS in the first six years of life (yes, no), duration of breastfeeding (months), child exposure to furry animals during first six years of life (yes, no) and presence of fireplace, gas stove, and fume hood in the home of the child during the first year of life (yes, no).

We checked and cleaned the data for errors by descriptive statistical analyses such as distribution patterns and correlations between pollutants. We examined the effects of maternal education on the asthma outcomes.

STATISTICAL METHODS AND DATA ANALYSIS

For the studies on asthma incidence, we followed each child from date of birth until: asthma diagnosis, end of the follow-up period on December 31, 2017, or the date of moving to an unknown address, emigration, or death during

the follow-up period, whichever came first. We analyzed the associations between air pollution exposure and asthma incidence using Cox Proportional Hazard models with age as the timescale.

To analyze the associations between air pollution and asthma prevalence in the DNBC we used logistic regression models with cluster-robust standard errors and generalized estimating equations for dependence between women being included more than once. We used this approach instead of, for example, restriction to the first child participating in DNBC and excluding those with participating siblings as well, to avoid further exclusions.

Associations between ambient air pollution and lung function were examined in mixed-effect linear regression models with random intercept for cohort, as we included children being enrolled in the two different cohorts of COPSAC. The lung function parameter was log-transformed, and the relative differences (RD) were calculated from estimated regression coefficients (β) as e^(β × IQR).

Immune mediators were normalized according to the total sum per sample to account for high collinearity between immune mediators with samples, log-transformed and z-scored. Associations between ambient air pollution and immunological and inflammatory markers were evaluated using linear regression models. To minimize the number of analyses we restricted these analyses to $PM_{2.5}$, PM_{10}, and NO_2.

We modeled time-weighted mean concentrations of each air pollutant in models of increasing levels of adjustment. We reported results of models with increasing levels of adjustment for interpretation of potential confounding patterns and for comparison with previous studies that do not always have the ability to control for all the covariates. For asthma incidence and prevalence, model 1 was adjusted for age (months), sex, and birth year to account for time-trends in exposure and asthma.

Model 2 was further adjusted for household income (continuous scale), maternal education (three categories), and parity (continuous scale). Model 3 was further adjusted for season of birth (four categories) and maternal smoking during pregnancy (yes/no). Model 4, which we consider the main model, was also adjusted for municipality (strata) — corresponding to 98 geographically defined areas — to account for variation across study areas. The adjustment for municipality captures area-level differences in potential asthma determinants, such as primary care or schooling, not explained by the variables already in the model.

For the DNBC study population, we could further adjust model 5 for maternal and paternal asthma (no, yes), pets during pregnancy (no, yes), house size at birth, breastfeeding (no, yes), daycare (no, yes), mold (no, yes), dampness (no, yes), postnatal exposure to ETS (no, yes), presence of gas stove (no, yes), presence of wood stove (no, yes), and candlelight burning in the home (no, yes).

For lung function, model 1 was adjusted for age (continuous scale), sex (binary), height (continuous scale), weight (continuous scale), and cohort (random intercept). Model 2 was also adjusted for maternal income (low, middle, high), education (low, middle, high), maternal smoking during pregnancy (no, yes), maternal exposure to ETS during pregnancy (no, yes), and for child exposure to ETS during the first six years of life (no, yes) and duration of breastfeeding (continuous scale). Model 3 was further adjusted for exposure to furry animals during the first six years of life (no, yes), and presence of fireplace (no, yes), gas stove (no, yes), and fume hood (no, yes) during the first year of life.

Results are presented as HR, odds ratios (OR), or percentage change and 95% CI for a fixed exposure increment, entering air pollution exposure as continuous variables without transformation. We used an IQR increase for each air pollutant to facilitate comparison of estimates among pollutants for asthma incidence and lung function analyses. For asthma prevalence we used the increments that were used in the ESCAPE collaboration to ease comparison with the previous studies on asthma prevalence (Fuertes et al. 2020; Gehring et al. 2015b; Mölter et al. 2015) and recurrent wheeze and asthma (Holst et al. 2020): 5-μg/m^3 for $PM_{2.5}$, SO_4^{2-}, and NO_3^-; 10-μg/m^3 for PM_{10}, NO_2, and O_3; 20-μg/m^3 for NO_x, and 1 unit for the remaining pollutants.

For all outcomes we modeled prenatal exposure using fixed exposure increments from conception to the date of birth. For asthma incidence we used time-varying 12-month running means for postnatal exposure without and with adjustment for prenatal exposure. All other associations with exposure during different windows were evaluated in separate models.

For asthma prevalence we modeled time-weighted exposure mean of the first year as well as from birth to the age of follow up (corresponding to approximately 7 years of age). For lung function we modeled postnatal exposure from birth to the age of lung function measurement (corresponding to 6 years of age) and for the annual mean exposure the year prior to the lung function measurement.

For asthma incidence, to evaluate the shape of exposure–response curves, we applied natural cubic splines with three degrees of freedom for prenatal and postnatal exposures using the confounder model 4. We selected the degrees of freedom a priori as previous studies conducted as part of the Effects of Low-Level Air Pollution: A Study in Europe (ELAPSE) have shown that this approach allows sufficient flexibility, and it is considered to be biologically plausible (Brunekreef et al. 2021). We also wanted to avoid using different degrees for each of the multiple pollutant–response relationships evaluated by selection of the most optimal degree of freedom using the Akaike Information Criterion and the Bayesian Information Criteria. We considered the distribution among the majority of the study population as the most relevant, as was done in the ELAPSE project (Brunekreef et al. 2021).

For asthma incidence and lung function, we performed two-pollutant models with adjustment for $PM_{2.5}$ and NO_2 and compared the results of these with single-pollutant models for prenatal exposure only, as single-pollutant model results for postnatal exposure were similar to prenatal results.

Finally, we conducted several sensitivity analyses to test the robustness of the associations. We repeated the main analyses for children with asthma diagnosed after four years of age for the studies on asthma incidence. For the DNBC, detailed information on the home indoor characteristics were collected at age 11, and not earlier in childhood before information on parental recall of doctor-diagnosed asthma in the child was available. Therefore, we repeated the analyses among the nonmoving children (i.e., children who did not change home address from birth to the age 11 follow up) to compare with findings reported in previous studies (Fuertes et al. 2020; Gehring et al. 2015b; HEI 2022). We also repeated the main adjusted analyses for asthma prevalence and exposure to $PM_{2.5}$ and NO_2 using a Poisson regression model with a robust error variance to estimate risk ratios (RR) and 95% CIs.

We examined the additional adjustment and stratified analyses by sex for the asthma incidence. Exposure effects and the potential interactions were tested using likelihood ratio tests with a significance level of 5%. We evaluated results of models with a cross-product term between each air pollutant and sex, fitted one-by-one separately to each models, and tested against models without the interaction terms.

Analyses for asthma incidence and lung function were performed using R (version 3.6.1). Analyses for asthma prevalence was performed in StataMP 14. All data linkage and analyses were performed on secure servers provided by Statistic Denmark. Exposure maps were created using features of the Spatial Analyst extension to the Esri ArcMap version (10.7.1; Esri, *www.esri.com*).

RESULTS

We first summarize the results for the nationwide cohort and then the results for the DNBC and COPSAC cohorts. In all sections, we first describe the study population and the ambient air pollution exposure. Next, we present the results of the main analyses and the additional analyses of the associations between exposure to ambient air pollution, asthma, and asthma-related outcomes.

NATIONWIDE COHORT

We included a total of 1,060,154 children in the nationwide cohort that contributed to 9,353,431 person-years at risk for the study on asthma incidence analyses (Pedersen et al. 2023). Relatively few children were excluded and we included 93% of children born in this study period.

Study Population Characteristics

Selected characteristics of the singletons included in the nationwide cohort are displayed in Appendix Table A2. A total of 65,143 children had a diagnosis of asthma within this study period corresponding to 6.1%. **Figure 3** illustrates that the incidence of asthma in children born between 1998 and 2016 varied across Denmark. A third of these children (33.7%) had a home residence in the capital region of Copenhagen at the time of birth (Appendix Figure A2).

Exposure

The mean concentrations of $PM_{2.5}$ and NO_2 during the prenatal period were 10.5 and 17.5 ($\mu g/m^3$), respectively. The air pollution concentrations differed substantially across Denmark as well as within smaller-sized areas (Figure 3). The full exposure distributions of $PM_{2.5}$ and NO_2 during the prenatal period are shown in **Figure 4**.

Almost all children were estimated to have been exposed to ambient air levels of $PM_{2.5}$ and NO_2 at their home residence that were below the current European Union limit values. Less than 0% were exposed to $PM_{2.5}$ above 25 $\mu g/m^3$ and only 2% were exposed to NO_2 concentrations above 40 $\mu g/m^3$. More than half of the children were exposed to ambient concentrations of $PM_{2.5}$ below the existing primary health-based US Environmental Protection Agency National Ambient Air Quality Standard of 12 $\mu g/m^3$. Few children were, however, estimated to be exposed to $PM_{2.5}$ and NO_2 concentrations below the new WHO air quality guideline values of 5 and 10 $\mu g/m^3$, respectively (Figure 4, WHO 2021). For instance, the 5th percentile of the annual $PM_{2.5}$ and NO_2 concentrations during the first year of life were 7.8 and 8.6 $\mu g/m^3$, respectively.

The air pollutant mean, standard deviation (SD), and IQR are provided in **Table 2**. For all pollutants, with the exception of O_3 and sea salt, the mean concentrations have been decreasing over the study period as illustrated in Appendix Figure A3.

The Spearman correlation coefficient (*Rs*) between $PM_{2.5}$ and NO_2 during the prenatal period was 0.71. The prenatal exposure to $PM_{2.5}$ concentrations were modestly to highly correlated with prenatal exposure to all other pollutants, with the exception of SOA and sea salt, as shown in Appendix Table A4. $PM_{2.5}$ and NO_2 were inversely correlated with O_3 and sea salt while all other correlations were positive. Correlations between the concentrations of the other air pollutants varied considerably depending on the pollutants.

The correlations between prenatal and annual mean of the first year of life were high ($Rs > 0.80$) for NO_2, NO_x, EC, SO_2, and SO_4^{2-} (Appendix Table A5).

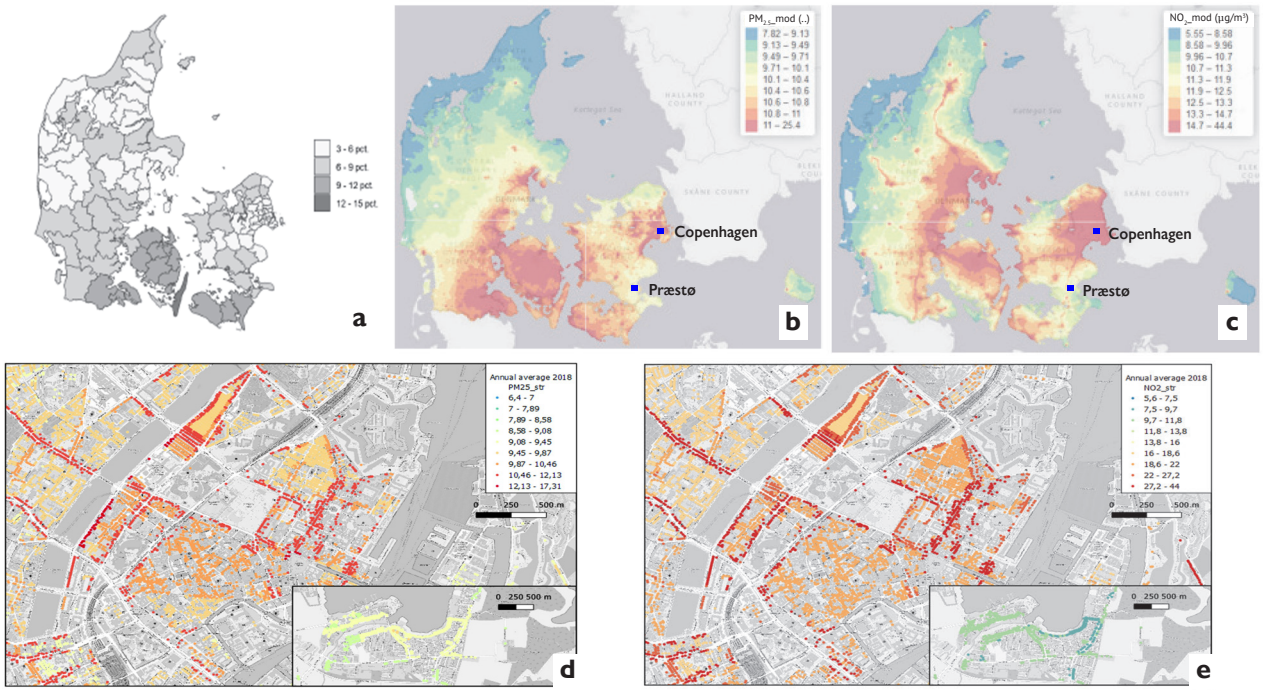

Figure 3. Child asthma (top) and ambient air pollution distribution (bottom) in Denmark. Map (**a**) illustrates the percentage of children with asthma ICD-10 codes out of all included children per municipality. Maps (**b**) and (**c**) show annual mean background concentrations (μg/m³) of $PM_{2.5}$ and NO_2 for 2005 for all of Denmark. Maps (**d**) and (**e**) are annual concentrations of $PM_{2.5}$ and NO_2 at the specific address locations estimated with OSPM, including the local traffic contribution for 2018 for smaller areas of the city center of Copenhagen and Præstø (inset) as examples of remote locations. The color scale is in quantiles (not equidistant level ranges), with blue colors referring to the lowest concentrations and red colors to the highest concentrations. (Maps in color from Pedersen et al. 2023.)

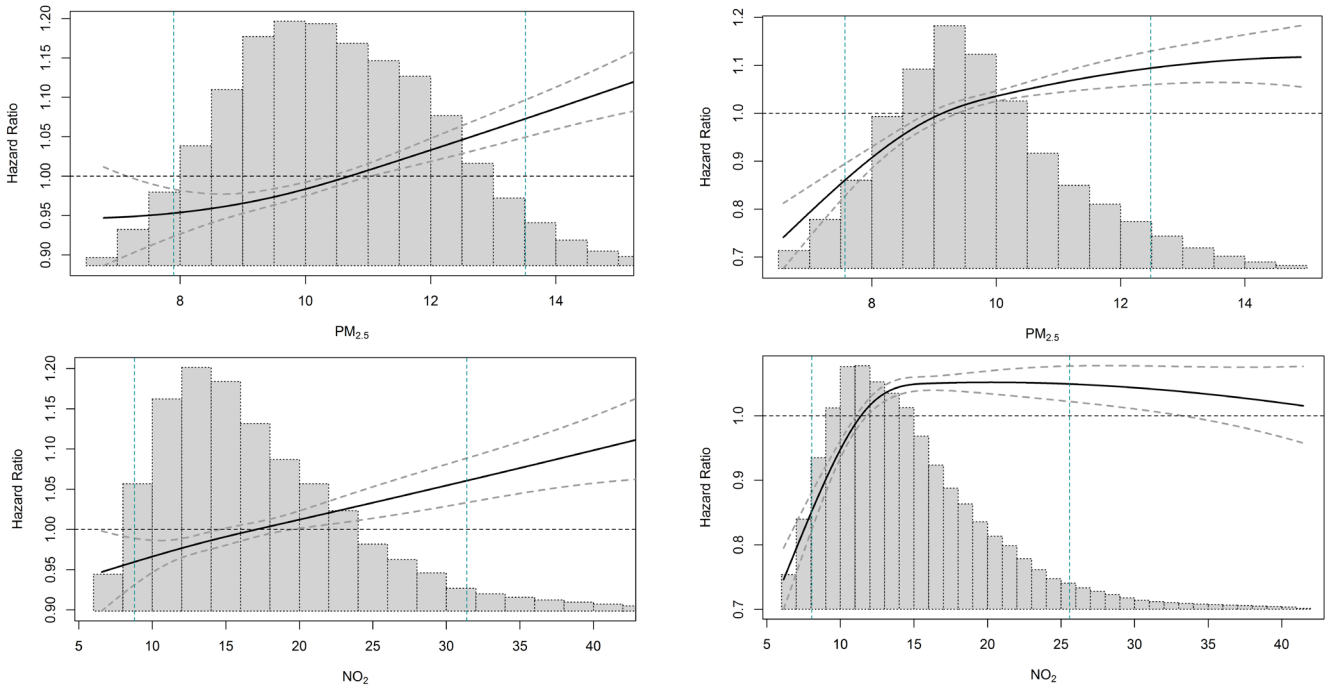

Figure 4. Exposure–response curves for prenatal (left) and postnatal (right) exposure to air pollution with $PM_{2.5}$ and NO_2 in association with asthma incidence. Natural splines with three degrees of freedom adjusted model 4 with HRs and 95% CI expressed relative to mean exposure. Black solid lines indicate log hazard ratio values and black dashed lines indicate their 95% confidence intervals. The histogram shows the exposure distribution. Blue vertical lines indicate the 5th and 95th percentiles of air pollutant concentrations (μg/m³). (From Pedersen et al. 2023.)

Table 2. Associations Between Exposure to Ambient Air Pollution and Asthma Incidence in the Nationwide Cohort of 1,060,154 Children Born in Denmark, 1998–2016[a]

	Prenatal Exposure Mean ± SD	Increment	Prenatal Exposure	Postnatal Exposure	Postnatal Exposure Adjusted for Prenatal Exposure
Pollutant	($\mu g/m^3$)	IQR ($\mu g/m^3$)	HR (95% CI)	HR (95% CI)	HR (95% CI)
$PM_{2.5}$	10.5 ± 1.8	2.4	1.06 (1.04–1.08)	1.08 (1.05–1.10)	1.08 (1.05–1.10)
PM_{10}	16.6 ± 2.2	2.7	1.05 (1.04–1.06)	1.10 (1.08–1.11)	1.11 (1.09–1.13)
NO_2	17.5 ± 7.4	8.7	1.04 (1.02–1.05)	1.02 (1.01–1.04)	1.03 (1.01–1.05)
NO_x	24.1 ± 17.3	13.4	1.01 (1.01–1.02)	1.01 (1.00–1.02)	1.01 (0.99–1.02)
EC	0.7 ± 0.3	0.3	1.03 (1.02–1.03)	1.04 (1.03–1.05)	1.06 (1.04–1.07)
OC	1.5 ± 0.3	0.5	1.08 (1.06–1.10)	1.18 (1.16–1.20)	1.19 (1.17–1.21)
SO_2	3.8 ± 2.3	2.7	1.02 (1.01–1.03)	1.08 (1.06–1.09)	1.10 (1.08–1.12)
O_3	53.1 ± 6.7	8.5	0.98 (0.96–0.99)	0.77 (0.76–0.78)	0.75 (0.73–0.76)
SO_4^{2-}	1.6 ± 0.5	0.9	1.04 (1.01–1.08)	1.02 (0.96–1.09)	1.02 (0.95–1.08)
NO_3^-	3.2 ± 0.5	0.6	1.02 (1.00–1.03)	0.89 (0.87–0.91)	0.89 (0.87–0.91)
NH_4^+	1.2 ± 0.3	0.4	1.01 (0.99–1.03)	1.04 (1.00–1.07)	1.04 (1.00–1.08)
SOA	0.3 ± 0.1	0.1	1.02 (1.01–1.04)	0.82 (0.81–0.83)	0.82 (0.81–0.83)
Sea salt	0.9 ± 0.2	0.2	0.99 (0.97–1.00)	1.21 (1.18–1.24)	1.22 (1.19–1.24)

[a] Hazard ratios (HR) and the 95% CIs from Cox regression models per fixed increments of the interquartile range (IQR) as indicated above with age (months) as the time dimension adjusted for year, sex (strata), household income (continuous scale), maternal education (three categories), parity (continuous scale), season of birth (four categories), smoking during pregnancy (yes/no) and municipality (strata). Prenatal exposure models refer to time-weighted average exposures to ambient air pollutants for the full prenatal period. Postnatal exposure models refer to time-weighted average exposures to ambient air pollutants for the 12 months before the event using running means of time-varying exposures.

The total number of children is 1,060,154 and the number of asthma cases is 65,143.

Associations Between Ambient Air Pollution and Asthma Incidence

Single-Pollutant Models Table 2 shows the HRs and 95% CIs for associations between prenatal exposure to air pollution and asthma incidence. HRs were positive and statistically significant for all pollutants, with the exception of O_3 and sea salt in fully adjusted models. The mean (SD) follow up was 8.8 (5.5) years, and it ranged from a few months to 19 years. Some children developed asthma during early infanthood and others later in adolescence. Because the length of follow up differed, we also evaluated associations between postnatal exposure and asthma onset, fitting the annual mean concentrations of ambient air pollution using time-varying exposure of the year prior to the asthma incidence rather than using fixed exposure of the first year of life annual average as was done in many previous studies. Increased risk was also evident for all pollutants with the exception of O_3, NO_3^-, and SOA for postnatal exposure. The HRs associated with postnatal exposure using running means were slightly larger than the corresponding effect estimates of prenatal exposures for PM, EC, OC, SO_2, NH_4^+, and sea salt, while the HRs from postnatal models were similar or smaller than those from models with prenatal exposure for NO_2, NO_x, SO_4^{2-}, NO_3^-, and SOA. The largest HRs were observed for postnatal exposure to sea salt and OC, where the latter is an indicator of biomass burning. The finding that increasing postnatal exposure to O_3 is protective against asthma incidence might seem odd and could reflect that other exposures are low, as O_3 is a secondary gas formed by reactions between NO_x and volatile organic compounds in the presence of sunlight. However, it is true of prenatal exposure to O_3 as well (although the magnitude per incremental change is lower, the HR for prenatal ozone exposure is also below 1).

Table 2 also shows that for most pollutants the effect estimates of postnatal exposures using running means of the annual exposure the year prior to asthma onset remained unchanged or increased slightly after mutual adjustment for prenatal exposure to the same pollutant. We fitted running

means of postnatal exposure as the annual mean prior to asthma and, therefore, could not calculate the effect estimates of prenatal exposure models adjusted for postnatal exposure. We did observe that the effect estimates of prenatal exposure were robust to adjustment for postnatal exposure in the first year of life in models fitted with fixed postnatal exposure annual means; we do not report these results as we believe the postnatal model with running means is more accurate. Despite the high correlations between prenatal and postnatal exposure, annual mean during the first year of life was high ($R_S > 0.80$) for pollutants like NO_2, NO_x, EC, and SO_4^{2-} (Appendix Table A5). We were able to fit postnatal models with adjustment of prenatal exposure as we used running means for the postnatal exposure occurring just before asthma onset, which could be years apart from prenatal exposure.

Different Degrees of Adjustment **Table 3** shows the HRs in four models with increasing levels of adjustment. Changes in associations after confounder adjustment differed among pollutants. Adjustment increased the HRs slightly to modestly for most pollutants but decreased consistently for NO_3^- and NH_4^+ after adjustment for the municipality. Adjustment for municipality had a very small effect on the HRs associated with $PM_{2.5}$ and PM_{10} as compared with the HRs of the other pollutants. Prenatal exposure to NO_2, EC, OC, SO_2, and SOA was associated with increased HRs in models with adjustment for municipality, but not in models without adjustment for municipality, whereas the opposite pattern was observed for prenatal exposure to O_3 and sea salt.

The results summarized in Table 3 suggest that adjustment explains the small differences in the estimated effect observed in the different models. In addition, we cannot rule out that exposure misclassification may also differ among the evaluated exposure–response relationships.

Exposure–Response Functions The graphs in the left column of Figure 4 show the shapes of the exposure–response curves that indicated monotonically positive linear relationships for prenatal exposure to $PM_{2.5}$ and NO_2 between the 5th and 95th percentile of exposure in the adjusted model 4, based on natural splines with three degrees of freedom.

For the models with the postnatal exposure the shape of curves differed from those of prenatal exposures as the curves were steeper at the lower concentrations and suggested that the increase of the curve leveled off at the highest concentrations (Figure 4, right). At the lowest and highest concentrations, confidence intervals are wide because of fewer observations, as illustrated by the heights of the bars in the histograms.

