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COMMENTARY BY THE
HEI REVIEW COMMITTEE

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

Pedersen et al.

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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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with a Commentary by the HEI Review Committee

Research Report 219

Health Effects Institute

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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 HEI Improved Exposure Assessment Studies Review Panel, 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 Panel are widely disseminated through HEI's website (*www.healtheffects.org*), reports, newsletters, annual conferences, and presentations to legislative bodies and public agencies.

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Research Report 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 the associations of air pollution and asthma incidence, they conducted various sensitivity analyses, including analyses

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.

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.

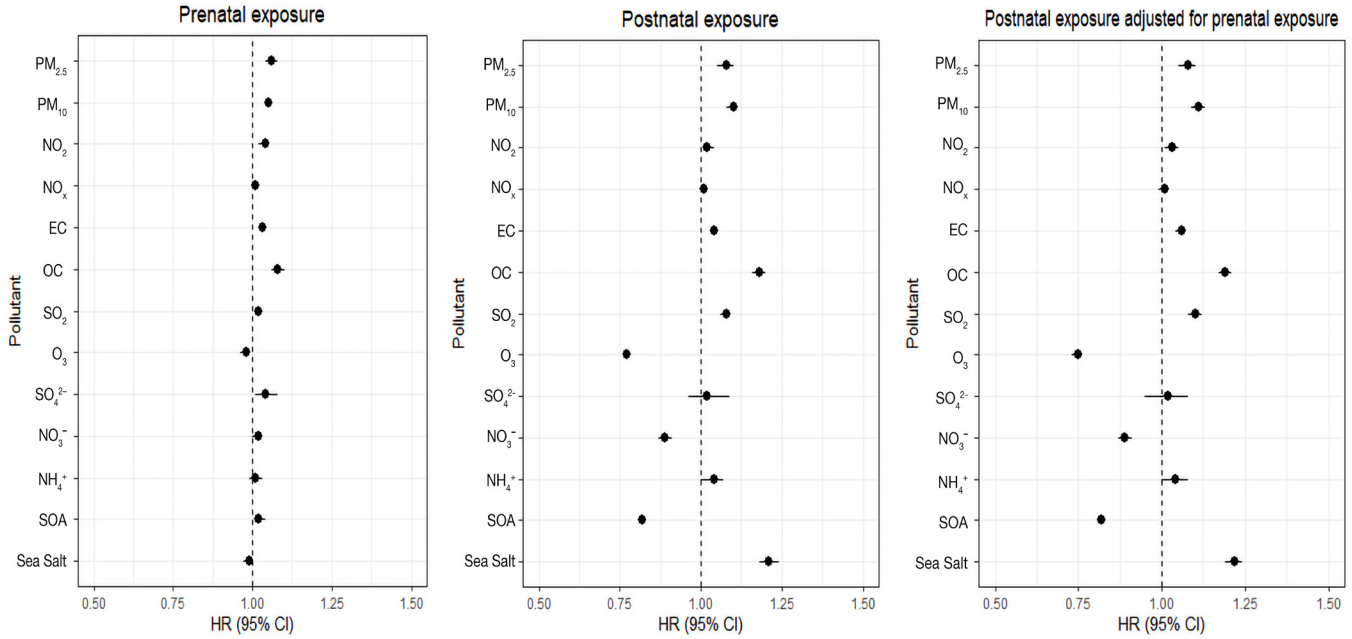
ASTHMA RISK IN THE DANISH NATIONWIDE COHORT

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**).

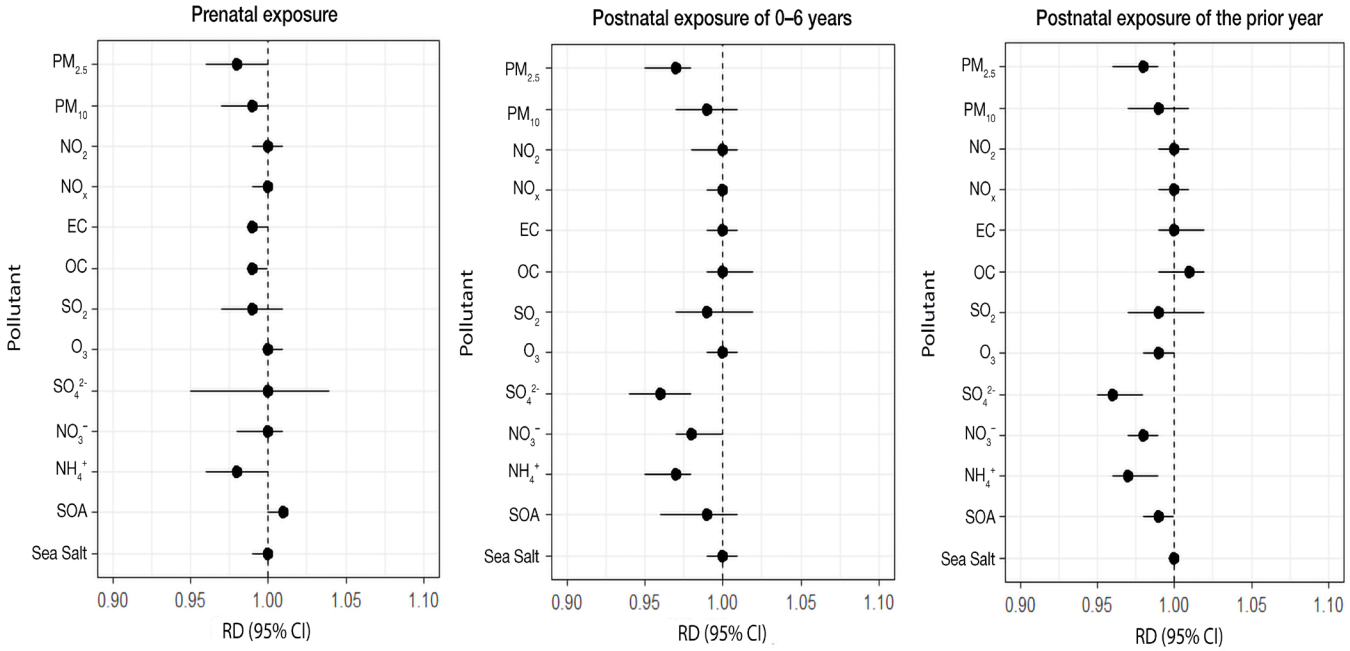
Similarly, postnatal exposure to most air pollutants was also associated with increased risk of developing asthma and associations were consistent after adjustment for prenatal exposures. However, postnatal exposure to ozone, nitrate, and secondary organic aerosols was inversely associated with risk 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



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.

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.

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.

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ABBREVIATIONS AND OTHER ITEMS

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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