EUROPEAN RESPIRATORY *journal*

FLAGSHIP SCIENTIFIC JOURNAL OF ERS

Early View

Original article

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Please cite this article as: Liu S, Jørgensen JT, Ljungman P, *et al*. Long-term exposure to low-level air pollution and incidence of asthma: the ELAPSE project. *Eur Respir J* 2020; in press (https://doi.org/10.1183/13993003.030992020).

Long-term exposure to low-level air pollution and incidence of asthma: the ELAPSE project

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Take home message

Long-term exposure to air pollution, especially from fossil fuel combustion sources such as motorized traffic, is associated with the development of asthma in adults, even at levels below the current EU and US limit values and possibly WHO guidelines.

Abstract

Background: Long-term exposure to ambient air pollution has been linked to childhood-onset asthma, while evidence is still insufficient. Within the multicentre project 'Effects of Low-Level Air Pollution: A Study in Europe' (ELAPSE), we examined the associations of long-term exposures to particulate matter with diameter < 2.5 µm ($PM_{2.5}$), nitrogen dioxide (NO_2), and black carbon (BC) with asthma incidence in adults.

Methods: We pooled data from three cohorts in Denmark and Sweden with information on asthma hospital diagnoses. The average concentrations of air pollutants in 2010 were modelled by hybrid land use regression models at participants' baseline residential addresses. Associations of air pollution exposures with asthma incidence were explored with Cox proportional hazard models, adjusting for potential confounders.

Results: Of 98,326 participants, 1,965 developed asthma during a 16.6 years mean follow-up. We observed associations in fully adjusted models with hazard ratios and 95% confidence intervals of 1.22 (1.04–1.43) per 5 $\mu g/m^3$ for $PM_{2.5}$, 1.17 (1.10–1.25) per 10 $\mu g/m^3$ for NO_2, and 1.15 (1.08–1.23) per 0.5 $10^{-5}m^{-1}$ for BC. Hazard ratios were larger in cohort subsets with exposure levels below the EU and US limit values and possibly WHO guidelines for $PM_{2.5}$ and NO_2. NO_2 and BC estimates remained unchanged in two-pollutant models with $PM_{2.5}$, whereas $PM_{2.5}$ estimates were attenuated to unity. The concentration response curves showed no evidence of a threshold.

Conclusions: Long-term exposure to air pollution, especially from fossil fuel combustion sources such as motorized traffic, was associated with adult-onset asthma, even at levels below the current limit values.

Introduction

Asthma is a complex and heterogeneous chronic respiratory disease affecting people of all ages [1]. Although lifestyles and genetic factors play important roles in asthma aetiology [2], environmental exposures are increasingly recognized as likely risk factors [3]. Ambient air pollution is one of the main contributors of morbidity and mortality worldwide [4]. The Global Burden of Disease Study ranked ambient air pollution the sixth most important risk factor for morbidity and mortality globally in 2016 and attributed 7.5% of all deaths to particulate matter with diameter < 2.5 μm ($PM_{2.5}$) [5]. While $PM_{2.5}$ levels are decreasing in most developed countries [6], evidence from studies with levels below current limit values suggests that the association with mortality likely has no safe threshold [7-10]. Evidence on morbidity outcomes, including asthma, is more limited.

The association between long-term exposure to air pollution and childhood-onset asthma has been extensively studied, and a recent meta-analysis of 41 studies demonstrated increased risks for nitrogen dioxide (NO_2), $PM_{2.5}$, particulate matter with diameter < 10 μm (PM_{10}), and black carbon (BC) [11]. However, the literature on adult-onset asthma is more limited [12], in part due to the lack of cohorts with information on asthma incidence in adults (Table S1) [13-22]. Of seven cohort studies on long-term exposure to NO_2 and adult-onset asthma, all observed positive associations [13, 14, 16-19, 21], with three observing non-significant associations [13, 16, 17]. The majority [13, 14, 16, 17], but not all [15], of the studies on $PM_{2.5}$ suggested positive associations. Two studies reported positive associations between air pollution and asthma incidence in non-smokers only, one with traffic-related PM_{10} [20] and the other with ozone (O_3) [22]. The studies differed in definition of adult asthma incidence, with the majority relying on self-reported asthma symptoms, doctor diagnosed asthma, and/or use of asthma medication [15-17, 19-22], while only three used more objective definitions based on first-ever hospital discharge diagnoses [13, 18] or asthma surveillance databases,

which combined physician insurance billing with emergency room and hospital visit data [14]. Although the studies on air pollution and adult-onset asthma all come from relatively low air pollution areas, such as Europe [16, 18-21], Canada [14], the United States [15, 17, 22], and Australia [13], few examined the shape of the concentration-response curve in the low exposure range.