Two-Pollutant Models **Table 4** shows the results of the two-pollutant-models analyses for asthma incidence. We present all the two-pollutant effect estimates also when the correlations between pollutants were high. The HRs for prenatal exposure to $PM_{2.5}$ remained unchanged or increased after adjustment for NO_x, EC, SO_2, O_3, SO_4^{2-}, NO_3^-, NH_4^+, SOA, and sea salt. The HRs decreased after adjustment for PM_{10} and OC in two-pollutant models (Table 4). The corresponding HRs of the copollutants decreased after adjustment for $PM_{2.5}$ in two-pollutant models except for OC, O_3, and sea salt. The HRs for OC remained unchanged at 1.08 (95% CI: 1.06–1.10) in two-pollutant models after adjustment for $PM_{2.5}$ or NO_2, while the HR for both $PM_{2.5}$ and NO_2 decreased after adjustment for OC. After adjustment for $PM_{2.5}$ or NO_2, the HR for O_3 increased slightly, but the HR for $PM_{2.5}$ or NO_2 didn't change. The HR for sea salt increased after adjustment for $PM_{2.5}$, but the HR remained unchanged for $PM_{2.5}$ after adjustment for sea salt. The HRs for NO_2 decreased in two-pollutant models after adjustment for $PM_{2.5}$, PM_{10}, EC, OC, and SO_2, while the HRs for these copollutants decreased less, increased, or remained unchanged after adjustment for NO_2. Like the two-pollutant model with $PM_{2.5}$ and O_3, when NO_2 and O_3 were fitted to the same model, both HRs increased slightly, and HR was larger than 1 for O_3.

Sensitivity Analyses In general, associations presented here for main results were similar to the associations found in sensitivity analyses.

HRs remained elevated and statistically significant for $PM_{2.5}$, PM_{10}, NO_2, NO_x, EC, OC, SO_2, and SOA after restricting to children with four or more years of follow up and defining asthma according to diagnosis after 4 years of age, but the magnitude of the effects weakened slightly (Appendix Table A6).

Appendix Table A7 shows the results of the additional analyses. In analyses restricted to children living in Greater Copenhagen (N = 276,773, n = 12,270), the HRs for $PM_{2.5}$, OC, SO_2, SO_4^{2-}, and NH_4^+ increased and remained unchanged for PM_{10}, NO_2, NO_x, and EC. The effect estimates of prenatal exposure in the main model (Table 2) were robust to additional adjustments for area-level SES and population density as shown in Appendix Table A7.

Appendix Table A8 shows the stratified analyses, which show larger HRs for girls as compared with boys with statistically significant P values ($P < 0.05$) of the interaction terms between sex and air pollutants for $PM_{2.5}$, PM_{10}, SO_2, SO_4^{2-}, NO_3^-, and NH_4^+, whereas the P values were nonsignificant ($P > 0.05$) for the remaining pollutants.

DNBC COHORT

We included a total of 22,084 children in the DNBC for the studies on asthma incidence and prevalence analyses (Pedersen et al. 2022). We restricted the study population to complete cases because we performed these studies as a supplement to the nationwide study. As compared with the nationwide cohort, we excluded many children because of loss to follow up (Appendix Figure A4), and we included 27.9% of the eligible singleton children with complete air pollution and covariate data and participation in the first DNBC interview.

Table 3. Associations Between Prenatal Exposure to Air Pollution and Asthma Incidence in the Nationwide Cohort With Increasing Level of Adjustment for Confounders of 1,060,154 Children Born in Denmark, 1998–2016 [a]

Pollutant	Increment IQR (μg/m³)	Model 1 HR (95% CI)	Model 2 HR (95% CI)	Model 3 HR (95% CI)	Model 4 HR (95% CI)
$PM_{2.5}$	2.4	1.00 (0.99–1.02)	1.02 (1.01–1.04)	1.04 (1.02–1.05)	1.06 (1.04–1.08)
PM_{10}	2.7	1.03 (1.01–1.04)	1.04 (1.03–1.05)	1.06 (1.04–1.07)	1.05 (1.04–1.06)
NO_2	8.7	0.89 (0.89–0.90)	0.91 (0.90–0.92)	0.92 (0.91–0.93)	1.04 (1.02–1.05)
NO_x	13.4	0.95 (0.94–0.96)	0.96 (0.95–0.97)	0.96 (0.96–0.97)	1.01 (1.01–1.02)
EC	0.3	0.94 (0.93–0.95)	0.95 (0.95–0.96)	0.96 (0.96–0.97)	1.03 (1.02–1.03)
OC	0.5	0.94 (0.93–0.95)	0.96 (0.95–0.97)	0.98 (0.97–0.99)	1.08 (1.06–1.10)
SO_2	2.7	0.97 (0.96–0.98)	0.97 (0.96–0.98)	0.98 (0.97–0.99)	1.02 (1.01–1.03)
O_3	8.5	1.11 (1.10–1.12)	1.09 (1.08–1.10)	1.09 (1.08–1.10)	0.98 (0.96–0.99)
SO_4^{2-}	0.9	1.05 (1.02–1.08)	1.06 (1.03–1.09)	1.06 (1.03–1.09)	1.04 (1.01–1.08)
NO_3^-	0.6	1.12 (1.11–1.13)	1.11 (1.10–1.13)	1.11 (1.10–1.12)	1.02 (1.00–1.03)
NH_4^+	0.4	1.24 (1.22–1.27)	1.23 (1.20–1.25)	1.23 (1.21–1.25)	1.01 (0.99–1.03)
SOA	0.1	0.98 (0.97–0.99)	0.99 (0.98–1.00)	0.96 (0.95–0.97)	1.02 (1.01–1.04)
Sea salt	0.2	1.08 (1.07–1.09)	1.07 (1.06–1.08)	1.07 (1.06–1.09)	0.99 (0.97–1.00)

[a] Hazard ratios (HR) and the 95% CIs from Cox regression models fitted with time-weighted average exposures to ambient air pollutants for the full prenatal period with fixed increments of the interquartile range (IQR) and age as the time dimension and different levels of adjustment. Model 1 is adjusted for age, sex, and birth year. Model 2 is further adjusted for household income, maternal education, and parity. Model 3 is further adjusted for season of birth and smoking during pregnancy. The main model, Model 4, is further adjusted for municipality.

The total number of children are 1,060,154 and the number of asthma cases are 65,143.

Table 4. Associations Between Prenatal Exposure to Air Pollution and Asthma Incidence in the Nationwide Cohort in Single- and Two-Pollutant Models of 1,060,154 Children Born in Denmark, 1998–2016 [a]

		Two-Pollutant Models			
Pollutant	Single-Pollutant Models HR (95% CI)	Copollutant Adjusted for $PM_{2.5}$ HR (95% CI)	$PM_{2.5}$ Mutually Adjusted HR (95% CI)	Copollutant Adjusted for NO_2 HR (95% CI)	NO_2 Mutually Adjusted HR (95% CI)
$PM_{2.5}$	1.06 (1.04–1.08)	–	–	1.05 (1.03–1.08)	1.01 (0.99–1.03)
PM_{10}	1.05 (1.04–1.06)	1.04 (1.01–1.07)	1.01 (0.98–1.05)	1.06 (1.04–1.09)	0.99 (0.96–1.01)
NO_2	1.04 (1.02–1.05)	1.01 (0.99–1.03)	1.05 (1.03–1.08)	–	–
NO_x	1.01 (1.01–1.02)	1.00 (0.99–1.01)	1.06 (1.04–1.08)	0.97 (0.95–1.00)	1.09 (1.04–1.13)
EC	1.03 (1.02–1.03)	1.01 (1.00–1.02)	1.05 (1.02–1.07)	1.02 (1.01–1.03)	1.01 (0.99–1.03)
OC	1.08 (1.06–1.10)	1.08 (1.06–1.10)	1.01 (0.99–1.03)	1.08 (1.06–1.09)	1.01 (1.00–1.03)
SO_2	1.02 (1.01–1.03)	1.01 (1.00–1.02)	1.05 (1.03–1.07)	1.01 (1.00–1.03)	1.03 (1.02–1.05)
O_3	0.98 (0.96–0.99)	1.00 (0.98–1.02)	1.06 (1.04–1.08)	1.01 (0.99–1.04)	1.05 (1.02–1.07)
SO_4^{2-}	1.04 (1.01–1.08)	0.94 (0.90–0.99)	1.08 (1.05–1.10)	1.03 (1.00–1.07)	1.04 (1.02–1.05)
NO_3^-	1.02 (1.00–1.03)	0.97 (0.95–0.99)	1.09 (1.06–1.11)	1.01 (1.00–1.03)	1.04 (1.02–1.05)
NH_4^+	1.01 (0.99–1.03)	0.92 (0.89–0.95)	1.11 (1.08–1.13)	1.00 (0.98–1.03)	1.04 (1.02–1.05)
SOA	1.02 (1.01–1.04)	1.01 (1.00–1.03)	1.05 (1.04–1.07)	1.02 (1.01–1.04)	1.04 (1.02–1.05)
Sea salt	0.99 (0.97–1.00)	1.01 (0.99–1.02)	1.06 (1.04–1.08)	0.99 (0.98–1.01)	1.04 (1.02–1.05)

[a] Hazard ratios (HR) and the 95% CIs from Cox regression models per fixed increments of the interquartile range (μg/m³) of the time-weighted average exposures to ambient air pollutants for the full prenatal period of 2.4 for $PM_{2.5}$, 2.7 for PM_{10}, 8.7 for NO_2, 13.4 for NO_x, 0.3 for EC, 0.5 for OC, 2.7 for SO_2, 8.5 for O_3, 0.9 for SO_4^{2-}, 0.6 for NO_4^-, 0.4 for NH_4^+, 0.1 for SOA, and 0.2 for sea salt with age as the time dimension adjusted for birth year, sex, household income, maternal education, parity, season of birth, smoking during pregnancy and municipality.

The total number of children is 1,060,154 and the number of asthma cases is 65,143.

Study Population Characteristics

Selected characteristics of the singletons included in the DNBC studies are displayed in Appendix Table A2. A fourth (25.3%) of the children were born in the capital region of Copenhagen (Appendix Figure A2), and the children of the DNBC were born mainly between 1998 and 2002. The prenatal exposure mean and standard deviations of the air pollutants for the DNBC study population are shown in the middle column of Appendix Table A3.

Slightly more girls than boys were included in these studies. The mothers of the DNBC study population were less frequently characterized as having asthma, low education, and low income as compared with the nationwide cohort, but smoking during pregnancy was more common among the mothers of the children included in the DNBC study; 19.2% vs. 13.9% in the nationwide cohort, which included more recent years where fewer women smoke. We have reported a detailed description of the home characteristics of the DNBC children (Groot et al. 2022); we observed that most of the children of the DNBC lived in a detached house that was owned, and they were living together with both parents at age 11. More than half of the children lived in a home with more than seven rooms, visible mold or dampness, and pets. Although the presence of a wood stove was common, it was seldom used (Groot et al. 2022). We have reported the associations between pet ownership and asthma at school age in a study that included the DNBC as well as eight other birth cohorts (Pinot de Moira et al. 2022).

In Appendix Table A9 we report that the included children differed from the excluded children of the DNBC. Excluded children were, for instance, more commonly characterized by low SES (low maternal education: 16.6% vs. 8.5% and low income: 20.3% vs. 13.5%), maternal asthma (9.0% vs. 8.2%), and child asthma (8.4% vs. 6.7%) than were included children. The prenatal exposure to air pollution was lower for the included study population than for the excluded population. We also show in Appendix Table A9 that the nonmoving subpopulation (n = 9,507), which had the same address from birth to age 11 when information on home characteristics was collected, differs from the population that moved. Low SES, first-time parents, as well as maternal and child asthma were less common among nonmovers than among movers. Mean prenatal exposures to most pollutants were lower among nonmovers as compared with movers.

Out of 22,084 children, a total of 1,475 had a diagnosis of asthma from birth to the end of follow up, corresponding to 6.7%, which is similar to the percentage observed in the nationwide cohort of children, while at age seven, 2,188 (9.9%) of the children had doctor-diagnosed asthma according to parental recall. **Figure 5** shows the overlap and the lack of overlap between the different asthma outcomes. Out of the children with doctor-diagnosed asthma ever at age 7, 44.6% had active asthma at age 7. At 7 years of age, 51.3% of the children with asthma according to ICD-10 codes also had asthma according to parental recall of a doctor-diagnosis, while 34.5% of children with a parental recall of a doctor-diagnosis and 47.7% of the children with active doctor-diagnosis asthma also had an ICD-10 code for asthma. The higher overlap between active doctor-diagnosis according to parental recall and asthma according to ICD-10 codes, than for doctor-diagnosed asthma ever, suggests that the phenotypes of active doctor-diagnosis according to parental recall and asthma according to ICD-10 codes are more similar than doctor-diagnosed asthma ever according to parental recall and asthma according to ICD-10 codes.

Exposure

The exposure distribution is summarized in Appendix Table A3. The mean pollutant concentrations were slightly higher for the DNBC study population than for the nationwide cohort, whereas the O_3 concentration was higher and SOA was the same. These differences reflect the different time periods and residential areas of the children included in these cohorts.

The *Rs* between $PM_{2.5}$ and NO_2 during the prenatal period was 0.84, which is higher than for the nationwide cohort (Appendix Table A4). The prenatal exposures to $PM_{2.5}$ concentrations were modestly to highly correlated with prenatal exposure to all other pollutants, with the exception of SOA and sea salt. $PM_{2.5}$ and NO_2 were inversely correlated with O_3 and sea salt, while all other correlations were positive. Correlations between the concentrations of the other air pollutants varied considerably depending on the pollutants.

The correlations between prenatal and annual mean of the first year of life were high (*Rs* > 0.80) for NO_2, NO_x, and OC (Appendix Table A5). The correlation coefficients between prenatal and mean of the first seven years of life were weaker than for the first year of life.

Associations Between Ambient Air Pollution and Asthma Incidence

Single-Pollutant Models With Different Degrees of Adjustment **Table 5** shows the HRs and 95% CIs for associations between prenatal exposure to air pollution and asthma incidence in the DNBC with increasing degrees of adjustment. As for the nationwide cohort, the HRs were positive for $PM_{2.5}$, PM_{10}, NO_2, NO_x, EC, SO_4^{2-}, and sea salt in model 4, which was considered to be the main model for the nationwide cohort. However, the associations did not reach statistical significance in the smaller-sized DNBC population, and HRs were not elevated for OC, SO_2, NO_3^-, NH_4^+, and SOA. Again, we noted that the changes in associations after confounder adjustment differed among pollutants. Additional adjustment for the DNBC-specific covariates (model 5) did not change the HRs from those observed in model 4 for most pollutants.

While increasing adjustment increased the HRs in the nationwide cohort for the DNBC study population, increasing adjustment modestly decreased the HRs for most pollutants.

Adjustment for municipality had a larger effect on the HRs associated with SO_4^{2-}, NO_3^-, and NH_4^+ as compared with the HRs of the other pollutants and did not change the effect estimates of NO_2, NO_x, and EC. The HRs of $PM_{2.5}$ and PM_{10} decreased after adjustment for municipality, which was not the case for the nationwide cohort.

Associations Between Ambient Air Pollution and Asthma Prevalence

Single Pollutant Models **Table 6** shows the ORs and the 95% CIs for associations between ambient air pollution and asthma prevalence ever and active at age 7 in the DNBC according to parental recall in adjusted models for exposure during prenatal life, the first year of life, and from birth to the age of the 7-year follow up.

For these asthma outcomes all the confidence intervals for all the associations evaluated included the null. For asthma ever, elevated ORs were observed for O_3 for all three exposure periods, but the 95% CIs included the null. For all associations the results differed across exposure periods. Elevated ORs were found for asthma ever and for sea salt, but only with prenatal exposure. For exposure during the first year of life, increased ORs were found for $PM_{2.5}$, OC, SO_4^{2-}, NO_3^-, and NH_4^+ for asthma ever.

For active asthma at age 7, ORs above one were found for prenatal exposure to OC and sea salt. ORs above one were observed for $PM_{2.5}$, OC, SO_4^{2-}, NO_3^-, and NH_4^+ in the first year of life. This was also true for asthma ever in the first year of life, but the OR for SO_2 was also above one. For postnatal exposure from birth to age 7, ORs were elevated for SO_2, SO_4^{2-}, NO_3^-, and NH_4^+.

Higher exposure to $PM_{2.5}$ in the first year of life was consistently associated with elevated ORs for asthma ever and active asthma at age 7, but the associations included the null, and there was no evidence of associations for exposures to $PM_{2.5}$ during prenatal life and the longer postnatal period.

Different Degrees of Adjustment As shown in **Table 7**, the degree of adjustment made little difference for the associations between prenatal exposure and active asthma at age 7. The additional adjustment for municipality increased the ORs for OC while it decreased the ORs for O_3 and sea salt.

We decided not to report two-pollutant model results for the DNBC as the reported single-pollutant tables did not provide evidence supportive of elevated ORs for asthma prevalence.

Sensitivity Analyses Comparing model 5 in Table 5 with Appendix Table A10 we show that the HRs and 95% CIs for associations between prenatal exposure to air pollution and asthma incidence in the DNBC, as well as the ORs for associations for the two asthma prevalence outcomes, were higher among the children who did not change address from birth to the 11-year follow up — when the detailed information on their home characteristic was collected. For instance, the associations between asthma incidence and an IQR in prenatal exposure to $PM_{2.5}$ and PM_{10} changed from 1.03 (95% CI: 0.91–1.16) to 1.12 (0.89–1.41) and from 1.02 (0.92–1.12) to 1.21 (1.01–1.45), respectively, in the most comprehensively adjusted models that included the DNBC-specific covariates. We observed the same patterns for asthma prevalence.

There were no marked differences between the estimated RR and 95% CI from the Poisson model and the results from the logistic model reported in Table 6 for $PM_{2.5}$ and NO_2 as summarized in Appendix Table A11.

COPSAC COHORT

We included 700 children in the $COPSAC_{2010}$ study on airway immune mediators, DNA methylation, gene expression, inflammation, asthma, and asthma-related outcomes at age 6. The prevalence of asthma from birth to age 6 and current asthma (defined as children who have asthma according to clinical judgment and a need for medication at age 6) was 22.3% and 6.5%, respectively. Additional study population characteristics of this population is described in detail elsewhere (Tingskov Pedersen et al. 2023).

For the study on lung function changes at age 6, we initially included 803 children with calibrated lung function parameters at age 6, air pollution data, and covariate data from both data collections (i.e., $COPSAC_{2000\ \&\ 2010}$). We are planning to extend the study population size by including more children with calibrated lung function parameters at ages close to age 6, and therefore we have not yet compared the included study population with those excluded.

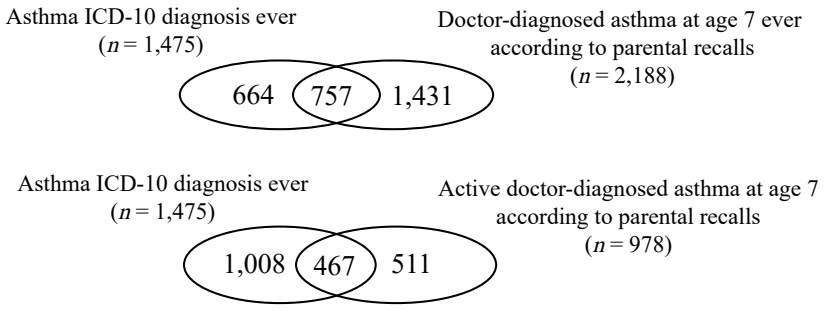

Figure 5. Overlap between asthma outcomes in the DNBC.

Table 5. Associations Between Prenatal Exposure to Air Pollution and Asthma (ICD-10) Incidence in the Danish National Birth Cohort (DNBC) with Increasing Level of Adjustment for Confounders of 22,084 Children Born in Denmark, 1998–2003 [a]

Pollutant	Model 1 HR (95% CI)	Model 2 HR (95% CI)	Model 3 HR (95% CI)	Model 4 HR (95% CI)	Model 5 HR (95% CI)
$PM_{2.5}$	1.10 (1.01–1.19)	1.12 (1.03–1.22)	1.12 (1.03–1.22)	1.03 (0.91–1.16)	1.03 (0.91–1.16)
PM_{10}	1.10 (0.99–1.15)	1.08 (1.00–1.16)	1.09 (1.01–1.18)	1.02 (0.93–1.13)	1.02 (0.92–1.12)
NO_2	0.99 (0.94–1.06)	1.01 (0.95–1.08)	1.02 (0.96–1.08)	1.02 (0.93–1.13)	1.02 (0.93–1.13)
NO_x	1.00 (0.97–1.04)	1.01 (0.97–1.05)	1.01 (0.98–1.05)	1.01 (0.97–1.06)	1.01 (0.97–1.06)
EC	0.99 (0.95–1.04)	1.00 (0.96–1.05)	1.01 (0.96–1.06)	1.01 (0.96–1.07)	1.01 (0.96–1.07)
OC	0.96 (0.88–1.05)	0.99 (0.90–1.08)	1,00 (0.91–1.10)	0.97 (0.83–1.13)	0.96 (0.82–1.13)
SO_2	0.97 (0.91–1.03)	0.98 (0.92–1.04)	0.98 (0.92–1.05)	0.99 (0.90–1.07)	0.98 (0.90–1.07)
O_3	1.02 (0.96–1.08)	1.00 (0.94–1.07)	0.98 (0.91–1.04)	0.97 (0.88–1.06)	0.97 (0.88–1.06)
SO_4^{2-}	1.35 (1.09–1.66)	1.40 (1.13–1.73)	1.39 (1.12–1.72)	1.13 (0.86–1.48)	1.11 (0.84–1.46)
NO_3^-	1.16 (1.08–1.24)	1.16 (1.08–1.24)	1.16 (1.08–1.25)	0.99 (0.89–1.11)	0.99 (0.89–1.11)
NH_4^+	1.30 (1.15–1.48)	1.30 (1.15–1.47)	1.30 (1.15–1.48)	0.98 (0.83–1.16)	0.97 (0.82–1.15)
SOA	1.01 (0.95–1.08)	1.01 (0.95–1.08)	0.99 (0.91–1.07)	0.99 (0.90–1.08)	0.99 (0.91–1.09)
Sea salt	1.04 (0.96–1.12)	1.02 (0.95–1.10)	1.04 (0.96–1.13)	1.02 (0.90–1.16)	1.03 (0.90–1.16)

[a] Hazard ratios (HR) and the 95% CIs from Cox regression models per fixed increments (μg/m³) of the time-weighted average exposures to ambient air pollutants for the full prenatal period of 2.4 for $PM_{2.5}$, 2.7 for PM_{10}, 8.7 for NO_2, 13.4 for NO_x, 0.3 for EC, 0.5 for OC, 2.7 for SO_2, 8.5 for O_3, 0.9 for SO_4^{2-}, 0.6 for NO_3^-, 0.4 for NH_4^+, 0.1 for SOA, and 0.2 for sea salt with age as the time dimension.

Model 1 is adjusted for age, sex, and birth year, Model 2 is further adjusted for household income, maternal education, and parity. Model 3 is further adjusted for season of birth and smoking during pregnancy. The main model, Model 4, is further adjusted for municipality. Model 5 is further adjusted for DNBC specific variables including maternal and paternal asthma, pets during pregnancy, house size at birth, breast-feeding, daycare, mold, dampness, ETS, and presence of gas stove, presence of wood stove, and candlelight burning in the home at age 11.

Total number of children were 22,084 and 1,475 had asthma.

Study Population Characteristics

Selected characteristics of the 803 singletons included in the $COPSAC_{2000\ \&\ 2010}$ study on lung function are displayed in Appendix Table A2. Most of these children (70.4%) were born in the capital region of Copenhagen (Appendix Figure A2). As with the DNBC, slightly more girls than boys were included in the COPSAC study (Appendix Table A2). The COPSAC children and their mothers were more frequently characterized as having asthma as compared with the nationwide cohort and the DNBC; the COPSAC mothers more frequently had high education and income and less frequently smoked during pregnancy, compared with those in the nationwide cohort (11.5% vs. 13.9%). Postnatal exposure to ETS, pets, gas, and wood stove in the home were, however, more common in the homes of the children of COPSAC than of the DNBC (Appendix Table A2).

Exposure

The exposure distribution of the COPSAC children (n = 803) is summarized in Appendix Table A3. The mean concentrations of $PM_{2.5}$ and NO_2 during the prenatal period were 10.8 and 20.4 (μg/m³), respectively. The mean concentrations of NO_2, NO_x, EC, and OC were slightly higher for the COPSAC study population, as compared with the nationwide cohort, whereas the mean O_3 concentration was lower and the concentrations of the other pollutants were similar. These differences mainly reflect the different residential areas of the children included in these cohorts.

The *Rs* between $PM_{2.5}$ and NO_2 during the prenatal period was 0.62, which is lower than for the nationwide cohort and the DNBC (Appendix Table A4). The prenatal exposure to PM concentrations were modestly to highly correlated with prenatal exposure to all other pollutants, with the exception of OC, SOA, and sea salt. $PM_{2.5}$ was inversely correlated with O_3 and with SOA, while all other correlations were positive. Correlations between the concentrations of the other air pollutants varied considerably depending on the pollutants.

The correlations between mean concentrations during the prenatal and the first six years of life were high ($Rs > 0.80$) for NO_2, NO_x, SO_2, SO_4^2 and NH_4^+ (Appendix Table A5). The correlation coefficients between the mean concentration of the prenatal period and the year prior to lung function measurement were smaller than those of the first six years.

Table 6. Associations Between Prenatal and Postnatal Exposure to Air Pollution and Asthma (Parental Recall) Prevalence in the Danish National Birth Cohort (DNBC) of 22,084 Children Born in Denmark, 1998–2003[a]

	Asthma Ever[b] (n = 2,188)			Active Asthma[c] (n = 978)		
Pollutant	Prenatal Exposure OR (95% CI)	Postnatal Exposure First Year OR (95% CI)	Postnatal Exposure Birth to Age 7 OR (95% CI)	Prenatal Exposure OR (95%CI)	Postnatal Exposure First Year OR (95%CI)	Postnatal Exposure Birth to Age 7 OR (95%CI)
$PM_{2.5}$	0.85 (0.70–1.04)	1.07 (0.87–1.30)	0.87 (0.64–1.18)	0.93 (0.70–1.23)	1.03 (0.77–1.38)	0.90 (0.58–1.40)
PM_{10}	0.82 (0.62–1.09)	0.92 (0.69–1.23)	0.80 (0.55–1.17)	0.89 (0.60–1.34)	0.87 (0.58–1.32)	0.72 (0.41–1.26)
NO_2	0.95 (0.87–1.03)	0.95 (0.87–1.03)	0.94 (0.85–1.05)	0.97 (0.86–1.09)	0.93 (0.82–1.05)	0.85 (0.73–1.00)
NO_x	0.97 (0.92–1.03)	0.96 (0.91–1.02)	0.94 (0.86–1.04)	0.97 (0.90–1.05)	0.94 (0.86–1.03)	0.85 (0.73–0.98)
EC	0.93 (0.81–1.07)	0.96 (0.82–1.12)	0.93 (0.74–1.17)	0.96 (0.79–1.17)	0.93 (0.75–1.16)	0.80 (0.57–1.12)
OC	0.92 (0.75–1.13)	1.08 (0.88–1.32)	1.00 (0.81–1.24)	1.02 (0.75–1.38)	1.10 (0.82–1.48)	1.00 (0.73–1.37)
SO_2	0.98 (0.96–1.00)	1.00 (0.97–1.02)	0.99 (0.96–1.02)	1.00 (0.89–1.12)	1.03 (0.91–1.17)	1.16 (0.96–1.39)
O_3	1.05 (0.97–1.14)	1.03 (0.94–1.12)	1.06 (0.93–1.20)	1.00 (0.97–1.04)	1.01 (0.97–1.04)	1.00 (0.95–1.04)
SO_4^{2-}	0.86 (0.66–1.12)	1.26 (0.97–1.65)	0.83 (0.43–1.59)	0.88 (0.60–1.30)	1.08 (0.73–1.59)	1.48 (0.58–3.77)
NO_3^-	0.66 (0.37–1.17)	1.70 (0.94–3.10)	0.83 (0.36–1.92)	0.85 (0.37–1.96)	2.02 (0.85–4.82)	1.99 (0.59–6.66)
NH_4^+	0.82 (0.62–1.10)	1.34 (0.99–1.81)	0.89 (0.57–1.40)	0.91 (0.60–1.39)	1.40 (0.90–2.16)	1.47 (0.76–2.84)
SOA	0.87 (0.47–1.60)	0.98 (0.48–2.00)	0.73 (0.06–8.91)	0.90 (0.37–2.16)	0.83 (0.30–2.33)	0.53 (0.01–20.10)
Sea salt	1.32 (0.90–1.94)	0.73 (0.49–1.10)	0.92 (0.50–1.71)	1.31 (0.75–2.29)	0.73 (0.41–1.31)	0.86 (0.35–2.12)

[a] Odds ratios (OR) and the 95% CIs from logistic regression models with generalized estimating equations for fixed increments (μg/m³) of the time-weighted average exposures to ambient air pollutants for the full prenatal period of 5 for $PM_{2.5}$, 10 for PM_{10}, 10 for NO_2, 20 for NO_x, 1 for EC, 1 for OC, 1 for SO_2, 10 for O_3, 1 for SO_4^{2-}, 5 for NO_3^-, 1 for NH_4^+, 1 for SOA, and 1 for sea salt with adjustments for birth year, sex, household income, maternal education, parity, season of birth, smoking during pregnancy, municipality, maternal and paternal asthma, pets during pregnancy, house size at birth, breastfeeding, daycare, mold, dampness, ETS, and presence of gas stove, presence of wood stove, and candlelight burning in the home at age 11.

[b] Asthma ever from birth to the age 7 follow up.

[c] Active asthma at the age 7 follow up.

Table 7. Associations Between Prenatal Exposure to Air Pollution and Prevalence of Active Asthma at Age 7 (Parental Recall) in the DNBC of 22,084 Children Born in Denmark, 1998–2003 With Increasing Level of Adjustment for Confounders[a]

Pollutant	Model 1 OR (95%CI)	Model 2 OR (95%CI)	Model 3 OR (95%CI)	Model 4 OR (95%CI)	Model 5 OR (95%CI)
$PM_{2.5}$	0.86 (0.68–1.08)	0.88 (0.70–1.11)	0.90 (0.71–1.13)	0.81 (0.63–1.04)	0.93 (0.70–1.23)
PM_{10}	0.88 (0.61–1.26)	0.88 (0.61–1.27)	0.94 (0.65–1.36)	0.85 (0.57–1.28)	0.89 (0.60–1.34)
NO_2	0.95 (0.87–1.04)	0.96 (0.88–1.06)	0.97 (0.88–1.06)	0.92 (0.83–1.02)	0.97 (0.86–1.09)
NO_x	0.96 (0.90–1.03)	0.97 (0.90–1.04)	0.97 (0.90–1.04)	0.95 (0.87–1.02)	0.97 (0.90–1.05)
EC	0.93 (0.78–1.10)	0.94 (0.79–1.12)	0.96 (0.81–1.14)	0.90 (0.74–1.09)	0.96 (0.79–1.17)
OC	0.85 (0.68–1.07)	0.90 (0.71–1.14)	0.98 (0.76–1.26)	0.88 (0.66–1.16)	1.02 (0.75–1.38)
SO_2	1.03 (0.95–1.13)	1.02 (0.93–1.12)	1.01 (0.91–1.11)	1.00 (0.97–1.03)	1.00 (0.89–1.12)
O_3	1.00 (0.97–1.03)	1.00 (0.97–1.03)	1.01 (0.98–1.04)	1.05 (0.94–1.17)	1.00 (0.97–1.04)
SO_4^{2-}	0.82 (0.60–1.11)	0.85 (0.63–1.16)	0.82 (0.60–1.12)	0.73 (0.53–1.02)	0.88 (0.60–1.30)
NO_3^-	0.69 (0.34–1.38)	0.72 (0.36–1.45)	0.67 (0.33–1.36)	0.57 (0.27–1.20)	0.85 (0.37–1.96)
NH_4^+	0.82 (0.56–1.20)	0.83 (0.56–1.22)	0.85 (0.58–1.25)	0.79 (0.53–1.19)	0.91 (0.60–1.39)
SOA	1.17 (0.62–2.22)	1.21 (0.64–2.30)	0.76 (0.34–1.70)	0.68 (0.29–1.58)	0.90 (0.37–2.16)
Sea salt	1.35 (0.89–2.04)	1.26 (0.83–1.91)	1.40 (0.90–2.18)	1.66 (1.04–2.65)	1.31 (0.75–2.29)

[a] Odds ratios (OR) and the 95% CIs from logistic regression models with GEE for fixed increments (μg/m³) of the time-weighted average exposures to ambient air pollutants for the full prenatal period of 5 for $PM_{2.5}$, 10 for PM_{10}, 10 for NO_2, 20 for NO_x, 1 for EC, 1 for OC, 1 for SO_2, 10 for O_3, 1 for SO_4^{2-}, 5 for NO_3^-, 1 for NH_4^+, 1 for SOA, and 1 for sea salt with increasing degrees of adjustment. Asthma refers to active asthma at age 7 and the models for all included (N = 22.084, n = 978).

Model 1: Adjusted for sex and birth year. Model 2: Further adjusted for maternal education, income, and parity. Model 3: Further adjusted for season of birth and maternal smoking during pregnancy. Model 4: Further adjusted for maternal and paternal asthma, pets during pregnancy, house size at birth, breastfeeding, daycare, mold, dampness, ETS, and presence of gas stove, presence of wood stove, and candlelight burning in the home at age 11. Model 5: Further adjusted for municipality.

Associations Between Ambient Air Pollution and Immune and Inflammatory Markers

Table 8 summarizes the effect estimates from linear regression models on cytokines that were measured in nasal mucosal fluid collected from the $COPSAC_{2010}$ children at 4 weeks of age. The effect estimates are expressed as standard deviation changes from the mean level per IQRs of prenatal exposure to ambient air pollution in basic adjusted models. We observed statistically significant associations for several cytokines after multiple-test correction, with primary cytokines contributing to a type 2 response that favors a strong humoral immune response (Table 8). Prenatal exposure to air pollution was associated with decreasing levels of C-C motif chemokine protein (CCL) 22 and CCL26 and increasing levels of interleukins (IL) — IL-5, IL-4, and IL-2.

For the inflammatory markers measured in blood at 6 months of age, prenatal exposure to air pollution was associated with decreasing levels of interleukin-1β (IL-1β) and IL-6 and increasing levels of IL-8 and the proinflammatory tumor necrosis factor-α (TNF-α). Associations for C-reactive protein (CRP) were null.

Associations Between Ambient Air Pollution and Lung Function

Single-Pollutant Models with Different Exposure Windows **Table 9** shows the effect estimates from the linear regression models expressed as RD and 95% CIs — where, for instance, a 0.98 effect estimate corresponds to a 2% reduction — for associations between the IQRs of ambient air pollution and lung function at age 6 (measured as the FEV_1) during the three different time periods — prenatal life, postnatal life from birth to the age of lung function measurement, and a year prior to lung function measurement.

For exposure during the prenatal exposure period and for the long postnatal from birth to age of lung function measurement and the shorter and more recent postnatal exposure periods a year prior to lung function measurement, $PM_{2.5}$, PM_{10}, and NH_4^+ were consistently associated with a small decrease in lung function in adjusted single-pollutant models. The magnitude of these associations was similar across the three different exposure windows. While the negative associations found for $PM_{2.5}$ and NH_4^+ were statistically significant, most of the associations summarized in **Table 9** included the null. The reduction associated with an IQR increase in exposure corresponded to a 1% or 2% decrease in lung function.

Single Pollutant Models with Different Degrees of Adjustment **Table 10** shows the associations between air pollution during the prenatal period and lung function in models with increasing degree of adjustment. Overall, adjustment made no or very little difference in the results.

Two-Pollutant Models **Table 11** shows the associations between air pollution during the prenatal period and lung function in single- and two-pollutant models. The decrease in lung function observed in single-pollutant models for prenatal exposure to $PM_{2.5}$ was robust to mutual adjustment for prenatal exposure to all pollutants, with the exception of PM_{10}, NH_4^+, and SOA where the difference associated with $PM_{2.5}$ attenuated after mutual adjustment. The decrease associated with prenatal exposure to PM_{10} increased, but the correlation between prenatal exposure $PM_{2.5}$ and prenatal exposure PM_{10} was high (*Rs* > 0.8; Appendix Table A4). Mutual adjustment for NO_2 had no effect on the effect estimates of the other copollutants.

DISCUSSION

MAIN FINDINGS

In our large prospective nationwide cohort study of all children born in Denmark, we found statistically significant associations between long-term exposure to air pollution and incidence of asthma. Higher exposure to ambient air pollution with several pollutants was associated with an increased incidence of asthma. Increased rates were evident for exposure during both prenatal and postnatal exposure windows. The children had residential $PM_{2.5}$ and NO_2 annual mean (SD) exposures in their first year of life of 10.3 (1.7) and 16.8 (7.0) ($\mu g/m^3$), respectively, which are below the European Union limit values of 25 and 40 $\mu g/m^3$, respectively. For prenatal exposure to these pollutants, the shapes of the concentration–response curves were linear; whereas, for these pollutants, the postnatal exposure models had steeper slopes at the low concentrations with some leveling off of the risk at the highest concentrations. We noted that for $PM_{2.5}$ and NO_2 and both exposure periods, there was no evidence of a threshold below which no increased risk was observed. The effect estimates of $PM_{2.5}$ were robust in two-pollutant models while the estimated effect of NO_2 attenuated after adjustment for $PM_{2.5}$. We also found that an increase in OC, for which biomass is an important source, was associated with increasing incident asthma risk, irrespective of adjustment for $PM_{2.5}$.

The associations remained in sensitivity analyses and after restriction to children with reported asthma diagnosed at older ages where this diagnosis is more certain. The findings of our study suggest that the adverse effect associated with air pollution was slightly higher for girls than for boys.

In the DNBC cohort study, we observed that exposure to air pollution during prenatal life, first year of life, or early childhood was not associated with prevalence of asthma ever according to parental recall of doctor-diagnoses from birth to age 7. This was also the case for active asthma at age 7 of the children according to parental recall. Higher exposure to $PM_{2.5}$ in the first year of life was, however, consistently associated with elevated ORs for asthma ever and active asthma at age 7, although associations were not statistically significant.

Secondly, in the DNBC cohort study, we found that additional adjustment for cohort-specific covariates available from the children of the DNBC made no difference on the effect estimates for the associations between exposure to ambient

Table 8. Association of Prenatal Exposure to Ambient Air Pollution with Nasal Mucosal Immune Mediators at Age 4 Weeks and Systemic Markers of Inflammation at Age 6 Months in 700 Children Born in Denmark 2008–2010 from the $COPSAC_{2010}$ Cohort [a]

	$PM_{2.5}$ β (95% CI)	PM_{10} β (95% CI)	NO_2 β (95% CI)
Nasal mucosal lining fluid, 4 weeks			
CCL11	**0.06 (-0.10 to 0.22)**	**0.05 (-0.08 to 0.17)**	**0.08 (-0.10 to 0.26)**
CCL13	**0.06 (-0.09 to 0.21)**	0.04 (-0.08 to 0.16)	**0.10 (-0.08 to 0.28)**
CCL17	**-0.03 (-0.17 to 0.11)**	-0.01 (-0.12 to 0.10)	**0.10 (-0.06 to 0.27)**
CCL2	**0.00 (-0.16 to 0.15)**	0.00 (-0.13 to 0.12)	**0.08 (-0.10 to 0.27)**
CCL22	**-0.36 (-0.51 to -0.21)**	**-0.31 (-0.43 to -0.19)**	**-0.33 (-0.51 to -0.16)**
CCL26	**-0.22 (-0.38 to -0.06)**	**-0.21 (-0.34 to -0.09)**	**-0.37 (-0.55 to -0.19)**
CCL4	0.05 (-0.10 to 0.19)	0.02 (-0.09 to 0.13)	**-0.07 (-0.24 to 0.09)**
CXCL10	0.03 (-0.13 to 0.19)	-0.01 (-0.14 to 0.12)	-0.01 (-0.20 to 0.18)
CXCL8	0.04 (-0.12 to 0.20)	0.01 (-0.11 to 0.14)	**-0.10 (-0.28 to 0.09)**
IFN-γ	**0.07 (-0.09 to 0.24)**	0.04 (-0.09 to 0.16)	**0.09 (-0.10 to 0.27)**
IL-10	**-0.09 (-0.25 to 0.07)**	-0.04 (-0.17 to 0.09)	**-0.14 (-0.33 to 0.05)**
IL-12p70	**0.00 (-0.17 to 0.16)**	0.01 (-0.12 to 0.15)	**-0.11 (-0.31 to 0.08)**
IL-13	**0.18 (0.01 to 0.35)**	**0.13 (-0.01 to 0.26)**	**0.07 (-0.13 to 0.26)**
IL-17A	**0.12 (-0.04 to 0.27)**	**0.07 (-0.05 to 0.19)**	**0.10 (-0.08 to 0.28)**
IL-1β	**0.07 (-0.07 to 0.22)**	0.02 (-0.09 to 0.14)	**-0.06 (-0.23 to 0.11)**
IL-2	**0.13 (-0.04 to 0.30)**	**0.14 (0.01 to 0.28)**	0.04 (-0.16 to 0.25)
IL-4	**0.03 (-0.14 to 0.20)**	**0.10 (-0.03 to 0.23)**	**0.36 (0.17 to 0.55)**
IL-5	**0.03 (-0.13 to 0.19)**	**0.16 (0.03 to 0.28)**	**0.26 (0.06 to 0.45)**
TGF-β1	**-0.04 (-0.18 to 0.11)**	**-0.05 (-0.16 to 0.07)**	0.01 (-0.16 to 0.18)
TNF-α	**0.05 (-0.11 to 0.21)**	0.00 (-0.12 to 0.13)	-0.02 (-0.20 to 0.17)
Blood, 6 months			
CRP	**0.00 (-0.17 to 0.17)**	-0.05 (-0.19 to 0.10)	0.00 (-0.26 to 0.27)
IL-1β	**-0.43 (-0.59 to -0.27)**	**-0.45 (-0.59 to -0.31)**	**-0.61 (-0.86 to -0.36)**
IL-6	**-0.06 (-0.23 to 0.11)**	**-0.16 (-0.31 to -0.01)**	**-0.36 (-0.63 to -0.10)**
IL-8	**0.35 (0.18 to 0.51)**	**0.37 (0.23 to 0.51)**	**0.57 (0.32 to 0.82)**
TNF-α	**0.11 (-0.06 to 0.28)**	**0.08 (-0.06 to 0.23)**	**0.15 (-0.11 to 0.41)**

CCL = C-C motif chemokine protein; CRP = C-reactive protein; IFN-γ = interferon-γ; TGF-β1 = transforming growth factor beta 1; TNF-α = tumor necrosis factor-α

[a]Estimates are expressed as standard deviation changes from the mean level per interquartile range (IQR) increase of prenatal exposure to ambient air pollution in models adjusted for season of birth and postnatal exposure from birth to 6 months of age for the systemic inflammatory markers. For this $COPSAC_{2010}$ sample the IQR was 1.5, 2.6, and 8.3 μg/m³ for $PM_{2.5}$, PM_{10}, and NO_2, respectively. Results of further adjusted models are presented elsewhere (Tingskov Pedersen et al. 2023).

$P < 0.05$ are in **boldface**.

air pollution and asthma incidence when we defined asthma using ICD codes. These findings suggest that these variables were unlikely to confound the associations observed in the larger nationwide cohort analyses. Finally, we observed that the estimated effects for asthma incidence (ICD-10) and asthma prevalence according to parental recall were higher among nonmoving children who had the same address from birth to the age 11 follow-up interview, during which the data on their home characteristics was collected, as compared with the children of the study population that included children whose home address changed during that time.

In the preliminary analyses of the COPSAC cohort, we found that exposure to air pollution with $PM_{2.5}$, PM_{10}, and NH_4^+ was associated with a small decrease in the lung function of the children at 6 years of age. The associations for these pollutants were evident for exposure in prenatal, early childhood, and with the annual mean in the year prior to lung function measurement.

Air Pollution and Asthma Incidence

Several studies have evaluated the associations between ambient air pollution and asthma incidence (onset) in children

Table 9. Associations Between Exposure to Air Pollution and Lung Function at Age 6 in 703 Children Born in Denmark 1998–2001 and 2008–2010 from the $COPSAC_{2000\ \&\ 2010}$ Cohorts [a]

Pollutant	Increment IQR (μg/m³)	Prenatal Exposure		Postnatal Exposure of 0–6 Years		Postnatal Exposure of Year Prior[b]	
		RD (95% CI)	*P* value	RD (95% CI)	*P* value	RD (95% CI)	*P* value
$PM_{2.5}$	2.0	0.98 (0.96–1.00)	0.04	0.97 (0.95–0.98)	<0.01	0.98 (0.96–0.99)	<0.01
PM_{10}	2.8	0.99 (0.97–1.00)	0.02	0.99 (0.97–1.01)	0.16	0.99 (0.97–1.01)	0.29
NO_2	8.0	1.00 (0.99–1.01)	0.35	1.00 (0.98–1.01)	0.64	1.00 (0.99–1.01)	0.83
NO_x	13.2	1.00 (0.99–1.00)	0.18	1.00 (0.99–1.00)	0.36	1.00 (0.99–1.01)	0.996
EC	0.3	0.99 (0.99–1.00)	0.19	1.00 (0.99–1.01)	0.65	1.00 (0.99–1.02)	0.60
OC	0.4	0.99 (0.99–1.00)	0.23	1.00 (0.99–1.02)	0.61	1.01 (0.99–1.02)	0.35
SO_2	1.9	0.99 (0.97–1.01)	0.25	0.99 (0.97–1.02)	0.55	0.99 (0.97–1.02)	0.64
O_3	8.1	1.00 (1.00–1.01)	0.27	1.00 (0.99–1.01)	0.90	0.99 (0.98–1.00)	0.20
SO_4^{2-}	0.8	1.00 (0.95–1.04)	0.84	0.96 (0.94–0.98)	<0.01	0.96 (0.95–0.98)	<0.01
NO_3^-	0.6	1.00 (0.98–1.01)	0.39	0.98 (0.97–1.00)	0.07	0.98 (0.97–0.99)	<0.01
NH_4^+	0.4	0.98 (0.96–1.00)	0.046	0.97 (0.95–0.98)	<0.01	0.97 (0.96–0.99)	<0.01
SOA	0.1	1.01 (1.00–1.01)	0.04	0.99 (0.96–1.01)	0.27	0.99 (0.98–1.00)	<0.01
Sea salt	0.1	1.00 (0.99–1.00)	0.35	1.00 (0.99–1.01)	0.69	1.00 (1.00–1.00)	0.60

[a] Relative difference (RD) and the 95% CI refers to forced expiratory volume in the first second (FEV_1) from mixed-effect linear regression models fitted with interquartile range (IQR) values as indicated above and adjusted for cohort, sex, age, height, and weight at the time of examination, maternal income, education, smoking during pregnancy, ETS during pregnancy and first six years of life, breastfeeding, exposure to furry animals during first six years of life and use of fireplace, gas cooking, and fume hood during the first year of life.

[b] The year prior to the lung function measurement.

(**Table 12**). The certainty of the evidence for an association between TRAP exposure and asthma incidence in children has recently been assessed to be moderate to high (HEI 2022). Out of these recently reviewed studies on TRAP and asthma in children, a total of 12 studies that evaluated associations between long-term perinatal exposure to NO_2 and asthma incidence were meta-analyzed. The pooled effect estimate of those meta-analyses (1.05 [95% CI: 0.99–1.12] per 10-μg/m³ increase in perinatal exposure to NO_2) (HEI 2022) was similar to the effect estimate observed in a study by Pedersen and colleagues (2023) (1.05 [1.02–1.06] per 10-μg/m³ increase in prenatal exposure). The certainty of the evidence for NO_2 and asthma incidence was high (HEI 2022). Most of the individual studies included in the meta-analyses reported elevated effect estimates in association with NO_2 (Carlsten et al. 2011; Clougherty et al. 2007; Gehring et al. 2010, 2015b; Jerrett et al. 2008; Krämer et al. 2009; Lavigne et al. 2018, 2019; Ranzi et al. 2014; Tétreault et al. 2016), but the reported associations from the individual studies often was not statistically significant. The lack of consistency across different exposures and exposure periods that were evaluated also added to the uncertainty; and a few of the included studies reported inverse associations (Oftedal et al. 2009; Sbihi et al. 2016).

There are fewer studies on $PM_{2.5}$ and asthma incidence. The pooled effect estimate of the meta-analyses of the five studies included in the most recent HEI report that evaluated perinatal exposure to $PM_{2.5}$ and asthma incidence in children (Carlsten et al. 2011; Gehring et al. 2010, 2015b, Lee et al. 2018; Sbihi et al. 2016) was 1.33 (95% CI: 0.90–1.98) per 5-μg/m³ increase (HEI 2022). This is higher than the effect estimate observed in our study (Table 2, in which 1.06 (1.04–1.08) when recalculated from a per 2.4-μg/m³ to a per 5-μg/m³ increase in prenatal exposure corresponds to an HR of 1.13 [1.09–1.17]). The certainty of the evidence for $PM_{2.5}$ and asthma incidence was evaluated to be very low, but there are several new studies on asthma incidence in children and adolescents published after July 2019 that were not included in this evaluation (Gehring et al. 2020; Holst et al. 2020; Lavigne et al. 2021; Olsson et al. 2021) (see Table 12), which are further discussed later in the report.