The aim of this study was to investigate the associations of long-term air pollution exposures ($PM_{2.5}$, NO_2, BC, and O_3) and asthma incidence in adults and to assess the shape of the concentration-response curves, particularly below current EU and US limit values or WHO guidelines.

Methods

Study Population

Within the 'Effects of Low-Level Air Pollution: A Study in Europe' (ELAPSE) project, individual data from 11 European cohorts were harmonized, pooled, and analysed using a secure, remote access server at Utrecht University. We used data from three cohorts which had information on asthma hospital discharge diagnoses: 1) the Cardiovascular Effects of Air Pollution and Noise in Stockholm (CEANS) study [23], which combined data from four sub-cohorts: the Stockholm Diabetes Prevention Program (SDPP), the Cohort of 60-year-olds (SIXTY), the Stockholm Screening Across the Lifespan Twin study (SALT), and the Swedish National Study on Aging and Care in Kungsholmen (SNAC-K); 2) the Danish Diet, Cancer and Health (DCH) study [24]; and 3) the Danish Nurse Cohort (DNC) study which included two sub-cohorts from recruitment rounds in 1993 and 1999 [25]. The confounder data from each cohort were collected through questionnaires at cohort recruitments, between 1992 and 2004. For more details on the three cohorts see online supplement. The study was

undertaken in accordance with the Declaration of Helsinki and all three cohorts were approved by the local ethics committees in accordance with the national regulations.

Outcome Definition

We defined incidence of asthma as the first hospital discharge diagnosis (inpatient, outpatient, or emergency room visits for Danish DNC and DCH, and inpatient visits for Swedish CEANS) in participants without asthma diagnoses before baseline. The follow-up period was from 1992−2004 (baseline years) until 2011 (CEANS) or 2015 (DCH and DNC). We used primary discharge diagnoses of asthma with International Classification of Diseases, 9th Revision (ICD-9) codes 493 or 10th Revision (ICD-10) codes J45-46.

Exposure Assessment

Annual average concentrations of $PM_{2.5}$, NO_2, BC, and warm season O_3 (April through September; the maximum running 8-hour averages) for 2010 were estimated at participants' baseline residential addresses, at a 100 × 100 m spatial resolution, using of standardized Europe-wide hybrid land use regression (LUR) models [26, 27], described in more detail in online supplement. Additionally, we back-extrapolated pollutants' concentrations for each year from baseline to the end of follow-up for two available cohorts (CEANS and DCH) for sensitivity analyses.

Statistical Analysis

We used Cox proportional hazard models to examine the associations between long-term exposures to air pollution and asthma incidence, with censoring at death, diagnosis of chronic obstructive pulmonary disease (COPD, principal diagnoses with ICD-9 codes 490-492 and 494-496 or ICD-10 codes J40-44), emigration, and the end of follow-up, whichever came first. Participants with asthma diagnoses at baseline were excluded from the analyses. We included the air pollutants separately as a linear variable and used age as the underlying timescale [28]. The associations with air pollution were estimated through three steps, with

an increasing level of adjustment for a priori defined individual and area-level confounders. Model 1 included age (time axis), sex (strata), sub-cohort (strata), and the cohort baseline year; Model 2 additionally adjusted for individual lifestyles and socio-economic status: smoking status (never, former, current), smoking duration (years), smoking intensity (linear and squared term; cigarettes/day), body-mass index (BMI; categorical variable according to WHO: <18.5, 18.5–24.9, 25.0–29.9, ≥30 kg/m^2), marital status (single, married/living with partner, divorced, widowed), employment status (employed, other), and educational level (primary school or less, secondary school, university degree or more); and Model 3 (main model) additionally adjusted for area-level mean income (continuous variable in euros), which is at municipality level in 2001 for DCH and DNC or at neighbourhood level in 1994 for CEANS. Participants with complete information for all variables in Model 3 were included in analyses.