Most of the evidence of effects of exposure to air pollution on asthma development in children come from cohort studies that relied on parental recall of a doctor-diagnosis of asthma and lack information on the precise time of onset (HEI 2022). There are a few studies based on objective asthma outcome data collected from administrative health, medicine, and

Table 10. Associations between Prenatal Exposure Air Pollution and Lung Function at Age 6 in 703 Children Born in Denmark 1998–2001 and 2008–2010 from the $COPSAC_{2000\ \&\ 2010}$ Cohorts with Increasing Level of Adjustment for Confounders [a]

Pollutant	Increment IQR (μg/m³)	Model 1 RD (95%CI)	*P* value	Model 2 RD (95%CI)	*P* value	Model 3 RD (95%CI)	*P* value
$PM_{2.5}$	2.0	0.98 (0.97–1.00)	0.05	0.98 (0.96–1.00)	0.03	0.98 (0.96–1.00)	0.04
PM_{10}	2.8	0.99 (0.97–1.00)	0.04	0.99 (0.97–1.00)	0.03	0.99 (0.97–1.00)	0.02
NO_2	8.0	1.00 (0.99–1.01)	0.42	1.00 (0.99–1.01)	0.34	1.00 (0.99–1.01)	0.35
NO_x	13.2	1.00 (0.99–1.00)	0.22	1.00 (0.99–1.00)	0.18	1.00 (0.99–1.00)	0.18
EC	0.3	1.00 (0.99–1.00)	0.21	0.99 (0.99–1.00)	0.17	0.99 (0.99–1.00)	0.19
OC	0.4	1.00 (0.99–1.00)	0.24	1.00 (0.99–1.00)	0.24	0.99 (0.99–1.00)	0.23
SO_2	1.9	0.99 (0.97–1.01)	0.35	0.99 (0.97–1.01)	0.24	0.99 (0.97–1.01)	0.25
O_3	8.1	1.00 (1.00–1.01)	0.35	1.00 (1.00–1.01)	0.27	1.00 (1.00–1.01)	0.27
SO_4^{2-}	0.8	0.99 (0.94–1.04)	0.72	0.99 (0.95–1.04)	0.79	1.00 (0.95–1.04)	0.84
NO_3^-	0.6	0.99 (0.98–1.01)	0.33	1.00 (0.98–1.01)	0.38	1.00 (0.98–1.01)	0.39
NH_4^+	0.4	0.98 (0.96–1.00)	0.07	0.98 (0.96–1.00)	0.04	0.98 (0.96–1.00)	0.046
SOA	0.1	1.01 (1.00–1.01)	0.055	1.01 (1.00–1.01)	0.045	1.01 (1.00–1.01)	0.04
Sea salt	0.1	1.00 (0.99–1.00)	0.34	1.00 (0.99–1.00)	0.35	1.00 (0.99–1.00)	0.35

[a] Relative difference (RD) and the 95% CI refers to forced expiratory volume in the first second (FEV_1) from mixed-effect linear regression models with increasing degree of adjustment with interquartile range (IQR) values of exposure as indicated above.

Model 1 is adjusted for cohort, sex, age, height, and weight at the time of examination. Model 2 is further adjusted for maternal income, education, smoking during pregnancy, ETS during pregnancy and first six years of life and duration of breastfeeding. Model 3 is further adjusted for use of exposure to furry animals during first six years of life and fireplace, gas cooking and fume hood during the first year of life.

insurance registries from Canada (Clark et al. 2010; Lavigne et al. 2018, 2019, 2021; Sbihi et al. 2016; Tétreault et al. 2016), the United States (Pennington et al. 2018), Sweden (Lindgren et al. 2013; Olsson et al. 2021; Oudin et al. 2017), and Denmark (Holst et al. 2018, 2020). These administrative health register-based studies rely on different study designs and methods in terms of the exposure assessment, availability of covariates, methods used for the statistical analyses, the length of follow up, and the asthma definitions used, all of which make direct comparison difficult. Some of the previous studies have used different combinations of asthma diagnosis with asthma-related medication dispensing (Holst et al. 2020; Pennington et al. 2018). Other studies have defined cases from asthma-related medication dispensing only (Lindgren et al. 2013; Oudin et al. 2017). The different asthma definitions applied are likely to capture different phenotypes of asthma with different severity. Especially when children of a wide range of ages are included, definition based on asthma-related medication dispensing is a more heterogenous outcome than are medical records of asthma diagnosis.

There are eight studies that have identified childhood asthma cases from administrative databases of doctor-based ICD diagnosis only that have evaluated the associations between perinatal exposure to air pollution and asthma incidence, which we consider the most similar to our nationwide study (Clark et al. 2010; Holst et al. 2018; Lavigne et al. 2018, 2019, 2021; Olsson et al. 2021; Sbihi et al. 2016; Tétreault et al. 2016).

Most recently, Olsson and colleagues (2021) have estimated exposure to air pollution at the address level using a very similar modeling approach as that in our study with the DEHM-UBM models with resolution 1 × 1 km (Frohn et al. 2022), but without the hyperlocal assessment by OSPM, for a population of singletons born in Stockholm, Sweden, 2006–2013. Out of 184,253 children who were followed 3–6 years, 20,920 asthma cases were identified from a hospital diagnosis of asthma using ICD-10 codes from in-patient and out-patient care. Children who had been diagnosed only at the primary health care were not included as cases. The associations for prenatal exposure and postnatal exposure during the first year of life were all close to null, while HR was 1.06 (95% CI: 1.01–1.10), 1.03 (0.97–1.09), and 1.05 (1.02–1.09) for an IQR of 1-, 0.2- and 0.03-μg/m³ increases in $PM_{2.5}$, EC, and primary OC, respectively, for the most adjusted models fitted with fixed exposure mean concentration of the first three years of life. While the findings for prenatal exposure differed from those of our study, the results for the first three years

Table 11. Associations between Prenatal Exposure to Air Pollution and Lung Function at Age 6 in 703 Children Born in Denmark 1998–2001 and 2008–2010 from the $COPSAC_{2000\ \&\ 2010}$ Cohorts in Single- and Two-Pollutant Models [a]

		Two-Pollutant Models			
Pollutant	Single-Pollutant Models RD (95%CI)	Adjusted for $PM_{2.5}$ RD (95%CI)	$PM_{2.5}$ Mutually Adjusted RD (95%CI)	Adjusted for NO RD (95%CI)	NO_2 Mutually Adjusted RD (95%CI)
$PM_{2.5}$	0.98 (0.96–1.00)	–	–	0.98 (0.95–1.00)	1.00 (0.99–1.02)
PM_{10}	0.99 (0.97–1.00)	0.98 (0.94–1.01)	1.01 (0.96–1.07)	0.98 (0.96–1.00)	1.01 (0.99–1.02)
NO_2	1.00 (0.99–1.01)	1.00 (0.99–1.02)	0.98 (0.95–1.00)	–	–
NO_x	1.00 (0.99–1.00)	1.00 (0.99–1.01)	0.98 (0.96–1.01)	0.99 (0.97–1.01)	1.01 (0.98–1.04)
EC	0.99 (0.99–1.00)	1.00 (0.99–1.02)	0.98 (0.95–1.00)	0.99 (0.97–1.01)	1.01 (0.98–1.03)
OC	0.99 (0.99–1.00)	1.00 (0.99–1.01)	0.98 (0.96–1.00)	1.00 (0.99–1.00)	1.00 (0.99–1.01)
SO_2	0.99 (0.97–1.01)	1.00 (0.98–1.02)	0.98 (0.96–1.00)	0.99 (0.97–1.01)	0.99 (0.97–1.01)
O_3	1.00 (1.00–1.01)	1.00 (0.99–1.01)	0.98 (0.95–1.00)	1.00 (0.99–1.02)	1.00 (0.99–1.02)
SO_4^{2-}	1.00 (0.95–1.04)	1.03 (0.97–1.10)	0.98 (0.96–1.00)	1.00 (0.95–1.05)	1.00 (0.95–1.05)
NO_3^-	1.00 (0.98–1.01)	1.00 (0.99–1.01)	0.98 (0.96–1.00)	0.99 (0.98–1.00)	0.99 (0.98–1.00)
NH_4^+	0.98 (0.96–1.00)	0.99 (0.97–1.01)	0.99 (0.96–1.01)	0.98 (0.96–0.99)	0.98 (0.96–0.99)
SOA	1.01 (1.00–1.01)	1.01 (1.00–1.01)	0.99 (0.97–1.00)	1.01 (1.00–1.01)	1.00 (0.99–1.02)
Sea salt	1.00 (0.99–1.00)	1.00 (0.99–1.00)	0.98 (0.96–1.00)	1.00 (0.99–1.00)	1.00 (0.99–1.00)

[a] Relative difference (RD) and the 95% CI refers to forced expiratory volume in the first second (FEV_1) from linear regression models fitted with increments of the interquartile range (μg/m³) of the time-weighted average exposures to ambient air pollutants for the full prenatal period of 2.0 for $PM_{2.5}$, 2.8 for PM_{10}, 8.0 for NO_2, 13.2 for NO_x, 0.3 for EC, 0.4 for OC, 1.9 for SO_2, 8.1 for O_3, 0.8 for SO_4^{2-}, 0.6 for NO_3^-, 0.4 for NH_4^+, 0.1 for SOA, and 0.1 for sea salt with adjustments for cohort, sex, age, height, and weight at the time of examination, maternal income, education, smoking during pregnancy, ETS during pregnancy and first six years of life, breastfeeding, exposure to furry animals during first six years of life and use of fireplace, gas cooking, and fume hood during the first year of life.

of life were very similar to the findings from our study. The mean exposure to $PM_{2.5}$ during the first three years of life was 7.4 μg/m³, which is lower than the mean concentration of our study (Table 2).

No evidence of an association between growing up close to traffic and higher incidence of asthma in the children ages 0–6 was reported in another study with 7,898 children born between 2005 and 2009 in Scania, Sweden (Lindgren et al. 2013). The results were similar for prenatal and postnatal exposure to traffic density and NO_x estimated at the residential home addresses using a dispersion model. Two different definitions of asthma were evaluated based on register-based diagnosis of asthma and inhaled asthma medication.

A similar ICD-10 based definition has also been used to identify 12,935 cases of asthma within the first 6 years of life for a case-control study of children born between 2000 and 2011 in Denmark to Danish-born parents (Holst et al. 2018). The DEHM model with a resolution of 5.6 × 5.6 km, but without UBM and the hyperlocal assessment by OSPM, was used to estimate the concentration of $PM_{2.5}$, NH_3^-, NH_4^+, and total inorganic ammonia three months prior to asthma diagnosis. Elevated effect estimates were indicated in models without adjustment for region, but not after adjustment for region. In our study, we observed elevated risk for asthma for $PM_{2.5}$ and NH_4^+ after more comprehensive adjustments that included maternal smoking and municipality. The differences in our findings might reflect the methodological differences in study design, exposure periods, methods used for exposure assessment, adjustment, and statistical analyses in these studies.

A number of similar studies have also been conducted in Canada. Clark and colleagues (2010) used a nested case-control design to examine the association between prenatal and postnatal exposure to air pollution in the first year of life and asthma incidence in children up to 3 and 5 years of age among all births from southwestern British Columbia in 1999–2000. A total of 3,482 asthma cases defined as children with a minimum of two primary care diagnoses within a year or a minimum of one hospital admission for asthma was identified out of 37,401 children.

The adjusted OR was 1.02 (95% CI: 1.00–1.03) and 1.01 (0.99–1.03) for a 1-μg/m³ increase in prenatal and postnatal exposure to $PM_{2.5}$, respectively, for exposure estimated with LUR, while prenatal exposure to $PM_{2.5}$ was not associated with increased asthma risk and the 95% CIs were wider for post-

Table 12. Summary of the Recent Studies Published and Meta-Analysis on the Associations between Long-Term Exposure to Ambient Air Pollution Exposure and Asthma Incidence in Children.

Exposure Pollutant, Exposure Assessment, Increment, Country	Outcome Definition, Age, Study Design	Adjusted Results for Prenatal Exposure (or mix of prenatal and postnatal)[a]	Reference
$PM_{2.5}$			
LUR, 5 µg/m³, multiple countries	Mix of parental records and register-based 0–16 years Random-effect meta-analyses	1.33 (0.90–1.98); 67%, 0.02; 5 studies; 70,019 children	HEI 2022
DEHM-UBM model, 1.47 (prenatal), 1.06 (first year of life) and 1.02 (first 3 years of life) µg/m³, Sweden	ICD-10, register-based, 3–6 years Cohort	All, prenatal exposure: 1.01 (0.97–1.05); 20,920 cases All, first year of life annual exposure: 1.00 (0.97–1.04); 20,920 cases All, postnatal exposure during first 3 years: 1.06 (1.01–1.10); 20,920 cases ≥3 years of age, postnatal exposure during first 3 years: 1.10 (1.01–1.21); 544 cases	Olsson et al. 2021
Chemical transportation models and remote sensing, 1 µg/m³, Canada	ICD-10, register-based, 0–6 years Cohort	All, postnatal exposure: 1.03 (1.02–1.03); 167,080 cases, 1,130,855 children	Lavigne et al. 2021
LUR, 1.2 µg/m³, the Netherlands (PIAMA)	Parental records of doctor-diagnosed asthma, wheeze and medicine in the past 12 m, 0–20 years Cohort	Birth address: 1.15 (1.02–1.30), 3,141 children Current address: 1.19 (1.04–1.36), 3,191 children	Gehring et al. 2020
DEHM-UBM model, 5 µg/m³, Denmark	Mix of ICD-10 and medicine, register-based, 0–15 years Case-control	All, postnatal: 1.05 (1.03–1.07); 122,842 cases <6 years of age: 1.05 (1.03–1.07); NA ≥6 years of age: 1.08 (0.99–1.16); NA	Holst et al. 2020
LUR, 5 µg/m³ ESCAPE, England (BIB), France (Eden), Italy (GASPII), Greece (RHEA), Spain (INMA)	Parental records of doctor-diagnosed asthma, wheeze and medicine in the past 12 m, 0–8 years Random-effect meta-analyses	4 years of age, birth address: 0.88 (0.54–1.54); 68%; 0.005; 7 studies; 5,600 children 8 years of age, birth address: 0.65 (0.35–1.21); 39%; 0.16; 5 studies; 2,150 children	Fuertes et al. 2020
NO_2			
LUR, dispersion models, surface monitoring, 10 µg/m³, multiple countries	Mix of parental records and register-based 0–16 years Random-effect	1.05 (0.99–1.12); 73%, $P < 0.01$; 12 studies; 1,312,985 children	HEI 2022
LUR, 9.2 µg/m³, the Netherlands (PIAMA)	Parental records of doctor-diagnosed asthma, wheeze and medicine in the past 12 m, 0–20 years Cohort	Birth address: 1.20 (1.10–1.32), 3,141 children Current address: 1.15 (1.04–1.27), 3,191 children	Gehring et al. 2020
LUR, 10 µg/m³ ESCAPE, England (BIB), France (Eden), Italy (GASPII), Greece (RHEA), Spain (INMA)	Parental records of doctor-diagnosed asthma, wheeze and medicine in the past 12 m, 0–8 years Random-effect meta-analyses	4 years of age, birth address: 0.91 (0.74–1.11); 49%; 0.067; 7 studies; 5,600 children 8 years of age, birth address: 0.94 (0.65–1.35); 69%; 0.013; 5 studies; 2,150 children	Fuertes et al. 2020
DEHM-UBM, 10 µg/m³, Denmark	Mix of ICD-10 and medicine, register-based, 0–15 years Case-control	All, postnatal: 1.04 (1.03–1.04); 122,842 cases < 6 years of age: 1.03 (1.02–1.04); N/A ≥ 6 years of age: 1.16 (1.11–1.22); N/A	Holst et al. 2020

BIB = Born in Bradford; GASPII = Gene and Environment Prospective Study in Italy; INMA = Infancia y Medio Ambiente; PIAMA = Prevention and Incidence of Asthma and Mite Allergy; RHEA = is inspired by the name of the mythological wife of Kronos (Cronus).

[a] Summary OR (95% CI); I^2 statistics provides an estimate of the variance that is due to heterogeneity; *P* for heterogeneity; number of studies; total approximate size.

natal exposure for exposures estimated with inverse-distance weighting (0.95 [95% CI: 0.91–1.00] and 1.05 [0.97–1.14]) (Clark et al. 2010). For exposure estimated with LUR, both prenatal and postnatal exposure to EC as well as postnatal exposure to NO_2 was significantly associated with increased asthma risk, but associations for prenatal exposure to NO_2 did not reach statistical significance. For NO_2 estimated from the LUR model, the adjusted ORs were 1.02 (95% CI: 0.97–1.07) and 1.13 (1.04–1.23), and the corresponding adjusted ORs were 1.10 (1.05–1.15) and 1.12 (1.07–1.17) for NO_2 estimated by inverse-distance weighting per 10-μg/m^3 increase in prenatal and postnatal exposure to NO_2, respectively.

Sbihi and colleagues (2016) expanded the study by Clark and colleagues (2010) to include children born between 1999 and 2002 and used a similar design, asthma definition, exposure assessment, and statistical methods. Out of the 65,254 children, 6,948 cases during preschool and 1,711 cases during school age were identified. Results for prenatal exposure in relation to asthma incidence during preschool and school age were reported. For exposures estimated with LUR, prenatal exposure to NO_2 and $PM_{2.5}$ was not associated with an elevated risk in preschool children or risk of incident asthma in children for whom asthma was only evident from age 6 (Sbihi et al. 2016). NO_2 was also estimated with inverse-distance weighting; this estimate was associated with elevated asthma among preschool children only (Sbihi et al. 2016). In our study we observed that the associations between prenatal exposure to air pollution were robust to restriction to children with asthma after age 4 (Appendix Table A6), and this was also the case when we restricted to the children for whom asthma was only evident from age 4 (results not shown).

Tétreault and colleagues (2016) have examined associations between air pollution and asthma incidence in a large cohort of children born in Québec from 1996 to 2011 at maternal residential postal code levels at birth. A total of 162,752 asthma cases — that were defined as children with a minimum of two physician claims for asthma (ICD codes) from an emergency department or physicians' offices within a 2-year period, or a minimum of one hospital admission for asthma — were identified out of 1,183,865 children. Perinatal exposure to NO_2 estimated by LUR and $PM_{2.5}$ exposure from satellite imagery were associated with elevated asthma risk (Tétreault et al. 2016). Associations were also observed for time-varying exposure. Associations for NO_2 were not evident in models adjusted for social and material deprivation. Similar to the findings of our study, the associations were more robust for $PM_{2.5}$ than for NO_2. This may indicate that the observed associations are driven by exposure to air pollution from sources more widely distributed than primarily traffic-related emissions. Our effect estimates are in line with the reported HR of 1.04 (95% CI: 1.01–1.06) per 5.5-ppb increase of NO_2 and 1.04 (1.02–1.06) per 1-μg/m^3 increase of $PM_{2.5}$ for the subset of 218,298 children from the Montreal Island from models adjusted for year of birth, sex, social and material deprivation, and indirectly for ETS. In models without indirect adjustment for ETS, an HR of 0.99 (0.97–1.01) per 5.5-ppb increase of NO_2 and 1.32 (1.30–1.33) per 6.5-μg/m^3 increase of $PM_{2.5}$ was reported. For $PM_{2.5}$ this model included a larger population of 1,133,938 children.

In a similar Canadian study by Lavigne and colleagues (2018), $PM_{2.5}$ exposure was estimated at maternal residential postal code levels during pregnancy and childhood from satellite surfaces, and NO_2 exposure was estimated from a temporal-adjusted LUR for all live-born singletons born during 2006–2012 in the Province of Ontario. The children were followed from birth to 6 years of age. Out of the 761,172 children, 110,981 asthma cases were identified according to a minimum of two physician claims for asthma (ICD codes) within a 2-year period and/or a minimum of one hospital admission for asthma. Similar to our study for prenatal exposure, an IQR with an 8.6-μg/m^3 increase in NO_2 was associated with an HR of 1.09 (95% CI: 1.07–1.12). The HR was 1.02 (0.99–1.04) for an IQR with a 3.7-μg/m^3 increase of $PM_{2.5}$, but in contrast to the findings in our study, exposure during the first year of life and during childhood was not found to be consistently associated with asthma incidence in this Canadian study. For NO_2, the HRs for the first year of life and childhood exposure, respectively, were 1.08 (1.06–1.09) and 0.99 (0.98–1.00); for $PM_{2.5}$ they were 1.00 (0.98–1.02) and 1.00 (1.00–1.01). Lavigne and colleagues (2018) reported that exposure during the first year of life was not associated with childhood asthma development before, and also after, adjustment for prenatal exposure, contrary to the findings in our study (Table 2). A few studies (e.g., the current report and Lavigne et al. 2018) have attempted to mutually adjust exposure during prenatal and postnatal exposure, but results are not consistent. Especially for relatively short exposure periods, such as prenatal and the annual mean concentration of the first year of life, the high correlation between the exposures may complicate the interpretation. In a recent study based on the same methods and data as in Lavigne and colleagues (2018) that included children born up till 2014, the number of cases was 167,080 out of 1,130,855 children with an HR of 1.03 (95% CI: 1.02–1.03) per 1-μg/m^3 increase of $PM_{2.5}$ in childhood exposure (Lavigne et al. 2021).

We found that in addition to total mass concentration of PM, exposure to air pollution with major components of PM such as OC, EC, NO_3^-, and NH_4^+ was also associated with an elevated risk of asthma incidence (Table 2), which was also observed by Lavigne and colleagues (2021). Interestingly, they also fitted a multiple-component model and estimated that the effects of $PM_{2.5}$ on childhood asthma incidence was 24% higher than when estimated from traditional approaches that examined the effects estimates from single-pollutant models.

Another large population-based study by Lavigne and colleagues (2019) estimated ultrafine particles (UFP) and $PM_{2.5}$ exposure at maternal residential postal code levels during pregnancy and childhood from satellite surfaces and estimated NO_2 from a temporal-adjusted LUR for all live-born singletons born between 2006 and 2012 in Toronto, Canada. The children were followed from birth to 6 years of age. Out

of the 160,641 children, 27,062 asthma cases were defined according to a minimum of two physician claims for asthma (ICD codes) within a 2-year period and/or a minimum of one hospital admission for asthma. In this study, the HR was 1.02 (95% CI: 0.98–1.06) for an IQR of 9.7-μg/m^3 increase in NO_2, 1.03 (1.00–1.06) for an IQR of 3.8-μg/m^3 increase of $PM_{2.5}$, and 1.03 (0.99–1.07) for an IQR of 10,820-counts/cm^3 increase in UFPs for prenatal exposure. The effect estimates for childhood exposure were 1.01 (0.97–1.05) per 8.7-μg/m^3 increase in NO_2, 1.02 (0.99–1.05) per 3.4-μg/m^3 increase in $PM_{2.5}$, and 1.03 (1.00–1.06) per 10,551-counts/cm^3 increase in UFPs. Lavigne and colleagues (2019) also reported two- and three-pollutant models. For prenatal exposures, the findings are similar to those from our study, where the association with NO_2 was attenuated after adjustment for prenatal exposure to $PM_{2.5}$, whereas the association of $PM_{2.5}$ was robust to adjustment for NO_2. For prenatal exposure to UFPs, associations attenuated after mutual adjustment for NO_2 and $PM_{2.5}$.

Pennington and colleagues (2018) have also provided evidence of associations between air pollution and asthma incidence from a study of 24,608 children from ages 2 to 6 using Kaiser Permanente Health Maintenance Organization data from Atlanta, Georgia, USA. Dispersion models were used to estimate prenatal and first-year-of-life exposure. Asthma was defined as at least one diagnosis and one asthma-related medication including steroid and nonsteroid controllers and relievers after the first year of life in the main analyses, but effect estimates associated with $PM_{2.5}$ were consistently elevated for 13 other definitions of asthma evaluated. The largest risk difference of 5.1% (95% CI: 2.6%–7.7%) per natural log increase in $PM_{2.5}$ was found for defining asthma as one diagnosis only, as used in our study, or two medication dispensings, one of which must be a steroid.

Additional Asthma Incidence Studies Based on Different Asthma Definitions

We made the decision to not include medication dispensings in our main asthma definition as many children with respiratory symptoms, especially infants, are prescribed asthma medications once. Similarly, to avoid misclassification of children with unspecific respiratory symptoms as asthmatic, at least two dispensings of asthma medications may be used. For instance, this definition has been used to define asthma in a Swedish study of all individuals under age 18 with residence in a large area of four counties (n = 745,171), among whom an OR of 1.02 (95% CI: 1.01–1.03) for a 10-μg/m^3 increase in annual NO_2 was found (Oudin et al. 2017).

A recent case-control study from Denmark defined cases as children with asthma diagnosis (ICD codes) obtained from the DNPR and/or at least two medication dispensings to study the associations between air pollution and asthma and persistent wheeze in children born from 1997 to 2014 to Danish-born parents (Holst et al. 2020). The associations for air pollution presented in this study was most robust for $PM_{2.5}$; an OR of 1.05 (95% CI: 103–1.07) per 5-μg/m^3 increase in $PM_{2.5}$ and 1.04 (1.03–1.04) per 10-μg/m^3 increase in NO_2 was reported.

Our results for asthma incidence are also in agreement with the evidence from the cohort studies that have linked NO_2 air pollution exposure with incident asthma that is defined by positive parental or child recall of doctor-diagnoses in questionnaire-based follow up. This includes (1) the Children's Health Study (CHS) in Southern California with follow up three years after enrollment of 2,497 children (McConnell et al. 2010) and at ages 10–18 of 208 (Gauderman et al. 2005) and 217 children (Jerrett et al. 2008); (2) the Netherlands Prevention and Incidence of Asthma and Mite Allergy (PIAMA) birth cohort studies with annual follow up of 3,863 children during the first eight years and every three years after age 8 until age 20 (Gehring et al. 2010, 2013, 2020); and (3) the pooled ESCAPE study on asthma up to ages 14–16 that included 14,126 children from the Dutch PIAMA, the Swedish BAMSE (Barn, Allergi, Miljö, Stockholm och Epidemiologi), the German GINI (German Infant Nutritional Intervention), and LISA (Influences of Lifestyle related Factors on the Immune System and the Development of Allergies in Childhood) cohorts (Gehring et al. 2015a). In this study asthma was defined as a positive reply to at least two of the following three questions: (1) *Has a doctor ever diagnosed asthma in your child?* (2) *Has your child had wheeze or whistling in the chest the last 12 months?* (3) *Has your child been prescribed asthma medication during the last 12 months?* The overall effect estimate for incident asthma was 1.13 (95% CI: 1.02–1.25) per 10-μg/m^3 increase in annual NO_2 and 1.25 (0.94–1.66) per 5-μg/m^3 increase in $PM_{2.5}$ at the birth address from the meta-analyses of these studies. Associations were attenuated for models with exposure at the current address at the time of the follow up (Gehring et al. 2015a).

In our study the two-pollutant models suggested that associations with $PM_{2.5}$ were robust against adjustment for NO_2, while in the Dutch PIAMA cohort associations for PM diminished or disappeared after adjustment for NO_2 (Gehring et al. 2020).

A few of these studies have evaluated the shape of the concentration–response curves. When the air pollutants were entered as quartiles of exposure into the model, the trend across quartiles was consistently linear for prenatal exposure to NO_2, but not for postnatal exposure to NO_2 in the Canadian study (Clark et al. 2010). The shape of the concentration–response curve reported for the Canadian study for prenatal exposure to $PM_{2.5}$ reported by Lavigne and colleagues (2021) looked similar to the linear exposure–response curve observed in our study (Figure 4). Evidence of a linear concentration–response relationship between prenatal exposure to UFPs during the second trimester and asthma incidence in children up to age 6 was also presented by Lavigne and colleagues (2021). Quintile and graphical presentations of log-linear concentration–response curves have also suggested that the change in risk was greatest at the lower concentration ends, which suggests a supralinear shape of the concentration–response relationship (Pennington et al. 2018).

As observed in other studies, boys had a higher incidence of asthma in our study; however, in our study we found that associations were more elevated for girls. Similar to the observations in our study (Appendix Table A8), regressions stratified by sex also revealed that the effect estimates for $PM_{2.5}$ were consistently higher for girls than for boys in the case-control study on asthma and persistent wheeze from Denmark (Holst et al. 2020), in the Canadian studies of asthma incidence in children age 3–5 (Clark et al. 2010; Sbihi et al. 2016), and in the study of children from Atlanta, Georgia, USA (Pennington et al. 2018). However, confidence intervals were overlapping, and somehow stronger associations for boys or no evidence of effect modification by sex on associations with air pollution have also been reported (Fuertes et al 2020; Gehring et al. 2002, 2015b; Lavigne et al. 2018, 2019; Mölter et al. 2015; Tétreault et al. 2016).

Air Pollution and Asthma Prevalence

Given the growing evidence of adverse effects of long-term exposure to air pollution on asthma development in children, our observed null findings for asthma prevalence according to parental recall in the DNBC study are more difficult to reconcile.

The findings of our studies with asthma incidence defined from ICD-10 codes pointed toward adverse association, both those of the nationwide cohort (Tables 2–4) and the DNBC (Table 5), whereas our studies with asthma prevalence defined from parental recall were null or pointed in the other direction, although confidence intervals were wide and included the null (Tables 6–7). A possible explanation could be that parental recall of asthma in children at age 7, as in the DNBC, reflect a more heterogeneous outcome than the ICD-10-based definition we used to define asthma incidence for children and adolescence in a country like Denmark.

Many studies have reported associations between long-term exposure to air pollution and asthma prevalence in children. A total of 45 studies on TRAP and asthma prevalence according to parental or child recall was recently reviewed (HEI 2022). Out of these studies, the associations between NO_2 and prevalence of asthma ever at any age were meta-analyzed for 21 studies, resulting in a pooled effect estimate of 1.09 (95% CI: 1.01–1.18) per 10-μg/m^3 increase in NO_2 (HEI 2022). The individual effect estimates of the majority of these studies were elevated, but the associations were often not statistically significant, and a few studies have reported null or inverse associations. For prevalent asthma ever and $PM_{2.5}$, only three studies were meta-analyzed; the pooled effect estimate of the meta-analyses was 1.29 (0.58–2.87) per 5-μg/m^3 increase in $PM_{2.5}$. The overall evidence for asthma ever prevalence in children was assessed to be moderate for TRAP and NO_2 exposure and very low for $PM_{2.5}$ (HEI 2022). For active asthma and NO_2, the findings from 12 studies were meta-analyzed, resulting in a pooled effect estimate of 1.12 (1.02–1.23) per 10-μg/m^3 increase in NO_2. There were too few studies for $PM_{2.5}$. The majority of the studies have reported elevated effect estimates with confidence intervals including the null, and a few have reported null and inverse associations. The overall evidence for active asthma prevalence in children was assessed to be moderate for TRAP and NO_2 (HEI 2022).

Although our observed null findings for asthma prevalence are in conflict with the findings of most other published studies, not all published studies based on parental recalls of asthma prevalence in children provide evidence of an adverse effect of air pollution on asthma prevalence (Fuertes et al. 2020; HEI 2022; Mölter et al. 2015; Ranzi et al. 2014). Indeed our findings for NO_2 and asthma prevalence are in line with the more recently published findings of two previous meta-analyses of European birth cohort data (Fuertes et al. 2020; Mölter et al. 2015). These studies rely on a harmonized study design with recruitment of the cohort participants between 1994 and 2011 and the ISAAC questionnaire to collect information on asthma and asthma-symptoms. Their ages for follow up, asthma definitions, statistical methods and adjustment are all similar to those used in our DNBC study. Apart from covering different regions of Europe, a main difference with our study is the exposure assessment methods used. We used the DEHM-UBM-AirGIS models while the other European birth cohorts have mainly used the same harmonized area-specific LUR developed from air sampling campaigns as part of the ESCAPE project. A strength of these studies is that the harmonized approach allowed pooling of the cohorts, which increases the size and variation in exposure. A limitation was that these air sampling campaigns were carried out only in 2009, which was several years after the births for most of these children and did not coincide with the exposure period during the prenatal and early life, which added uncertainty to their assessment of the exposure.

Lack of evidence has been reported for active asthma prevalence defined from parental recall from birth until 4 and 8 years of age in children from five other European birth cohorts from: (1) England, Born in Bradford (BiB); (2) France, Étude des Déterminants pré et postnatals du développement de la santé de l'enfant (EDEN); (3) Italy the Gene and Environment: Prospective Study on Infancy in Italy cohort (GASPII); (4) Greece (RHEA); and (5) Spain, Infancia y Medio Ambiente (INMA) (Fuertes et al. 2020). For exposure at the birth address in relation to active asthma at age 8, the pooled effect estimate from the meta-analyses of these five cohorts with 2,320 children was 0.94 (95% CI: 0.65–1.35) for a 10-μg/m^3 increase in NO_2 and 0.65 (0.35–1.21) for a 5-μg/m^3 increase in $PM_{2.5}$. The pooled effect estimates were similar for active asthma at age 4 and for exposure at the address at the follow-up time. For doctor-diagnosed asthma ever at age 8, only, were the pooled effect estimates consistently elevated for exposure at both the birth and the current address at age 8. However, none of the associations reached statistical significance, and elevated effect estimates were only observed in some, but not all cohorts.

Although most of the effect estimates were elevated, a lack of statistically significant associations between long-term exposure to air pollution and active asthma prevalence

defined by parental recall of doctor-diagnoses, wheeze, and medication (as in our study) has been observed for the children who were followed until 10 years of age in these five European birth cohorts: (1) England, (MAAS, Manchester Asthma and Allergy Study); (2) Sweden (BAMSE); (3) the Netherlands (PIAMA); (4 & 5) Germany (GINI and LISA) (Mölter et al. 2015). For exposure at the birth address and asthma ever at age 8, the pooled effect estimate from the meta-analyses of these children was 1.10 (95% CI: 0.81–1.49) for a 10-μg/m^3 increase in NO_2 and 1.23 (0.78–1.95) for a 5-μg/m^3 increase in $PM_{2.5}$. Effect estimates greater than one were observed in three out of the five cohorts and most of the cohort-specific associations were not statistically significant. Lack of evidence for an association between air pollution with NO_2 and PM_{10} and infant asthma and asthma-related outcomes was also found in a study of the French EDEN cohort (Pedersen et al. 2013). Exposure to TRAP was also only weakly associated with respiratory symptoms in a study based on children participating in the GASPII cohort from Rome, Italy (Ranzi et al. 2014).

Although mean concentrations during prenatal and postnatal periods are correlated (Appendix Table A5), in our study the effect estimates for $PM_{2.5}$ were elevated for postnatal exposure in the first year only for both asthma ever and active asthma, but none of the associations were statistically significant (Table 6). Meta-analyses of previous studies on active asthma that prioritize either prenatal or postnatal exposures provide no indication that one exposure period is more critical than another (HEI 2022). While associations for exposure at the birth address were stronger than for exposure at the current address for asthma incidence in the pooled ESCAPE study — that reported on incidence and prevalence of active asthma up to age 14–16 for 14,126 children from the Dutch PIAMA, the Swedish BAMSE, and the German GINI and LISA cohorts — the difference was smaller for active asthma prevalence (Gehring et al. 2015b). In this study, for active asthma prevalence the pooled meta-analyses were 1.06 (95% CI: 0.88–1.26) for a 10-μg/m^3 increase in NO_2 and 1.34 (1.00–1.79) for a 5-μg/m^3 increase in $PM_{2.5}$ at the birth address.

In our DNBC study, more than half of the children moved during early childhood (Appendix Table A9). Our finding that the effect estimates for both asthma incidence and prevalence were larger for nonmovers (Appendix Table A10) is in line with the reporting of larger and significant effects of $PM_{2.5}$ on asthma incidence and prevalence in nonmovers of the Dutch PIAMA birth cohort (Gehring et al. 2010).

Air Pollution and Lung Function

For our report, we present the effect estimates for FEV_1, which is a measure of airway obstruction, from cross-sectional analyses using the data available at this time point from age 6 of the COPSAC children. We found that $PM_{2.5}$ exposure both during prenatal and postnatal periods of life was associated with a small reduction in FEV_1, which is in line with the findings from a large number of studies supportive of associations between long-term exposure to air pollution and reduced lung function (Garcia et al. 2021; Götschi et al. 2008; Schultz et al. 2017). We did not, however, observe an adverse effect of NO_2 on FEV_1 at age 6, which differs from most, but not all previous studies. There are many other commonly used measures that have been studied in relation to air pollution. For instance, forced vital capacity (FVC) is a measure of the total volume that can be exhaled after a maximum inspiration, and the FEV_1/FVC ratio is a marker of airflow obstruction. Other measures include: peak expiratory flow and forced expiratory flow between the 25th and 75th percentile of FVC ($FEF_{25–75}$), also called maximum midexpiratory flow.

We decided to report here the first results for FEV_1 only. In prior studies with long-term exposure, associations were more consistent for FEV_1 compared with FVC, which may indicate greater impacts on airway obstruction than on overall lung size (Garcia et al. 2021; Götschi et al. 2008; Schultz et al. 2017). Large differences in terms of the study designs, the exposure assessment, pollutants, and lung function measurements evaluated in the individual studies have hindered a quantitative summary of the existing evidence (Garcia et al. 2021).

Among the more recent studies from Europe and the United States that we consider most similar to our study, as they rely on advanced exposure assessments of exposure at the individual level, we are aware of several studies that have evaluated the cross-sectional analyses of the associations between long-term exposure to $PM_{2.5}$ in early life and FEV_1 in children (Fuertes et al. 2015; Gehring et al. 2013, 2015a; Milanzi et al. 2018; Rice et al. 2016; Urman et al 2014; Wang et al. 2015; Yang et al 2016; Zhao et al. 2021). Several recent studies have also evaluated associations between NO_2 and FEV_1 measured at a single time point in children (e.g., Fuertes et al. 2015; Gehring et al. 2013, 2015a; Milanzi et al. 2018; Morales et al. 2015; Usemann et al. 2019; Wang et al. 2015; Zhao et al. 2021).

Gehring and colleagues (2013) have performed a large, standardized study on FEV_1 measured at age 6 or 8 in 5,921 children from the Dutch PIAMA, the Swedish BAMSE, the British MAAS, and the German GINI and LISA cohorts in which long-term exposure to air pollution was associated with a small decrease in lung function. Higher exposure was associated with lower lung function in most of these cohorts, but the associations were not statistically significant for the smaller-sized cohorts. In our study of the COPSAC children, we found adverse effects only for $PM_{2.5}$, and we observed no difference for the associations with $PM_{2.5}$ among the different exposure periods evaluated. This differs from what was found in the ESCAPE study (Gehring et al. 2013), as the pooled meta-analyses effects estimates were significant for both NO_2 and $PM_{2.5}$ at the current address and borderline for birth address for the analyses of the five cohorts. The epidemiological evidence of a period of heightened vulnerability during early-life development is mixed, and not all studies have evaluated effects of both prenatal and postnatal exposures.

Prenatal exposure to NO_2 during the second trimester, when the respiratory airways start to develop in utero, has been associated with lower FEV_1 at age 4.5 in a study of 620 children from the Spanish INMA Sabadell and Gipuzkoa cohorts (Morales et al. 2015). Although higher exposure during the first year was also associated with lower FEV_1, associations were weaker compared with prenatal exposure in this study. A BAMSE cohort study has reported that exposure to PM_{10} during the first year of life had a stronger effect on FEV_1 than did exposures during prenatal and periods later in life (Schultz et al. 2012, 2016). Several studies from the PIAMA cohort have reported adverse effects for postnatal exposures. Long-term exposure to air pollution has been associated with lower FEV_1 for analyses of measurement from age 8 in 1,058 (Gehring et al. 2013), age 12 in 1,249 children (Gehring et al. 2015a), and age 16 in 721 participants of the Dutch PIAMA cohort (Milanzi et al. 2018). For PIAMA and FEV_1 measured at age 12, associations with exposure at the current address was significant for NO_2 and borderline for $PM_{2.5}$, while few associations were observed for exposures at the birth address (Gehring et al. 2015a). For FEV_1 measured at age 16, significant associations were reported for both $PM_{2.5}$ and NO_2 for exposure during preschool, primary school, and secondary school periods (Milanzi et al. 2018). These studies were based on exposure estimated with LUR models, but the associations for age 8 with the PIAMA cohort were similar for exposure estimated with a dispersion model, according to a comparison study (Wang et al. 2015). Similar to the findings of the ESCAPE and PIAMA studies, a study of 232 children from Switzerland has reported that current exposure at age 6, as well as postnatal exposure from birth to age 6 to NO_2, were associated with lower FEV_1 measured at age 6 (Usemann et al. 2019). Inverse associations were also observed for prenatal exposure and exposure during the first year of life, but associations were weaker.

Exposure to $PM_{2.5}$ in the year prior to lung function measurement has also been associated with lower FEV_1 at 8 years of age in a study of 614 children from the Project Viva cohort from the area around Boston, Massachusetts, USA (Rice et al. 2016). In this study a satellite-based model with daily calibration of the estimates according to stationary monitors was used. The associations with lung function were weaker for exposure during the first year and postnatal exposure from birth to lung function measurement.

Not all European birth cohort studies have reported evidence of associations between long-term exposure to air pollution and FEV_1. For instance, associations were null for FEV_1 at age 15 in a cross-sectional analysis of 2,266 children from the German GINI/LISA cohort (Fuertes et al. 2015). However adverse effects were observed for children with asthma in this study. Null associations between long-term exposure to TRAP with NO_x and FEV_1 at 8–9 years of age have also been reported in a study of 788 children from Paris, France (Bougas et al. 2018). Adverse effects of postnatal exposure to NO_x on FEV_1 were observed for the subset of children with repeated lower respiratory tract infections, but not for prenatal exposure.

The evidence of adverse effects of long-term exposure to air pollution on lung function is supported by the strong evidence of adverse effects of short-term exposure to air pollution on lung function from experimental studies, as well as from panel and epidemiological studies with children (Garcia et al. 2021; Li et al. 2012). In addition to studies on acute effects and adverse effects of exposure to air pollution on lung function measured at a single point in time, there is a growing number of longitudinal studies that have provided evidence of adverse effects of long-term exposure to air pollution on lung function growth in childhood, but not all studies report adverse effects and effects are small (Garcia et al. 2021; Götschi et al. 2008; Korten et al. 2017; Schultz et al. 2017). These longitudinal studies have used repeated measurements of lung function at different time points during childhood to estimate the size of the increase (calculated as the difference between the first and last lung function measure) and used it as proxy of lung function growth and development. For instance, Gauderman and colleagues (2007, 2015) presented evidence from CHS in Southern California supporting the hypothesis that long-term exposure to TRAP may adversely affect lung function growth in healthy children and adolescents. Although the evidence of adverse effects of air pollution on lung development and health continues to mount (Garcia et al. 2021; Götschi et al. 2008; Korten et al. 2017; Schultz et al. 2017), the long-term effects of early-life exposure to air pollution on lung function trajectories in childhood are not fully understood (Garcia et al. 2021).

The authors of a review of 37 studies with children have concluded that there is strong evidence of adverse effects of long-term exposure to ambient air pollution on lung function growth in children, resulting in deficits of lung function at the end of adolescence (Götschi et al. 2008).

Air pollution is a complex mixture of gases and PM consisting of different chemical components that vary in concentration as well as composition over space and time, depending on the distribution of the sources of emission and meteorological factors. Since the toxicity and sources vary between the specific components, a growing number of epidemiological studies attempt to evaluate associations with multiple air pollutants, including components of PM. For respiratory outcomes in children, the epidemiological studies largely focused on NO_2, NO_x, $PM_{2.5}$, and PM_{10} total mass concentrations, BC or EC, and O_3. Other pollutants, including those formed in the atmosphere and from other sources than combustion process-related emissions (e.g., agricultural emissions), have been far less studied. In our study we also found that long-term exposure to NH_4^+, which is formed from agricultural emissions of ammonia and other components of PM, was associated with a lower FEV_1 as well as with increased asthma risk. However these sparse studies on other pollutants are more difficult to compare than are those with the more common pollution metrics.

In our nationwide study, the inverse associations for O_3 summarized in Table 2 are likely to reflect that exposure to a higher concentration of O_3 is typically accompanied by lower

NO_2 concentrations due to atmospheric chemical reactions between NO_x and O_3, rather than by protective effects of O_3. The associations for O_3 were not inverse after adjustment for NO_2 or $PM_{2.5}$ (Table 4).

EARLY-LIFE EXPOSURE AND BIOLOGICAL MECHANISMS

We focused on early-life exposure because it was the most cost-effective period for preventive actions. Exposure in early life is critical for asthma development as asthma is largely a developmental disease (Pinkerton and Joad 2000; Sly and Holt 2011) and because there is substantial evidence that it is important to focus on exposure to air pollution in children with respect to asthma development and reduced lung function (Bateson and Schwartz 2008; Gehring et al. 2020; Gheissari et al. 2022). It is now well recognized that fetuses and infants are especially vulnerable to the effects of exposure to risk factors, such as ambient air pollution, that disrupt the developmental process. There is growing evidence that exposure to ambient air pollution in early life, both before and after birth, can result in permanent changes in immune maturation, airway structure, lung growth, and lung function that underlie the development of asthma in children and young adults (Dick et al. 2014; Garcia et al. 2021; HEI 2010, 2022; Khreis et al. 2017; Sly and Holt 2011). Still, little is known about potential critical windows of exposures that heighten vulnerability within these years of early life, as most studies have evaluated mean exposure during the annual mean only during the first year of life. A few studies have reported the effect estimates of both the prenatal period, trimester-specific periods, and the annual mean during the first year of life, but the high correlation for individuals residing at the same home address make interpretation difficult (HEI 2022; Khreis et al. 2017). Hence, in order to fill this gap of knowledge for all the outcomes evaluated we evaluated the associations between prenatal exposure and a relevant window of postnatal exposure that was dependent on age for the outcome assessment.

We investigated exposure during the prenatal period because we hypothesized it to be a critical window of exposure of heightened vulnerability toward exposures to ambient air pollution for all the outcomes. Because the age of asthma incidence and lung function varied in our study population, we evaluated the annual mean the year before diagnosis for asthma incidence and lung function. Prior studies, including a case–control study from Denmark, have reported that the effect estimates between air pollution and asthma from models fitted with postnatal exposure time-weighted mean concentrations of 3, 6, and 12 months prior to the asthma incidence were similar (Holst et al. 2020). Furthermore, since our aim was to study the effect of long-term exposure, we considered the annual means most relevant as these cover all seasons, which is not the case for shorter exposure windows. We did not evaluate longer postnatal exposure windows for the studies on asthma incidence, although it could have been relevant as we wanted to evaluate exposure preceding the onset of asthma and to minimize the overlap between the prenatal and postnatal exposure window for the children with onset of asthma very early in life.

For the studies with assessment of asthma prevalence and lung function around a fixed age, we evaluated a longer postnatal exposure window from birth to the age of follow up as we considered it biologically plausible that exposure throughout the entire infanthood could have an impact on these outcomes, given the continued development of the immune and respiratory systems. For the biomarkers measured at 6 months of age and 6 years of age, we furthermore reported effect estimates adjusted for short-term exposure means to report the main effect of long-term exposure independently from short-term exposure (Tingskov Pedersen et al. 2023).

In our nationwide study, the adjusted HRs of postnatal exposure did not change much nor did the 95% CI widths change much after adjustment for prenatal exposure (Table 2); suggesting that pre- and postnatal exposures have independent effects (since HR estimates adjusted and unadjusted are about the same), and that pre- and postnatal exposures are not actually highly correlated (since the CI widths do not increase in the adjusted model as would be expected if pre- and postnatal exposures were collinear).

The biological mechanisms by which air pollution affects our lungs and contributes to asthma development are not fully understood, but many pathways have been proposed to be induced by exposure to air pollution (HEI 2022; Korten et al. 2017). Our motivation for studying risk associated with exposure both pre- and postnatally was to possibly separate the timing of the mechanisms (e.g., inflammation and oxidative stress, epigenetic changes in the mother, the placenta, and/or the developing child) occurring during prenatal and early-life growth and development that could be contributing to asthma development and reduced lung function (Korten et al. 2017). A few studies have like ours attempted to examine both prenatal and postnatal exposures to identify critical windows of exposure; however, as they attempt to distinguish the effects of exposure mean concentrations of air pollutants during specific time periods from each other, the modest to high correlations between these mean concentrations make these examinations challenging, especially for exposure periods that are close in time to each other (e.g., prenatal vs. postnatal exposure during the first year). This makes it difficult to distinguish between prenatal and postnatal exposure, as evident by the existing evidence summarized earlier.

As part of our research on asthma related to long-term exposure to air pollution and asthma in early life we investigated a range of asthma-related mechanisms including systemic inflammation in blood collected at 6 months of age, airway immune mediators at 4 weeks of age and 6 years of age, airway epithelial epigenetic, and gene expression in nasal cells collected at 6 years of age in approximately 700 of the $COPSAC_{2010}$ children (Tingskov Pedersen et al. 2023).

First, in line with our nationwide study on asthma incidence (ICD-10 codes) (Pedersen et al. 2023), for asthma at age 6 we observed that an IQR of 5.2 μg/m^3 in postnatal exposure to air pollution with NO_2 from birth to age 6 was associated with an OR of 1.39 (95% CI; 1.09–1.77) for asthma ever, defined according to a detailed quantitative symptom algorithm and an OR of 1.73 (1.19–2.50) for active asthma at age 6 in the $COPSAC_{2010}$ (Tingskov Pedersen et al. 2023). Similar effect estimates were observed for $PM_{2.5}$ and PM_{10} and for postnatal exposure during the year before the follow up at age 6. For prenatal exposure to NO_2, the OR for asthma was 1.22 (0.91–1.63) and 1.34 (0.82–2.11) for active asthma, defined as the need for controller medication at age 6. Ambient air pollution exposure was also associated with elevated odds for sensitization to aerosol inhalants and allergic rhinitis at age 6 in these children, but associations did not reach statistical significance.

We also found that prenatal exposure to ambient air pollution was associated with changes in pro-inflammatory cytokines measured in blood obtained from the children at 6 months of age (Table 8), which remained robust after adjustment for both postnatal air pollution exposure and urbanicity in the study by Tingskov Pedersen and colleagues (2023). Consistently for air pollution with $PM_{2.5}$, PM_{10}, and NO_2, we found that higher prenatal exposure was associated with increased levels of IL-8 and decreased levels of IL-1β, whereas an inverse association between NO_2 and IL-6 was suggested in our study (Tingskov Pedersen et al. 2023). Data on comparable effects in children is very sparse.

In contrast to our findings, studies with blood collected from children at older ages have reported that postnatal exposure to NO_2 in the first year of life was associated with increasing levels of IL-6 in blood collected at age 8 from the children of the BAMSE cohort (Gruzieva et al. 2017); in children of the GINI/LISA cohort, postnatal exposure to NO_2 at age 6 was associated with increasing levels of responsiveness for IL-6 in blood collected at age 6 (Klümper et al. 2015).

A number of studies have evaluated prenatal exposure to ambient air pollution in associations with cytokine profiles or cytokine production in cord blood cells (García-Serna et al. 2022; Hahn et al. 2021; Latzin et al. 2011), but cell composition and immune response maturity of umbilical cord blood differ from those of peripheral blood obtained later in life. Maternal and perinatal factors such as the mode of delivery and the presence and intensity of labor have a greater influence on cord blood cells than on peripheral blood cells collected later in life, so direct comparison is difficult.

Prenatal exposure to NO_2 has been associated with increased levels of IL-1β and IL-6 in 235 cord blood samples from Spain (García-Serna et al. 2022), while prenatal exposure to $PM_{2.5}$ was associated with decreased production of IL-6 in a cord blood study of 463 participants of the Project Viva from Massachusetts, USA (Hahn et al. 2021). In that study the exposure was estimated with a LUR model, and inverse associations were also observed for another pro-inflammatory cytokine (TNF-α) and IL-10, an anti-inflammatory cytokine. Although cytokine production is a marker of immune response, it is not directly comparable to our COPSAC study. Short-term exposure to PM_{10} in the week prior to birth has been associated with decreasing levels of IL-6 in a study of 199 cord blood samples from the region of Bern, Switzerland (Latzin et al. 2011). However, in contrast to our finding, higher prenatal exposure to PM_{10} in the last trimester was associated with increased levels of IL-1β in this cord blood study (Latzin et al. 2011). This study relied on air pollution data from the nearest central monitoring station and did not evaluate exposure at the address level during the full prenatal period.

Ambient air pollution exposure was not robustly associated with immune, epithelial DNA methylation or gene expression changes in the airways at age 6 in the study by Tingskov Pedersen and colleagues (2023). Although a few genes were differentially methylated according to prenatal or postnatal exposure, none were related to the 4-week nasal immune mediator fingerprint, were among the genes previously associated with asthma and allergy, or were related to air pollution patterns that were associated with the immunological changes in the blood samples. Data on comparable effects measured in airways of children is very sparse and this area of research deserves further research in a larger well-characterized study population.

A growing number of studies have investigated ambient air pollution exposure in relation to global, candidate-gene, or epigenome-wide DNA methylation in placenta tissue, cord blood, saliva, and peripheral blood from children (Isaevska et al. 2021; Suhaimi et al. 2020). Both long-term and short-term exposure to $PM_{2.5}$ have been associated with higher DNA methylation in the NOS3 gene and lower DNA methylation in the NOS2A gene in a study based on buccal cells collected from 940 children participating in the southern California CHS (Breton et al. 2012). A panel study of 18 school-aged children with asthma from the United States have reported that short-term exposure to BC is associated with lower methylation in the NOS3 gene in buccal cells with time lags in terms of hours (Ji et al. 2021). There are fewer studies on DNA methylation in nasal epithelial cells from children, like ours. A study with DNA-wide methylation in nasal cells collected from the participating children of the project Viva cohort at school age reported that long-term exposure to ambient air pollution with $PM_{2.5}$, modeled at the residence for up to one year of age, was associated with a larger set of differentially methylated regions implicated in cell cycle, immune, and inflammatory pathways (Sordillo et al. 2021). An earlier study of African American children with asthma and their siblings without asthma from Cincinnati, Ohio, United States, provides evidence supporting a possible role of gene-specific DNA methylation in the mechanisms underlying the associations between air pollution and asthma (Somineni et al. 2016). These studies can improve our understanding of disease etiology and guide preventive actions at earlier stages, as DNA methylation can regulate gene expression and hereby be an essential mechanism in, for example, asthma development

(Suhaimi et al. 2020; Xu et al. 2018) and in other adverse health effects associated with exposure to air pollution.

Finally, we found that higher exposure to air pollution was associated with an altered airway immune profile at 4 weeks — conferring an increased risk of allergic sensitization and allergic rhinitis — and with an altered immune profile in blood at age 6 months — conferring an increased risk of asthma at age 6 (Tingskov Pedersen et al. 2023). We concluded that these findings support that the early immune system plays a role in the adverse health effects induced by exposure to ambient air pollution (Tingskov Pedersen et al. 2023). These findings add to emerging evidence that prenatal exposure to ambient air pollution is associated with early immunological changes and support the hypothesis that alterations in infant inflammatory cytokines can predispose children to respiratory morbidity.

STRENGTHS AND LIMITATIONS

This study adds to the emerging and somewhat conflicting literature on adverse effects on the respiratory health of children and adolescents from long-term exposure to air pollution at relatively low levels.

The study has several strengths. It included all children born in Denmark and followed a large fraction of the children from birth into early adult life. This eliminated the risk of bias rising from selection and loss to follow up. The large sample sizes provided sufficient statistical power to study small effects and to conduct stratified and sensitivity analyses for older ages, when diagnoses are more certain. Our study leverages extensive data on air pollution, detailed and largely complete residential and health registries for the entire population of live-born singletons born in Denmark over the span of two decades. The study population has access to free health care, relatively low inequality, and relatively high quality of housing standards. Also, the Danish population is very homogenous in race and ethnicity as compared with the United States, for instance, reducing the risk of confounding by these factors. The study design allowed us to compare the findings on asthma incidence observed in the nationwide study with those of the DNBC for whom a wider set of covariates were available for a large population of children, much larger than most birth cohorts (HEI 2022). The study design also enabled us to compare the differing asthma definitions in a large population of children.

We estimated exposure during prenatal and postnatal life to a wide range of pollutants using the DEHM-UBM-AirGIS modeling system with OSPM, which has high spatial (at house number and street address level and 1×1 km^2) and temporal (hourly) resolutions that have been shown to perform well when compared with measured concentrations both for Denmark (Brandt et al. 2001; 2012; Hvidtfeldt et al. 2018; Ketzel et al. 2011, 2012; Khan et al. 2019) and for the continental Nordic countries (Frohn et al. 2022). This is a novel aspect of our study; exposure is assessed at this fine spatial and temporal resolution, adding to the existing evidence on asthma development from early life on. Several previous epidemiological studies have benefitted from this unique modeling approach, but only NO_2 and NO_x were modeled in the older studies, and the modeling is improving over time (Cantuaria et al. 2021; Holst et al. 2020; Monrad et al. 2017; Pedersen et al. 2017a,b,c, 2019; Puett et al. 2020; Raaschou-Nielsen et al. 2011, 2016, 2020, 2022; Ritz et al. 2016, 2018; Sørensen et al. 2013, 2015, 2017, 2021, 2022a,b; Taj et al. 2022; Thacher et al. 2021; Thygesen et al. 2020; Wesselink et al. 2022).

Ambient air contains a mixture of pollutants that originates from multiple sources and our models include local sources, such as emissions from motorized road vehicles and other combustion sources, power plant emissions, ship emissions, emissions from agricultural activities, and natural emissions from soil, vegetation, and lightning. Another strength of our exposure assessment is that it is based on the validated DEHM-UBM-AirGIS modeling system, which includes the emissions from traffic and also from a large range of nontraffic sources (e.g., industry, households [including wood stoves], agriculture, or natural emissions). The accuracy of the predictions for our air pollution models can be described by evaluating the model output with measurements at rural or urban background locations with only minor traffic contributions. Our air pollution models achieved very high correlations at those background stations of 0.89, 0.92, 0.93, and 0.78 for NO_x, NO_2, CO, and $PM_{2.5}$, respectively (Brandt et al. 2001; Ketzel et al. 2012). This makes us confident that both the traffic and the nontraffic sources are modeled correctly in our modeling system.

These advanced models are forced by actual meteorology (not statistical dependencies), and the resulting modeled air pollutant concentrations allow us to study contrasts in exposure at the finest possible individual scale, as well as offering the possibility of studying the causality between air concentrations and emission-source locations. We consider this data to be superior for examining associations with asthma compared with most previous studies. We included all of Denmark and performed sensitivity analyses restricted to Greater Copenhagen. Most previous studies focused on urban TRAP exposure, and we found that effect estimates were slightly higher among the participants living in Greater Copenhagen (Appendix Table A7).

Importantly, we had complete residential histories for the mothers during pregnancy and for the children after birth, which allowed us to account for each address and the time lived at each address, not just for the residence at birth or at the time of follow up, as in many studies. This allowed us to compare associations of asthma and related outcomes with exposure to many different pollutants and with exposure averaged over different critical periods of early-life development and growth. Then results from two-pollutant models could be compared with the single-pollutant models.

Comparison across different outcomes is possible as we applied the same exposure assessment for multiple studies

with different asthma and asthma-related outcomes. Consistently across different studies we found that higher exposure to $PM_{2.5}$ was associated with elevated risk for incident asthma and lower FEV_1; we have also observed this for asthma at age 6, according to the COPSAC definition in $COPSAC_{2010}$ (Tingskov Pedersen et al. 2023).

Asthma is a highly heterogeneous condition, which can present as several phenotypes with varying degrees of severity. We defined asthma incidence from clinical records, which enables studies of onset, eliminates the potential for recall bias, and is less prone to variation in clinical practice than are questionnaire studies. A strength of the asthma definition derived from the DNPR limits misclassification since it is based on validated ICD criteria. This definition reflects more certain and possibly more severe cases than parental recall of child asthma and asthma-like symptoms (Hansen et al. 2012). However, administrative health registry data might suffer from misclassification of the outcome. As we observed in our study, the prevalence of asthma is lower when defined from ICD criteria than when asthma is defined according to various other criteria (e.g., asthma medications in an administrative health registry, a questionnaire of parental recall of doctor-diagnosed asthma, or asthma symptoms). We did not use data on medication prescribed to treat and prevent asthma to define asthma, as we included infants and preschool-age children in our study and medication is often prescribed to ease asthma-like symptoms. Especially for infants and preschool-age children, it can be difficult to distinguish between asthma and asthmatic symptoms such as wheezing, chest tightness, breathlessness, and coughing related to viral infections (Martinez et al. 1995). Since our incident asthma definition most likely reflects cases of severe asthma and leaves out cases of mild to moderate asthma diagnosed by the general practitioners, the asthma prevalence definitions available from the parental recalls in DNBC are complementary. We used the date of the first registration of asthma diagnosis according to ICD-10 records as an indicator of asthma onset, as done for many different kinds of diseases and complications in epidemiological studies. However, we acknowledge that such clinical records could in some cases reflect late-stages of the asthma development for whom the real onset of asthma has started earlier in time with milder signs and symptoms that were not recorded. Asthma is a heterogenous outcome; the diagnosis can be difficult to distinguish from related diseases, especially in infants. Although this approach is not ideal and the terms incidence and onset of the asthma — that we have used to match existing literature — are proxies of the real asthma onset, we do consider this approach to be the best available for a nationwide study of asthma development when the study population includes infants and when the aim is to evaluate associations with long-term exposure. This means that we do consider the Cox proportional hazard modeling using ICD-10 diagnosis as the most desirable approach for studies like ours. In addition to uncertainty in terms of relying on the date of a medical encounter as proxy of the real date of asthma onset, we cannot rule out misclassification of case status when we rely on registered asthma diagnosis. Both false positives and false negatives are likely to have occurred and are almost certain to be nondifferential with respect to ambient air pollution exposure.

When planning our study, we decided to treat asthma defined according to an ICD-10 diagnosis separately from asthma defined from asthma medication prescribed and parental recall of doctor-diagnosed asthma because a comparison study of the DNBC children at age 7 had recommended doing so, as these different definitions reflect different phenotypes (Hansen et al. 2012). As observed in our study, in this DNBC study 6.6% of the children had asthma according to ICD-10, 32.2% according to the medication prescribed using the definition used by Hansen and colleagues, and 12% according to parental recall of doctor-diagnosed asthma (Hansen et al. 2012). The prevalence of asthma ever observed in the DNBC according to parental recall is very similar to the prevalence reported in other European birth cohorts. For instance, at age 8 the prevalence of asthma ranged from 4.7% in GASPII to 15.7% in INMA-Sabadell and BIB (Fuertes et al. 2020); at age 8 or 10 it ranged from 12% in GINI/LISA to 23% in MAAS (Mölter et al. 2015). A sensitivity of 90%, specificity of 99%, and positive predictive value of 85% has been reported when medical records were used to validate inpatient discharge diagnosis of asthma in the DNPR among children ages 6–14 years (Moth et al. 2007). While such survey-based diagnoses for prevalence at age 7 (based on parental recall of an asthma diagnosis) and for active asthma at age 7 (based on parental recall of a child's asthma medication and symptoms in the year prior to the survey administration) are considered appropriate, are ascertained using conventional survey methods, and are therefore used in multiple previous studies (HEI 2022), outcome misclassification is certainly possible, for example due to errors in parental recall. However, they are likely to be nondifferential with respect to exposure status, as exposure was measured independently (and objectively) from outcome status.

A more recent study of the 466 DNBC children at age 15 reported that asthma defined from ICD-10 codes, and/or two medications prescribed within 12 months, had a higher specificity of capturing individuals with parental recall of asthmatic bronchitis (recurrent wheezing) than individuals with doctor-diagnosed asthma (82% vs. 66% specificity). These findings suggest that wheezing is not the optimal predictor of asthma in these children (Stensballe et al. 2017).

Vulnerability and diagnosis validity differ across ages with more certainty at ages above 4 years (Moral et al. 2019). For diagnoses using ICD-10, age 4 has been proposed as the reliable age (Moral et al. 2019). A strength of our study is that the positive associations observed for all children remained after restriction to asthma in children year 4 and older (Pedersen et al. 2023). Although many of the studies evaluating asthma in populations with infants have reported age-specific results in sensitivity analyses, some studies exclude cases before a certain age and others redefine asthma, making direct

comparison of the results difficult and inconsistent. Prenatal exposure to air pollution was not associated with an elevated risk of incident asthma in children for whom asthma was only evident from age 6 (Sbihi et al. 2016). More consistent associations in children older than 4 years, as compared with those before that age, have been reported in other studies (Gehring et al. 2015b).

Another notable strength of our study design relates to our ability to study lung function and a range of asthma-related biomarkers in addition to the various asthma outcomes. Lung function is an important objective measure of respiratory health and is a predictor of morbidity and mortality. Deficits in lung function growth develop in early childhood, and children with asthma and bronchial hyper-responsiveness and allergic comorbidity are at risk (Koefoed et al. 2021).

In all of the studies in this report we were able to adjust for maternal smoking as well as SES at both individual- and area-specific levels. This is not always possible in studies based on administrative cohorts like the ones from Canada (Clark et al. 2010; Lavigne et al. 2018, 2019, 2021; Sbihi et al. 2016; Tétreault et al. 2016). We were unable to consider postnatal exposure to smoking, breastfeeding, pet ownership, and other personal characteristics that could confound and/or modify the effect of air pollution exposure on asthma development in the large nationwide study. However, findings from our DNBC study demonstrated that further adjustment for a comprehensive set of potential individual-, family-, and home-level confounders made no difference on the main findings on incident asthma (Table 5).

Mold and dampness are strong risk factors of asthma. We could not adjust for them in our nationwide studies, but we adjusted for SES using both education and income data at the individual level. We are not that concerned about the lack of information on mold and dampness in the nationwide study, because higher parental educational and income strata had more favorable indoor and housing environments in the DNBC (less secondhand smoking, gas stove use, mold, and dampness; and higher house ownership, detached house dwellings, and newer building age) (Groot et al. 2022).

Furthermore, we could account for other geographically related confounding, such as variation in asthma incidence due to, for instance, geographical differences in health services, by adjustment for municipality, thus capturing mainly associations with local variation in air quality. The findings on asthma incidence were robust to several sensitivity analyses that further aimed to rule out potential confounding by asthma risk factors such as urbanicity and SES (Appendix Table A7).

Still, there are limitations in our study. We estimated individual long-term exposures to outdoor air with multiple pollutants at the residential level of the mother during pregnancy and for the child address(es) after birth, but the exposure indoors as well as during commuting, work, and elsewhere were not estimated. Although most women in Denmark work and most children born in Denmark attend daycare starting around one year of age, the daycare, school, and after-school activities are most often located in the same area as their residence.

We also did not investigate the effects of short-term exposure to ambient air pollution. Several studies have linked short-term high exposures to asthma exacerbations (Orellano et al. 2017), which can range from mild to severe conditions that require emergency room visits, hospitalization, or both. The evidence includes studies from Denmark in which short-term exposure to TRAP has been associated with hospital admissions for asthma in children from Copenhagen (Iskandar et al. 2012). Short-term exposure to TRAP has also been associated with wheezing symptoms in the $COPSAC_{2000}$ children (Andersen et al. 2008). Most recently, short-term increases in PM and NO_2 have also been associated with increased asthma consultations as well as preventer and reliever inhaler prescriptions in a recent study from London (Ashworth et al. 2021). Adverse effects of short-term exposure to air pollution on lung function in healthy children are evident, with a larger impact in children with respiratory diseases (Garcia et al. 2021; Li et al. 2012).

Our study includes many comparisons. For this reason, we limited the pollutants to the main pollutants in the asthma-biomarker studies (Tingskov Pedersen et al. 2023). We also focus our conclusions on consistency of associations and not on tests of statistical significance.

Our studies included a population from Denmark, a country characterized by relatively low levels of air pollution, free health care, relatively high levels of social support, and of predominantly white and educated parents and their children. Generalizability to populations with greater socioeconomic and ethnic/racial variation may be limited. Our study included very few families in poverty. On one hand it is possible that the estimated effects would have been larger if more low-income families were included. On the other hand, it might also have been that other unmeasured risk factors would have masked the effects of air pollution in Denmark as opposed to, for instance, the United States. In Denmark, higher exposure to TRAP is not associated with low SES but with high SES, as reported in a recent nationwide study of the home addresses of adults (Raaschou-Nielsen et al. 2022) and for the home addresses during pregnancy of the DNBC (Pedersen et al. 2017c).

Selection bias is a concern, despite the many strengths and the relatively large study population of women enrolled from all parts of Denmark into the DNBC. Women not working and with no or low education were more likely to decline to participate. Single women were also underrepresented in the DNBC (Jacobsen et al. 2010).

Although women participating in the DNBC are of higher SES and are healthier than all those eligible for the DNBC, differential selection has been reported to be modest, and the influence of selection bias on several selected exposure–

outcome associations was found to be limited (Nohr and Liew 2018). Inverse probability weighting using a reference population has been used in a similar ongoing DNBC study to explore to which extent the included DNBC study population differed from the population of those lost to follow up or excluded for other reasons; weighting made little difference (Keller et al. 2023).

We restricted our analyses to complete cases, so loss to follow up is also a concern (Appendix Figure A4). The excluded population differed from that included in our DNBC study (Appendix Table A9). We did, however, detect associations for asthma incidence in the DNBC study population with complete information from the postnatal follow ups that were very similar to those of the nationwide population (Table 5), which suggests that selection is not likely to bias the findings for DNBC. We observed that the effect estimates were higher for nonmovers (Appendix Table A10), and we performed this sensitivity analyses to be sure that the children were living in the same home they were living in when information on home characteristics was collected. We present evidence that the nonmovers differed from movers (Appendix Table A9).

Despite the strong assessment of confounding, the measurements of many confounders were likely to be subject to error. Such errors in confounder measurement (e.g., misspecification of SES and copollutant exposures) would result in residual confounding by the mismeasured variable. Further, confounding of air pollutant–asthma associations by potential determinants of asthma risk that are also associated with, but not caused by, pollution exposure (e.g., mold exposure, pet exposure, and other causes of early-life immune differentiation) is likely in the registry-based analysis that included little covariate information. That said, the comparatively smaller birth cohorts included information on some of these potential confounders, and additional adjustment did not change results much. Indirect associations and surrogate variables have not been explored.

Bias due to residual confounding remains a potential alternative explanation for the findings of this observational investigation. Given the small magnitude of the observed associations (e.g., a 6% increase in asthma risk per interquartile range increase in prenatal exposure to $PM_{2.5}$), nonmeasurement or mismeasurement of moderately prevalent factors that are strongly and positively associated with both asthma risk and exposure to a specific air pollutant, or that are strongly negatively associated with both asthma risk and exposure to a specific air pollutant, could induce a bias of the corresponding HR that is equal in magnitude to the association observed.

FUTURE STUDIES

In ongoing analyses, we are applying more advanced multipollutant approaches in terms of explorative Lasso-based models to identify which air pollutants are most strongly associated with incidence of asthma in children and adolescents.

Although short-term exposure to specific ambient air pollutants have been widely observed to have associations with childhood asthma outcomes (Orellano et al. 2017), the relative importance of peak exposures and exposure at critical points in time during fetal development or during early-life immune differentiation was not investigated in this study, nor has it been fully established in the existing epidemiological literature, as studies like ours on long-term exposure are not set up to address the potentially important impact of short-term air pollution exposure on asthma etiology. One way for future studies to address this could be to use an approach similar to that used in a recent study with adults from Copenhagen, in which daily counts of hospital admission data were linked with daily air pollutant concentrations from monitoring stations (Bergmann et al. 2023).

It could be relevant to examine more specific asthma phenotypes and the severity of asthma in future studies. It could be interesting in future analyses to distinguish between allergic and nonallergic asthma, as Gehring and colleagues (2015b) found that the association for NO_2 is driven by nonallergic asthma. Asthma and asthma-related symptoms in early childhood are often transient, and not all asthma cases with onset early in life persist into later life. It could also be interesting to examine different phenotypes of asthma related to the age of onset and the persistence of asthma. We are working on longitudinal studies of associations between long-term exposure to air pollution and lung function growth to further study if the adverse effects we observed in the cross-sectional analyses on lung function at age 6 can be observed from earlier childhood, if they track until early adulthood, and if the effect is greater in children with a low initial lung function.

CONCLUSIONS

Long-term exposure in early life to ambient air pollution from multiple sources was associated with increased rates of asthma incidence (ICD-10). Associations for asthma incidence were evident for most of the pollutants evaluated ($PM_{2.5}$, PM_{10}, NO_2, NO_x, EC, OC, SO_2, O_3, SO_4^{2-}, NO_3^-, NH_4^+, and SOA) in adjusted single-pollutant models with prenatal exposure. The findings of our study suggest that both prenatal and postnatal exposure contribute to asthma development. Most of the associations observed for asthma incidence in the nationwide cohort study population were also evident after additional adjustment for risk factors such as home characteristics available in the nested subset of the DNBC children participating in the postnatal follow ups. Overall, long-term air pollution exposure in early life was not associated with asthma prevalence at age 7, according to parental recall of doctor-diagnosed asthma ever and active asthma at age 7 in the DNBC children. The findings of our study suggest that the associations between long-term exposure to ambient air pollution and asthma development in children depend more on the asthma definition than on further adjustment for cohort-specific variables in settings with rich registry data like

Denmark. Prenatal exposure to PM and NO_2 was associated with immunological changes in blood and the airways but not with DNA methylation or gene expression changes in nasal epithelial cells. For lung function, we found that long-term air pollution exposure with $PM_{2.5}$ and NH_4^+ was associated with reduced lung function in children at age 6 years in the COPSAC study, while for most of the other air pollutants the associations with lung function were null.

IMPLICATIONS OF THE FINDINGS

The results of these studies strengthen the existing evidence indicating that long-term exposure to ambient air pollution contributes to the development of asthma in early life through an altered immune profile. We observed these associations at levels of exposure that were generally below the European Union regulations for the levels of $PM_{2.5}$ and NO_2. Our findings support the new WHO air quality guidelines of 5 ug/m^3 for $PM_{2.5}$ and 10 ug/m^3 for NO_2, as annual mean levels with the observed increased risk for asthma incidence occur at levels just above these guidelines. Consistently, adverse effects were evident for $PM_{2.5}$ from multiple sources for all outcomes evaluated, while associations were less consistent for NO_2. The findings from our study support preventive actions toward cleaner motorized road vehicles, but they also indicate that additional actions resulting in a reduction of emissions from other sources, such as biomass burning, will be needed to protect the respiratory health of current and future generations of children.

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HEI QUALITY ASSURANCE STATEMENT

The conduct of this study was subjected to an independent audit by Westat staff members Dr. Susan Viet, 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: June 2023–September 2023; review of revisions December 2023–February 2024

Remarks: The Pedersen et al. study underwent an independent quality assurance (QA) audit by a Westat team consisting of four 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, presentation and interpretation of results, and appropriateness of study conclusions in the final report was performed by Drs. Abraham, Giangrande, Viet, and Wright of Westat.

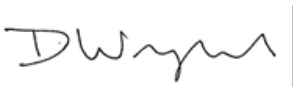
The Westat QA review of the final Pederson et al. report focused on adherence to the study protocol, appropriateness of the documentation of the study methods (e.g., data processing, exposure modeling, and statistical modeling), whether study assumptions and limitations were adequately addressed, and whether the investigators' conclusions were reasonable given the study findings and in consideration of the limitations. The QA team also evaluated whether the report was easy to understand.

The Westat QA audit team provided a written report to HEI and the study investigators. The Westat QA auditors concluded that the study was well conducted in accordance with the study protocol, and that the report was well written. The auditors also provide HEI and the investigator team with specific recommendations for improvement. Areas of QA feedback included clarification of the statement of objectives and the nature of the hypotheses guiding evaluation of exposure interactions, clarification of the potential consequence on the findings of several study limitations (e.g., missing data, exposure misclassification, outcome misclassification, and residual confounding), clarification of the hypothesized causal relationships as depicted in the directed acyclic graphs presented in the report, clarification of statistical models and model assumptions (e.g., covariance structure), clarification of results summaries, and clarification of inherent limitations of the study design.

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

Susan Marie Viet, Ph.D., Environmental and Exposure Scientist, Quality Assurance auditor

Joseph Abraham, Sc.D, Epidemiologist, Quality Assurance auditor



David Wright, Ph.D., Statistician, Quality Assurance auditor

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

Rebecca Jeffries Birch, M.P.H., Epidemiologist, Quality Assurance auditor

Date: July 15, 2024

SUPPLEMENTARY APPENDIX

Appendix A contains 4 figures and 11 tables not included in the main report. It is available on the HEI website at *www.healtheffects.org/publications.*

Appendix A: Supplementary Figures and Tables

ABOUT THE AUTHORS

Marie Pedersen is Associate Professor of Epidemiology in the Department of Public Health at the University of Copenhagen in Denmark and is also affiliated with the Statens Serum Institute, Department of Epidemiology, Copenhagen, Denmark. She received her PhD in Environmental Epidemiology from the University of Copenhagen. Her doctoral thesis was focused on transplacental exposure to environmental pollutants from ambient air and diet that was assessed by analyses of air and dust from the homes of pregnant women, questionnaire data, and biomarkers of exposures and effects in blood from mother–newborn pairs. She did her postdoctoral research at ISGlobal, Spain, and at Inserm, France, and has previously worked at the Danish Cancer Society Research Center, Denmark. Her research focuses on understanding the damaging and beneficial effects of environmental exposures on pregnant women and children's health from the earliest parts of the life course onward. She has experience with epidemiological studies, evaluating the associations between ambient air pollution and birth, pregnancy, and respiratory outcomes as well as integration of biomarkers of internal dose and early biological effects, to improve the assessment of early-life exposure to complex environmental and dietary exposures.

Shuo Liu is Medical Supervisor with the title of Dr. at Sinovac Biotech Co., Ltd in Beijing, China and he recently obtained his PhD from the Department of Public Health at the University of Copenhagen in Denmark under the supervision of Zorana Jovanovic Andersen, Marie Pedersen, Bert Brunekreef, and Torben Sigsgaard. His doctoral thesis was focused on the associations between long-term exposure to air pollution, road traffic noise and risk of asthma, COPD, and pneumonia in adults. He contributed to the data preparation and the statistical analyses of the asthma incidence studies as well as to several of the Danish studies of the ELAPSE project. Finally, Shuo Liu has also contributed to the training of Jiawei Zhang.

Zorana Jovanovic Andersen has a PhD from the Department of Public Health at the University of Copenhagen, where she is Professor in Environmental Epidemiology and the chair of the European Respiratory Society Environment and Health Committee. Her main research is on health effects of air pollution, including lung health (asthma, COPD, pneumonia, COVID-19), cardiovascular diseases, diabetes, cancer, and dementia. Prof. Andersen is passionate about advocacy on clean air and translation of knowledge from research to policy makers, as a member of the Copenhagen Municipality Air Pollution Expert Group, the Danish Council for Disease Prevention, the International Society of Environmental Epidemiology Policy Committee, International Network on Policy in Epidemiology, and the WHO Global Air Pollution and Health Technical Advisory Group.

Anne-Marie Nybo Andersen has an MD and is Professor of Epidemiology at the Department of Public Health, Faculty of Health Sciences, University of Copenhagen. She has a PhD in epidemiology. Her research group is working with maternal and child health, mainly using epidemiological approaches but also some health services research. The group finds special interest in the fetal, childhood, and long-term health effects of exposures in pregnancy, particularly gestational duration, social factors (including maternal and paternal age), infections and health behavior during pregnancy, reproductive immunology, and reproductive conditions. Birth cohort research is a key interest, and she was part of establishing the DNBC in 1995; since 2017 she has been the Principal Investigator for this large-scale cohort. She was a co-Principal Investigator of European Union-funded projects CHICOS and LifeCycle, which built up a close scientific collaboration among more than 15 birth cohorts in Europe, taking advantage of large numbers and great diversity, resulting in a number of research projects addressing common and rare, but important, child health outcomes. Additionally, she is leading research projects about the health effects of indoor pollution, causes of spinal pain in children, and cross-cohort analyses of preterm birth causes and consequences, with the aim of improving causal inference from epidemiological studies of childhood metabolic, respiratory, and mental health.

Jørgen Brandt is Professor of Atmospheric Modeling, Department of Environmental Science, Aarhus University. He received his PhD in Atmospheric Modeling from the University of Copenhagen. He is former Head of Section for Atmospheric Modeling and former Centre Director for the interdisciplinary center, iClimate (*iclimate.au.dk*). His main research areas are understanding the physical and chemical processes governing the atmosphere and impacts from human interactions. His research areas include atmospheric short- and long-range chemistry-transport modeling, climate change and air pollution interactions, epidemiological studies relating air pollution and health, integrated high-resolution forecasting of weather and air pollution from the local to the global scale, and the development of integrated model systems — coupling emissions and atmospheric models with human exposure models, health impacts (mortality and morbidity) and related socioeconomic valuation, and impacts on welfare.

Esben Budtz-Jørgensen is Professor and Head of the Section of Biostatistics at the Department of Public Health, University of Copenhagen. He has considerable experience in statistical analysis of complex multivariate data. One of his main research topics has been how to use latent variable models in environmental epidemiology. He has also researched methods for identifying safe exposure levels, consequences of exposure measurement error, methods for confounder selection, and modeling of genetic and neuroimaging data.

Klaus Bønnelykke is the head of research at COPSAC, a senior hospital physician, MD, PhD at the Gentofte hospital, and Professor of Pediatrics at the University of Copenhagen. His research is based at the COPSAC research center where he has a leading role in the clinical and genetic groups. His research area can be described as clinical translational research combining clinical data from birth cohort studies with basic research methodologies. The focus is early origins and functional subtypes of asthma, allergy, and eczema with a particular emphasis on genomics. This has resulted in novel discoveries of susceptibility genes and other risk factors for asthma, eczema, and allergy.

Lise Marie Frohn is Senior Scientist of Atmospheric Modeling, Department of Environmental Science, Aarhus University. She received her PhD in atmospheric modeling from the University of Copenhagen in 2003. Her research focuses on the composition and dynamical change of ambient air pollution on local, regional, and global scales. Her special interest is the environmental impacts of air pollution, both with respect to human health (mortality and morbidity) and natural environments (biodiversity decline, critical load, and level exceedance).

Matthias Ketzel is Professor of Atmospheric Modeling at the Department of Environmental Science, Aarhus University, Roskilde, Denmark, and Visiting Professor at the Global Centre for Clean Air Research (GCARE), University of Surrey, UK He received his PhD from Lund University, Sweden. He has a background in physics and fluid dynamics and has more than 30 years of experience within the field of atmospheric science, particularly in human exposure assessment and local-scale atmospheric dispersion modeling. His main scientific focus is on aerosol dynamics modeling and human exposure estimation at regional, urban, and street scales with a strong focus on particles and gaseous air pollutants.

Jibran Khan is Assistant Professor in Atmospheric Environment, Atmospheric Modeling Group, Department of Environmental Science, Aarhus University. He is involved in the Danish Big Data Centre for Environment and Health (BERTHA) project. He received his PhD in Environmental Science with Specialization in Atmospheric Modeling from Aarhus University in 2019. His PhD study focused on developing a new TRAP and noise exposure modeling system. His research interests lie in the integrated assessment based on modeling and measurements of air pollution, noise, and human exposure. Working closely with national and international researchers during his postdoc, he is broadening his research horizons toward climate science, COVID-19, artificial intelligence, data science, and smart and sustainable cities.

Casper-Emil Tingskov Pedersen is a postdoctoral research fellow in COPSAC where his work focuses on disentangling the effects of epigenetic markers on asthma risk in children and whether these markers co-occur with environmental factors, such as smoking and pollution. He completed his PhD in bioinformatics in 2017, working on demographic inferences from large-scale next-generation sequencing (NGS) data sets. He has been working extensively with sequence data and has published within fields spanning from conservation genetics to human genetics.

Leslie Thomas Stayner is Professor Emeritus of Epidemiology in the Division of Epidemiology and Biostatistics at the University of Illinois School of Public Health in Chicago. Previously he worked at the National Institute for Occupational Safety and Health for nearly 25 years and in his last position was the Chief of their Risk Evaluation Branch. His research interests are primarily in occupational and environmental factors, for example, NO_3^- in drinking water, asbestos, 1,3-butadiene, formaldehyde, diesel exhaust, hexavalent chromium, cadmium, silica, and ethylene oxide associated with cancer and reproductive outcomes, and epidemiological methods particularly with regard to quantitative risk assessment. He is serving as an advisor to numerous agencies including the International Agency for Research on Cancer, Agency for Toxic Substances and Disease Registry, US Environmental Protection Agency, National Research Council, Occupational Safety and Health Administration, Mine Safety Health Administration, the WHO, and the New York World Trade Center Health Registry.

Jiawei Zhang is a PhD candidate at the Department of Public Health at the University of Copenhagen in Denmark, under the supervision of Zorana Jovanovic Andersen, Youn-Hee Lim, and Rudi GJ Westendorp. In his doctoral research he evaluates the associations between long-term exposure to air pollution and the risk of morbidity and mortality from COVID-19, pneumonia, and other lower respiratory infection diseases. He is contributing to the statistical analysis of the lung function studies as well as to several Danish national studies in the ELAPSE project.

Bert Brunekreef is Professor Emeritus of the Institute for Risk Assessment Sciences, Utrecht University, the Netherlands, with a PhD from Wageningen University, the Netherlands. He has long-standing experience in research on the health effects of outdoor and indoor air pollution. He serves as an advisor to the WHO.

Steffen Loft is Professor of Environmental Medicine in Environmental Health, Department of Public Health, University of Copenhagen. He has long-standing experience in research on the health effects of outdoor and indoor air pollution, including experimental models, human intervention studies, and epidemiology that leverages the unique and rich Danish data infrastructure with large well-described cohorts as well as with the entire population.

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Research Report 219, *Birth Cohort Studies of Long-Term Exposure to Ambient Air Pollution in Early Life and Development of Asthma in Children and Adolescents from Denmark,* M. Pedersen et al.

INTRODUCTION

HEI established the Walter A. Rosenblith New Investigator Award as a career development award to provide funding for outstanding early career investigators. Dr. Marie Pedersen of the University of Copenhagen submitted an application entitled "Impact of Exposure to Air Pollution on Asthma: A Multi-Exposure Assessment" in response to Request for Applications 16-1. Dr. Pedersen proposed to test the hypothesis that early-life exposure to ambient air pollution from multiple sources has individual and joint effects on the risk of development of asthma in children and adolescents. Additionally, Dr. Pedersen proposed to investigate the mechanistic basis for these effects by studying changes in lung function, nasal epithelial DNA methylation, gene expression, nasal mucosal immune mediators, and systemic immunological markers measured in children. HEI's Research Committee recommended funding Dr. Pedersen's proposed study because they thought it had several strong features, including the assessment of three large birth cohorts, a novel multipollutant approach, and a focus on asthma incidence, which is an important but understudied topic.

Due to several delays encountered during the study, including staffing issues related to the global COVID-19 pandemic, Dr. Pedersen was not able to complete the original goal of conducting multipollutant analyses; she did conduct single- and two-pollutant modeling.

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 both the strengths and limitations of the study and by placing the results presented in the Investigators' Report into a broader scientific and regulatory context.

Dr. Marie Pedersen's three-year study, "Impact of Exposure to Air Pollution on Asthma: a Multi-Exposure Assessment," began in January 2018. Total expenditures were $330,135. The draft Investigators' Report from Pedersen and colleagues was received for review in August 2022. A revised report, received in April 2023, was accepted for publication in June 2023. During the review process, the HEI Review Committee and the investigators had the opportunity to exchange comments and to 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.

SCIENTIFIC AND REGULATORY BACKGROUND

Exposure to air pollutants is associated with a myriad of health effects, including cancer, adverse birth outcomes, and respiratory, cardiovascular, and neurological diseases (International Agency for Research and Cancer 2016; US Environmental Protection Agency [US EPA*] 2019; World Health Organization 2021). Even though air pollution levels have decreased over the past few decades in high income countries, associated health effects are still observed at levels at or below current air quality standards (Brauer et al. 2019, 2022; Brunekreef et al. 2021; Chen and Hoek 2020; Dominici et al. 2019, 2022).

Based on this mounting evidence, the World Health Organization released new Air Quality Guidelines in 2021 (World Health Organization 2021). It recommended that annual mean concentrations of particulate matter <2.5 µm in aerodynamic diameter ($PM_{2.5}$) and nitrogen dioxide (NO_2) should not exceed 5 and 10 µg/m^3, respectively, and noted that adverse health effects have been documented to occur above these values (World Health Organization 2021). The US EPA recently lowered the annual $PM_{2.5}$ National Ambient Air Quality Standards from 12 µg/m^3 to 9 µg/m^3 (US EPA 2024).

Exposure to $PM_{2.5}$ and other air pollutants is associated with increased risk of asthma, a chronic disease that affects 262 million people worldwide (Vos et al. 2020) and is the most common chronic disease in children. Asthma leads to reduced quality of life, emergency room visits, hospitalizations, and missed school and work days. It is associated with high health care costs (World Health Organization 2007). Asthma prevalence (see **Sidebar 1**) among children and adolescents in high-income countries has increased in recent decades (Eder Waltraud et al. 2006), and better knowledge of the contribution of modifiable risk factors to asthma is needed. In particular, studies on the associations between exposure to individual and joint air pollutants in relation to childhood asthma incidence and on relevant windows of exposure are scarce as was found in the comprehensive scientific review conducted by HEI (2022). That review examined the evidence for associations between several adverse health effects and traffic-related air pollution (TRAP) and was conducted by a panel of 13 renowned experts who evaluated 353 published scientific reports on traffic pollution and related health effects between 1980 and 2019. Additionally, the biological mechanisms of the association between air pollution exposure and asthma are not well understood (Kayalar et al. 2024; Korten et al. 2017). Because of those gaps, Dr. Pedersen proposed to

SIDEBAR 1. Asthma onset, incidence, prevalence, and exacerbation

Asthma is a complex and poorly defined syndrome characterized by several phenotypes as a result of different etiologies, especially in children (Martinez et al. 1995). The definition and ascertainment of respiratory disease end points, such as asthma, has been problematic in epidemiological studies and in clinical settings. The reason for such difficulties lies in the distinct physiopathological mechanisms, namely, subtle and progressive onset, presentation of a wide array of potentially transient symptoms (especially in children), persistent or chronic course, and objective measures (e.g., lung function tests) that are not uniformly available and sometimes not entirely informative (Bakke et al. 2011; Kemp et al. 1996; Pekkanen et al. 2005; Subbarao et al. 2009). Several considerations regarding asthma are summarized below as they help in the interpretation of this report.

- Asthma incidence or risk refers to the number of persons newly diagnosed with asthma among the people at risk in the study population. In this study, asthma incidence has been defined as the first physician diagnosis of asthma or by algorithms based on medication and health services used for that condition.
- Asthma prevalence is the proportion of the total number of persons with asthma among the total study population (i.e., both newly diagnosed and pre-existing). Asthma prevalence can be further divided into *having ever been diagnosed with asthma* (or lifetime asthma) and *active asthma*. Prevalence of having ever been diagnosed with asthma is the proportion of people who have had a diagnosis of the disease during their lifetime. This is mainly based on questionnaire responses but also on medical records or drug prescriptions. In this study, active (or current) asthma refers to a prevalence measure using questionnaires and based on either asthma diagnosis in the last 12 months or asthma symptoms in the last 12 months when an asthma diagnosis was given in the past. There is an overlap between the measures *having ever been diagnosed with asthma* and *active asthma* because active cases are also classified as having ever had asthma.
- Asthma onset is the first appearance of the disease during the life course. Often, asthma and asthma-like symptoms at a very young age are transient and do not result in asthma that persists into adulthood. The term asthma onset can be misleading when it is used in studies of young children because asthma is difficult to diagnose before age six or seven.
- Asthma exacerbation refers to exacerbation of the disease among individuals with pre-existing asthma. Asthma exacerbations are common in children and adults with asthma, and the main goal of asthma management is the prevention of exacerbations and airflow limitation. Asthma exacerbations can range from mild to severe with the most severe forms generally requiring an emergency room visit and likely hospitalization and can be fatal.
- The most important window of exposure for asthma onset or for incidence of asthma in children is not known. Different periods can be relevant, such as prenatal, postnatal, or early life, but critical exposure windows remain difficult to investigate in epidemiological studies. This report contributes to our knowledge of critical windows of exposure for a range of air pollutants.

investigate early-life air pollution exposures from multiple sources and in different exposure windows in relation to asthma, asthma-related outcomes, and biomarkers of disease using data from three longitudinal birth cohort studies in Denmark. Dr. Pedersen proposed to investigate exposures to an array of air pollutants, including the criteria pollutants — particulate matter (PM), ozone, sulfur dioxide, NO_2, and combinations of those pollutants.

STUDY OBJECTIVES

The overarching goals of this study were to examine associations between asthma and both prenatal and postnatal exposure to ambient air pollutants among children born in Denmark between 1998 and 2016. Dr. Pedersen and colleagues assessed four outcomes related to childhood asthma: (1) risk of developing asthma based on physician diagnosis (asthma incidence); (2) total proportion of children with asthma based on parental-reported asthma and asthma-related symptoms at age seven (asthma prevalence); (3) biomarkers of inflammation that are suspected to be in the biological pathway for asthma development, DNA methylation, and gene expression in nasal epithelial cells at four weeks and in blood at six months; and (4) lung function in children at age six by assessing airway obstruction, which is one of the main tests in asthma diagnosis.

Dr. Pedersen and colleagues used data from four longitudinal birth cohort studies of live-born singletons born in Denmark to investigate early-life air pollution exposures from multiple sources in relation to asthma and asthma-related outcomes. They assessed exposure to an array of ambient air pollutants, including $PM_{2.5}$, PM_{10}, and NO_2, using prenatal averages and mean averages for various periods in early life. Their modeling system for human exposures to air pollution from multiple sources was developed by the Department of Environmental Science at Aarhus University, Denmark. They investigated the associations between those air pollutants and asthma incidence, asthma prevalence, lung function — assessed as forced expiratory volume in 1 second (FEV_1) — and asthma-related biomarkers. Additionally, they conducted single- and two-pollutant analyses for asthma incidence and lung function.

Commentary Table. Characteristics of Four Danish Study Populations Used to Investigate Associations Between Exposure to Ambient Air Pollution and Childhood Asthma

	Study Populations			
	Nationwide Cohort	**DNBC**	**$COPSAC_{2010}$**	**$COPSAC_{2000}$ + $COPSAC_{2010}$**
Study area	Denmark (nationwide)	Denmark (nationwide)	Zealand, Denmark	Zealand, Denmark, and Greater Copenhagen, Denmark
Years of birth	1998–2016	1998–2003	2008–2010	1998–2001, 2008–2010
Population size	1,060,154	22,084	700	803
Inclusion/ Exclusion criteria	Live-born singletons with data on exposures and maternal data on education, income, smoking, asthma, and parity	Live-born singletons with data on exposures, DNBC interview 1, asthma at 7 years, asthma at 11 years, and maternal data on education, income, smoking, asthma, parity, and breastfeeding	Live-born with data on exposures, outcomes, and covariates	Live-born singletons with data on exposure, outcomes, and covariates
Outcomes	Asthma Incidence (ICD-10 codes)	Asthma incidence (ICD-10 codes), asthma prevalence at age 7 (parental recall of physician-diagnosed asthma)	Cytokines in blood from 6 months of age Nasal epithelial DNA methylation and gene expression at age 4 weeks Asthma prevalence at age 6 (parental recall and clinical judgment) Allergic sensitization prevalence at age 6 (skin prick test) Allergic rhinitis at age 6 (parental recall and clinical judgment)	Lung function at age 6 (forced expiratory volume in 1 second, FEV_1)
Statistical analyses	Incidence: Cox proportional hazards models	Incidence: Cox proportional hazards models Prevalence: logistic regression and Poisson regression	Linear regression	Mixed-effect linear regression
Single- and two-pollutant models	Single- and two-pollutant models	Single-pollutant models	Single-pollutant models	Single- and two-pollutant models

COPSAC = Copenhagen Prospective Studies on Asthma in Childhood, DNBC = Danish National Birth Cohort, ICD = International Classification of Diseases

SUMMARY OF METHODS AND STUDY DESIGN

STUDY POPULATION

Dr. Pedersen and colleagues linked different data sources to create a nationwide cohort and additionally used three existing Danish population-based cohort studies (see **Commentary Table**) to investigate associations between exposure to ambient air pollution and childhood asthma: (1) a nationwide registry-based cohort of all live-born singletons born in Denmark (n = 1,060,154); (2) a subset of the nationwide cohort, the Danish National Birth Cohort (DNBC) (n = 22,084 live-born singletons); and (3) the Copenhagen Prospective Studies on Asthma in Childhood cohorts ($COPSAC_{2000}$ and $COPSAC_{2010}$) on the island of Zealand where Copenhagen is located (n = 803 live-born singletons). Pedersen and colleagues restricted their analyses to children born during 1998–2016 based on the availability of information on air pollution exposure and maternal tobacco smoking during pregnancy. The incorporation of smaller cohorts with individual covariate information and very large administrative cohorts (although with less detailed information) leveraged the merits of both approaches.

EXPOSURE ASSESSMENT

Dr. Pedersen and colleagues used the DEHM-UBM-AirGIS air pollution modeling system with the Operational Street Pollution Model for ambient air pollution, which was developed by the Department of Environmental Science at Aarhus University, Denmark (Brandt et al. 2001, 2012; Hvidtfeldt et al. 2018; Jensen et al. 2017; Khan et al. 2019). This air pollution modeling system has been extensively validated and applied in many earlier studies. Dr. Pedersen and colleagues used this system to model ambient air pollution concentrations of 13 pollutants, including $PM_{2.5}$, PM_{10}, and NO_2, from all sources at a fine spatial and temporal resolution. Pollutant concentrations were estimated at each residential address and each time period on an hourly basis for the entire study population from January 1, 1997 to December 31, 2017. Pedersen and colleagues estimated prenatal and postnatal (first year of life) time-weighted mean exposures, taking residential mobility into account. Additionally, they estimated mean long-term exposure from birth to the age of follow up and the annual mean the year prior to outcome assessment for analyses that investigated asthma prevalence at age 7 and lung function at age 6.

OUTCOME ASSESSMENT

Dr. Pedersen and colleagues assessed four outcomes related to childhood asthma. First, they assessed the risk of developing asthma from birth until asthma diagnosis, end of follow up on December 31, 2016, date of emigration, or death during follow up, whichever came first, based on ICD-10 codes among the nationwide cohort. Within this cohort, the risk of asthma was also assessed in children with four or more years of follow-up time because asthma is difficult to diagnose in young children.

Second, they assessed the total proportion of children with asthma among the DNBC participants (i.e., asthma prevalence). In this analysis, they used parental-reported asthma and asthma-related symptoms from questionnaires at age seven to identify children who were ever diagnosed with asthma and those who had active asthma (see Sidebar 1 and **Sidebar 2**).

Third, they assessed biomarkers of inflammation that are suspected to be in the biological pathway for asthma development, including cytokines, interleukins (IL), and tumor-necrosis-factor-α (TNF-α), DNA methylation, and gene expression in nasal mucosal lining fluid collected at 4 weeks and in blood collected at 6 months of age in the $COPSAC_{2010}$ participants.

Fourth, and finally, they assessed lung function in children at age six in the $COPSAC_{2000}$ and the $COPSAC_{2010}$. They used spirometry data of FEV_1, which assesses airway obstruction and is one of the main tests in asthma diagnosis.

COVARIATES

Dr. Pedersen and colleagues used a directed acyclic graph to identify potential confounders of the association of air pollution exposure and asthma. They obtained information on a vast array of individual-level confounders, including covariates related to pregnancy and birth, maternal smoking during pregnancy, seasonality, socio-economic status, maternal and paternal asthma, presence of indoor sources of air pollutants, breastfeeding, and lifestyle factors. They also obtained information on neighborhood-level confounders, including municipality (which reflects differences in land and water cover, population size, schooling, primary care, and other public services) and area-level socio-economic status. Finally, Dr. Pedersen and colleagues adjusted for short-term exposures to investigate associations between long-term exposures and biomarkers of inflammation.

STATISTICAL ANALYSES

Dr. Pedersen and colleagues used Cox proportional hazards models to estimate associations between ambient air pollution exposure and asthma incidence using hazard ratios (HR) with 95% confidence intervals (CI). They used logistic regression models to estimate associations between ambient air pollution exposure and asthma prevalence using prevalence odds ratios (POR) with 95% CIs. They used mixed-effects linear regression analyses with random effects to estimate associations between air pollution exposure and lung function. The results were reported using relative difference (RD) and 95% CIs. All models were performed with increasing level of adjustment for selected covariates. The investigators performed analyses using linear single-pollutant models separately in each exposure period (prenatal, first year of life, and until follow up). Additionally for asthma incidence and lung function, they performed analyses using two-pollutant models with $PM_{2.5}$ and NO_2 as the second pollutant. To assess robustness of

SIDEBAR 2. Asthma outcome assessment in children

Most previous studies have used self-administered questionnaires to define asthma and asthma-like symptoms, with parents responding on behalf of their children (Kemp et al. 1996). Questionnaires are useful in epidemiological studies because they have lower administrative costs and allow larger sample sizes compared with intensive and expensive data-collection methods. The appropriateness of using self-reported data to assess asthma in etiological studies has been debated, mainly due to problems associated with participants' recall of events and individual differences in symptom perception. These concerns are especially relevant to studies related to potential exposures to air pollution because knowledge of exposure could favor increased reporting of symptoms and result in reporting bias. However, the use of a medical diagnosis of asthma in epidemiological studies can overestimate or underestimate the occurrence of the disease in a population, depending on various factors, including physician practices and the availability of medical care (Kemp et al. 1996). For those reasons, questionnaires of self-reported symptoms (or parental report) have become the method of choice for large comparative prevalence studies (Asher et al. 1995; Burney et al. 1994), especially those assessing wheezing (the dominant symptom of asthma). However, use of self-reported symptoms to identify asthma cases can cause the occurrence of asthma to be overestimated in populations of preschool aged children because asthmatic symptoms (including wheezing, chest tightness, breathlessness, and coughing) might be related to viral infections rather than to a true asthmatic condition (transient wheezing), and the children might be too young for a medical diagnosis of asthma (Martinez et al. 1995).

In many countries, it is possible to obtain information about asthma diagnosis by using population-based registry data or administrative data, such as emergency room visits, hospitalizations, or prescriptions for specific drugs (e.g., bronchodilators). Those methods can be useful as they do not depend on participants' recall, but they primarily capture more severe asthma and the potential remains for disease misclassification. A validation study aimed at determining the prevalence of asthma in a population of children in Denmark that used three classification methods (self-report, population-based hospitalization data, and population-based prescription data) in a large prospective birth cohort did not find a substantial overlap among cases identified by the three methods (Hansen et al. 2012). That result suggests that the three methods might identify asthma cases with biologically distinct phenotypes. For example, the hospitalization registry might capture more severe phenotypes than would the prescription registry or maternal self-reporting.

the associations of air pollution and asthma incidence, they conducted various sensitivity analyses, including analyses based on residential location, testing for effect modification by sex, and restricting the analyses to participants who had not changed residence during the study period (nonmovers).

SUMMARY OF KEY RESULTS

AIR POLLUTION EXPOSURE

Children in the nationwide cohort were exposed to prenatal average $PM_{2.5}$ concentrations of 10.5 µg/m^3 (standard deviation [SD]: 1.8), PM_{10} concentrations of 16.6 µg/m^3 (SD: 2.2), and NO_2 concentrations of 17.5 µg/m^3 (SD: 7.4). Dr. Pedersen and colleagues observed decreasing mean concentrations of all pollutants over the study period, except for ozone and sea salt. Spearman correlation coefficients (*Rs*) between prenatal and postnatal exposure were high ($Rs > 0.80$) for NO_2, nitrogen oxides, elemental carbon, and sulfate.

ASTHMA RISK IN THE DANISH NATIONWIDE COHORT

In the nationwide cohort of about one million children, 6.1% were diagnosed with asthma over the mean course of 8.8 years of follow up. Prenatal exposure to all air pollutants except for ozone and sea salt was associated with increased risk of developing asthma (i.e., asthma incidence) (**Commentary Figure 1**).

Similarly, postnatal exposure to most air pollutants was also associated with increased risk of developing asthma and associations were consistent after adjustment for prenatal exposures. However, postnatal exposure to ozone, nitrate, and secondary organic aerosols was inversely associated with risk of developing asthma, in other words, exposure to higher concentrations of these pollutants was associated with lower risk of asthma. In two-pollutant models, the investigators observed that the association between prenatal exposure to $PM_{2.5}$ and asthma incidence was more consistent than was the association between prenatal exposure to NO_2 and asthma incidence.

ASTHMA PREVALENCE IN THE DANISH NATIONAL BIRTH COHORT

In the study of 22,084 children in the DNBC, 2,188 (9.9%) had ever been diagnosed with asthma and 978 (4.4%) had active asthma at age 7 (asthma prevalence). Neither prenatal nor postnatal air pollution exposures were significantly associated with asthma prevalence at age 7 based on parental recall. Within this subpopulation, Dr. Pedersen and colleagues conducted sensitivity analyses that compared associations among those who had not changed addresses (assessed at age

11, when data on home characteristics were collected) and among those who had moved between birth and age 7 (when asthma information was collected). Effect estimates were slightly higher among nonmovers compared with those who had moved since birth, although CIs were wide and included the null.

LUNG FUNCTION AND IMMUNE MEDIATORS IN THE COPENHAGEN PROSPECTIVE STUDIES ON ASTHMA IN CHILDHOOD COHORTS

Finally, lung function was assessed in the study of 703 children in the $COPSAC_{2000}$ and $COPSAC_{2010}$. Prenatal exposures to $PM_{2.5}$ and ammonium were associated with a 2%–3% (95% CI: 1%–5%) reduction in mean FEV_1 at age 6 (**Commentary Figure 2**). Additionally, prenatal exposure to PM_{10} and postnatal exposures to sulfate and nitrate were also associated with reduced lung function. Prenatal exposures to $PM_{2.5}$, PM_{10}, and NO_2 were associated with altered profiles of biomarkers of immune mediators. At age 4 weeks, altered profiles included decreased levels of cytokines CCL22 and CCL26, whose functions are ambiguous, and increased levels of interleukins IL-5, IL-4, and IL-2, which are associated with asthma and anti-inflammatory type 2 immune responses. At age 6 months, pro-inflammatory markers IL-8 and TNF-α were increased, while other pro-inflammatory markers IL-1β and IL-6 were decreased, presenting a unique immune signature.

HEI REVIEW COMMITTEE'S EVALUATION

In its independent review of the study, the HEI Review Committee commended Dr. Pedersen on her impressive study, which was a great achievement for an early career investigator. The Review Committee emphasized several study strengths, including the use of two-pollutant models, the robust study approach, and the study contributions to our understanding of the associations between exposure to ambient air pollutants and childhood asthma. The study demonstrated that long-term exposure early in life to ambient air pollution from traffic and other sources was associated with increased rates of physician-diagnosed asthma incidence in children. The associations were consistent for a range of air pollutants, with the exception of ozone and sea salt. However, long-term exposure to ambient air pollution was not associated with increased rates of asthma prevalence based on parental recall. The Committee agreed with Dr. Pedersen and colleagues that the findings suggest that both prenatal and postnatal ambient air pollution exposures affect asthma development. They also agreed that how and when asthma and asthma-related outcomes are assessed influences the observed associations, thereby playing a critical role in our understanding of asthma risk factors.

STRENGTHS OF THE STUDY

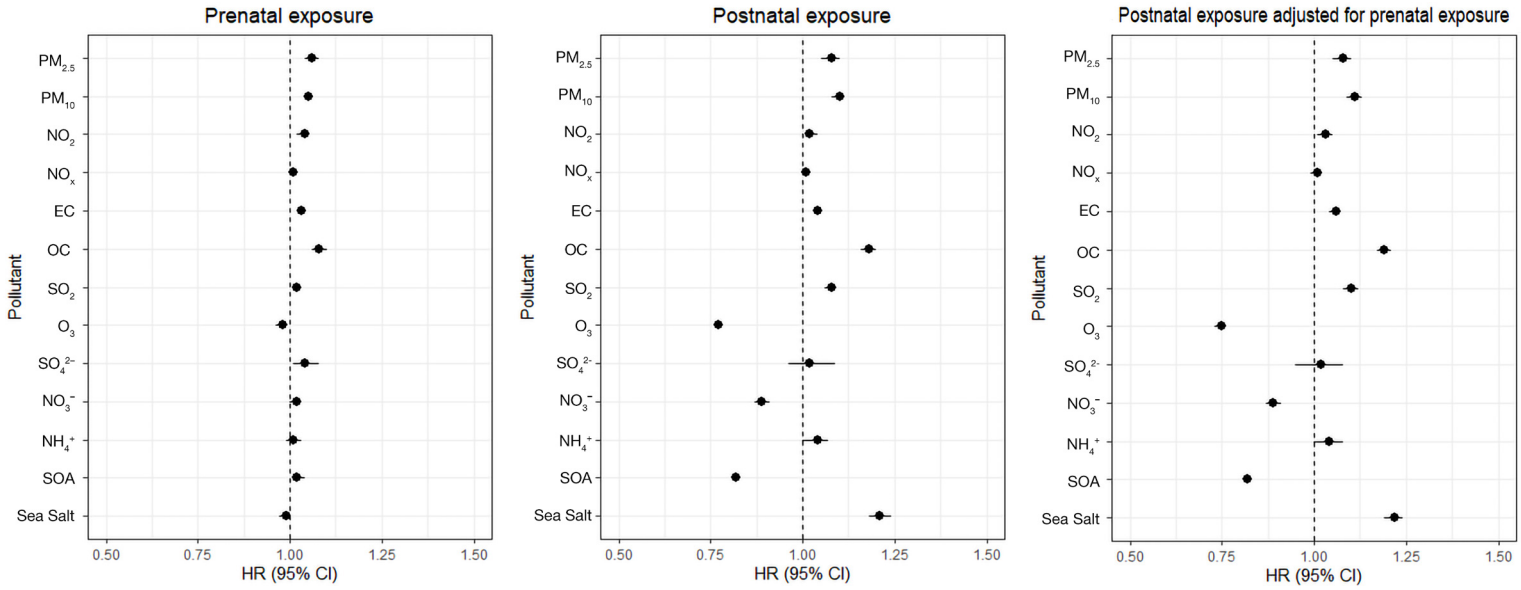
A major strength of the study was the Danish population-based setting, which uses a unique personal identification number system. Dr. Pedersen and colleagues leveraged many valuable registers with information on the entire population in Denmark. The national registries include complete residential address history and near-complete information on health care data, which is accessible for register-based research without informed consent under Danish law. Leveraging data from the nationwide cohort bolstered the study with a very large sample size (1.1 million children) and was nationally representative 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 validated in previous Danish studies and that allows exposure estimations for a range of air pollutants from multiple sources for the entire population in Denmark at a fine spatial and temporal scale. The two-pollutant approach to supplement the single-pollutant analyses of 13 pollutants was another study strength, as was the robustness of the sensitivity analyses and repeated analyses using Poisson regression models.

LIMITATIONS

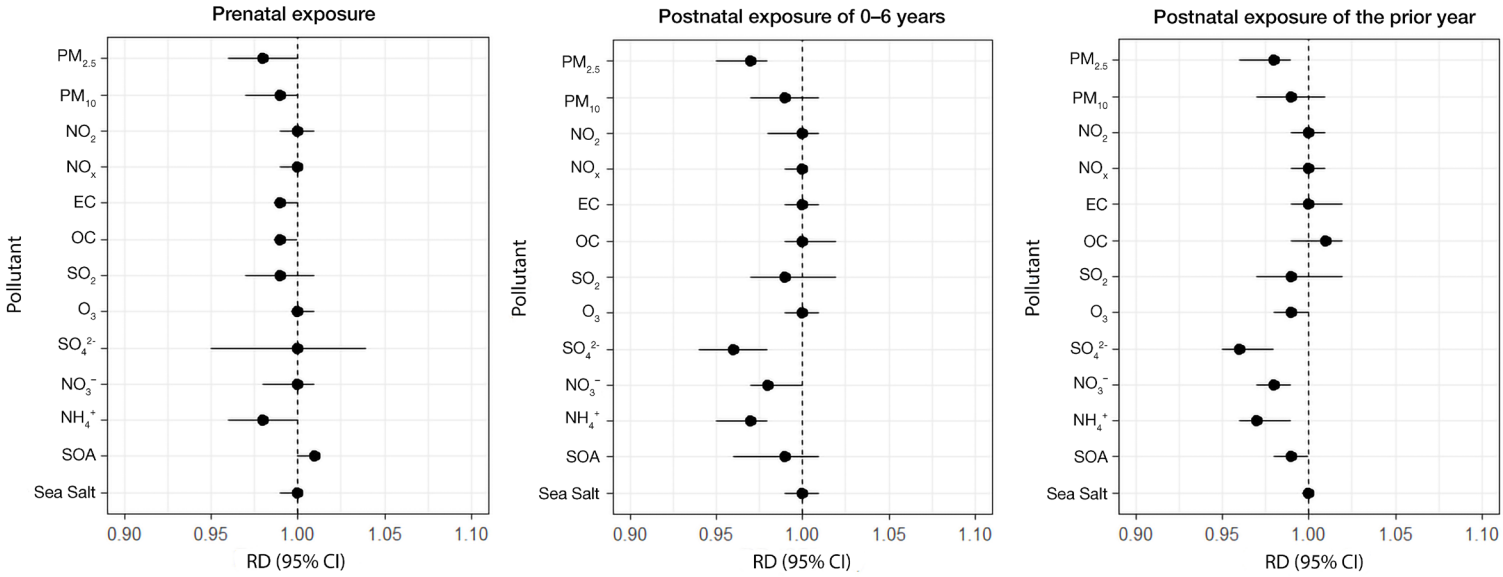
The committee noted some limitations to the study, including the low interquartile ranges for most modeled air pollutants in the nationwide cohort, indicating that there was not a wide range in exposures within the study. A lower interquartile range makes it more difficult to detect an association if there is one, and a narrow range in exposures can reduce the generalizability of the findings. Although exposure estimates were available at a fine temporal scale for each residential address, this study did not estimate exposure to air pollutants during time away from the home — a limitation in many epidemiological studies. However, another European study found that residential air pollution exposure estimates sufficiently captured annual exposure estimates among 8-year-old children in the Netherlands (Ntarladima et al. 2021). Finally, the Review Committee noted that it would have been more appropriate to estimate prevalence ratios (PR) and 95% CIs instead of PORs and 95% CIs in the DNBC cohort (Pearce 2004; Thompson et al. 1998). However, the results between the PR and POR analyses were similar.

GENERALIZABILITY

The Review Committee had some concerns about the generalizability of the study. Although the Danish health care setting is a strength of the study, medical care is more accessible in Denmark compared with other countries, such as the United States, which might influence the results that rely on physician diagnosis. Reliance on physician diagnosis compared with parental recall for assessing asthma incidence and prevalence potentially limits the generalizability of the findings. Additionally, although Dr. Pedersen and colleagues included a nationwide cohort, the Danish population is predominantly white, receives relatively high levels of social support, and has relatively high levels of education, compared with most other countries. Thus, the findings may not be generalizable for populations with greater racial, ethnic, and socio-economic diversity.



Commentary Figure 1. Associations between exposure to ambient air pollution and asthma incidence in the Nationwide Cohort of 1,060,154 children born in Denmark, 1998–2016. CI = confidence interval, HR = hazard ratio.



Commentary Figure 2. Associations between exposure to ambient air pollution and lung function (FEV_1) at age 6 in 703 children born in Denmark 1998–2001 and 2008–2010 from the Copenhagen Prospective Studies on Asthma in Childhood ($COPSAC_{2000\ \&\ 2010}$) cohorts. CI = confidence interval; RD = relative difference.

TWO-POLLUTANT AND MULTIPOLLUTANT MODELING

The novel multipollutant analyses proposed in the application were considered one of the strengths of the proposed work by the Research Committee. Although the completed study did not include the multipollutant analyses as intended, partly due to delays related to the COVID-19 pandemic, the Review Committee commended the work presented in Dr. Pedersen's report and the use of two-pollutant analyses when multipollutant modeling was not possible. Multipollutant models have proven to be a major challenge in epidemiological research, and statistical methods for multipollutant assessments remain an important area of development (Coull et al. 2015; Dominici et al. 2010; Joubert et al. 2022; Molitor et al. 2016; Park et al. 2015). Additionally, interconnections among individual pollutants (such as some pollutants being in the formation pathway of others), data and exposure limitations, and reliance on dimension reduction techniques pose challenges in assessing multiple exposures.

One example where two-pollutant and multipollutant assessments might provide further insights is in better understanding the observation of the inverse association between ozone exposure and risk of asthma exposure in the nationwide cohort. Dr. Pedersen hypothesized that this finding might be due to higher concentrations of ozone typically being accompanied by lower concentrations of NO_2 (Janssen et al. 2017). Although this is beyond the scope of the report, the Review Committee noted that further investigation using two-pollutant models for ozone and NO_2 would provide an opportunity to test that hypothesis. Other European studies have also observed reduced risk of adverse health outcomes associated with ozone exposure, in contrast to studies based in the United States (Brunekreef et al. 2021). The discrepancies in findings on ozone exposure between studies based in North America and Europe is an active area of investigation and might provide some explanation for findings in this study.

CONCLUSIONS

In summary, this study represents an important contribution to our knowledge about exposure to ambient air pollutants in relation to childhood asthma and immune mediators. The study's findings suggest that both prenatal and postnatal ambient air pollution exposures affect asthma development. These findings were observed at fine particulate matter and nitrogen dioxide levels below the current (25 and 40 μg/m^3) and even the proposed (10 and 20 μg/m^3) annual European Union air quality standards. Additionally, the study found that asthma outcome assessment methods are critical in better understanding asthma risk factors and prevalence.

The study observed less consistent results for associations of air pollution exposures with asthma-related immune mediators and with lung function. However, the report presents an important step toward the better understanding of air pollution exposure in relation to asthma development, including specific risk factors and critical windows of exposure.

Continued development of two-pollutant and multipollutant models would further advance our understanding of asthma risk and development. Ultimately, this study has documented that prenatal and postnatal exposures to ambient air pollutants are associated with increased risk of childhood asthma in Denmark.

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 both the strengths and limitations of the study and by placing the results presented in the Investigators' Report into a broader scientific and regulatory context.

ACKNOWLEDGMENTS

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ABBREVIATIONS AND OTHER TERMS

AirGIS	a Geographical Information Systems-based air pollution and human exposure modeling system
ATS	American Thoracic Society
BAMSE	Barn, Allergi, Miljö, Stockholm och Epidemiologi (Children, Allergy, Milieu, Stockholm, Epidemiology)
BIB	Born in Bradford
BC	black carbon
CHS	Children's Health Study
CI	confidence interval
CCL	C-C motif chemokine protein
COPSAC	Copenhagen Prospective Studies on Asthma in Childhood
COPD	chronic obstructive pulmonary disease
CRP	C-reactive protein
DEHM	Danish Eulerian hemispheric model
DNA	deoxyribonucleic acid
DNBC	Danish National Birth Cohort
DNPR	Danish National Patient Register
EC	elemental carbon
EDEN	Étude des Déterminants pré et postnatals du développement de la santé de l'enfant (study on the pre- and early postnatal determinants of child health and development)
ELAPSE	Effects of Low-Level Air Pollution: A Study in Europe
ESCAPE	European Study of Air Pollution Effects
ETS	environmental tobacco smoke
FEV_1	forced expiratory volume in 1 second
FVC	forced vital capacity
GASPII	Gene and Environment Prospective Study in Italy
GINI	German Infant Nutritional Intervention
HR	hazard ratio
ICD	International Classification of Diseases
IFN-γ	interferon-γ
IL	interleukin
INMA	Infancia y Medio Ambiente (Childhood and Environment)
IQR	interquartile range
ISAAC	International Study of Asthma and Allergies in Childhood
LISA	Influences of Lifestyle related Factors on the Immune System and the Development of Allergies in Childhood
LSV	Low Volume Sampler
LUR	land use regression
MAAS	Manchester Asthma and Allergy Study
MeDALL	mechanisms of the development of allergy
NH_4+	ammonium
NO_2	nitrogen dioxide
NO_x	nitrogen oxides
NO_3-	nitrate
O_3	ozone
OC	organic carbon
OR	odds ratio
OSPM	Operational Street Pollution Model
POR	prevalence odds ratio
PR	prevalence ratio
PIAMA	Prevention and Incidence of Asthma and Mite Allergy
PM	particulate matter
$PM_{2.5}$	particulate matter ≤2.5 μm in aerodynamic diameter
PM_{10}	particulate matter ≤10 μm in aerodynamic diameter
RD	relative difference
RR	risk ratio
Rs	Spearman correlation coefficient
SES	socioeconomic status
SD	standard deviation
SOA	secondary organic aerosols
SO_2	sulfur dioxide
SO_4^{2-}	sulfate
TGF-β1	transforming growth factor beta 1
TNF-α	tumor necrosis factor-α
TRAP	traffic-related air pollution
UFP	ultrafine particles
UBM	urban background model
US EPA	United States Environmental Protection Agency
WHO	World Health Organization

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196	Developing Multipollutant Exposure Indicators of Traffic Pollution: The Dorm Room Inhalation to Vehicle Emissions (DRIVE) Study	J.A. Sarnat	2018
192	Multicenter Ozone Study in oldEr Subjects (MOSES)		
	Part 1. Effects of Exposure to Low Concentrations of Ozone on Respiratory and Cardiovascular Outcomes	M.W. Frampton	2017
	Part 2. Effects of Personal and Ambient Concentrations of Ozone and Other Pollutants on Cardiovascular and Pulmonary Function	D.Q. Rich	2020
190	The Effects of Policy-Driven Air Quality Improvements on Children's Respiratory Health	F. Gilliland	2017
183	Development of Statistical Methods for Multipollutant Research		
	Part 1. Statistical Learning Methods for the Effects of Multiple Air Pollution Constituents	B.A. Coull	2015
	Part 2. Development of Enhanced Statistical Methods for Assessing Health Effects Associated with an Unknown Number of Major Sources of Multiple Air Pollutants	E.S. Park	2015
	Part 3. Modeling of Multipollutant Profiles and Spatially Varying Health Effects with Applications to Indicators of Adverse Birth Outcomes	J. Molitor	2016
142	Air Pollution and Health: A European and North American Approach	K. Katsouyanni	2009
139	Effects of Long-Term Exposure to Traffic-Related Air Pollution on Respiratory and Cardiovascular Mortality in the Netherlands: The NLCS-AIR Study	B. Brunekreef	2009
Special Report			
23	Systematic Review and Meta-analysis of Selected Health Effects of Long-Term Exposure to Traffic-Related Air Pollution	Health Effects Institute	2022
Perspectives			
1	Airborne Particles and Health: HEI Epidemiologic Evidence	Health Effects Institute	2001

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