We investigated if associations persisted at low air pollution concentrations by excluding participants exposed to levels above pre-defined cut-off values based on existing EU and US limit values and WHO guidelines. To evaluate the shape of the concentration response curves between air pollutants and asthma incidence, we applied natural cubic splines with three degrees of freedom in Model 3 and tested for linearity by comparing it with linear models using likelihood ratio test. We also performed threshold analyses, in which the pollutants were set to zero for exposures below certain (threshold) values, assuming no effect below the thresholds. The performance of threshold models were evaluated by comparison of the Akaike Information Criterion (AIC) with the corresponding linear model. We also fitted two-pollutant models in Model 3, in an attempt to account for mutual correlation of pollutants.

We conducted several sensitivity analyses. First, to examine the robustness of using air pollution exposure modelled for 2010, we re-ran Model 3 with 1) time-varying air pollution concentrations, by linking back-extrapolated annual averages for each year from baseline

until the end of follow-up for cohorts with complete residential address history (only CEANS, DCH), using 1-year or 5-year strata of calendar time to account for secular time trend in asthma incidence and air pollution; and 2) back-extrapolated annual average concentrations at baseline for all cohorts. Secondly, we estimated associations in Model 3 by separately including each of the three cohorts or by excluding one cohort each time. We also graphically showed the trend of yearly back-extrapolated pollutants' concentrations during follow-up period using the ratio and the absolute difference method in the CEANS (N=19,320) and DCH (N=51,991) cohorts, which had available address history information.

We also performed effect modification by age (<65, ≥65 years), BMI, smoking status, marital status, employment status, educational level, and COPD status at baseline. Effect modification was evaluated by introducing an interaction term into Model 3 and tested by the Wald test.

The results are presented as hazard ratios (HRs) and 95% confidence intervals (CIs). All analyses were performed in R software (version 3.4.0).

Results

From a total of 106,727 participants from the three cohorts with complete air pollution exposure data (21,986 from CEANS, 56,308 from DCH, and 28,433 from DNC), we excluded 821 with asthma diagnoses before the beginning of follow-up, and 7,580 with missing information on confounders, leaving 98,326 participants for analyses. During a mean follow-up of 16.6 years, 1,965 participants developed asthma (Table 1). The mean age at baseline was 55.8 years. Participants who developed asthma were more likely to be women, obese, and have higher levels of $PM_{2.5}$, NO_2, and BC at the residence than asthma-free participants. For NO_2, all cohorts showed some exceedances of the EU limit value and the WHO recommendation of 40 μg/m³, while the individual levels in all cohorts complied with

the EU limit value for $PM_{2.5}$ of 25 µg/m³ (Figure 1). More details on the characteristics of study participants, air pollution levels in each sub-cohort, and by quintiles of NO_2 concentrations are shown in Table S2, Table S3, and Table S4, respectively. We found that participants living in the highest quintiles of exposure to NO_2 were more likely to be smokers, single, less educated and have lower income, but similar age and BMI than those living in areas with low NO_2 levels (Table S4). We observed that air pollution levels were decreasing during follow-up time (Figure S1). $PM_{2.5}$, NO_2, and BC were generally moderate-to-highly correlated with each other (Pearson correlation coefficients > 0.6), while O_3 was negatively correlated with the other pollutants (Table S5). NO_2 and BC were highly correlated in all (0.67–0.93) sub-cohorts except for SNAC-K (0.43).

We observed positive associations between $PM_{2.5}$, NO_2, and BC and asthma incidence in all three models, with minor attenuations of estimates from Model 1 to Model 3 (Table 2). We observed larger HRs in subsets of participants (Model 3) with $PM_{2.5}$ levels below 15, 12, and 10 µg/m^3 (Table 3). HRs for NO_2 were also slightly higher when only including participants with concentrations below 40, 30, and 20 µg/m^3. Likewise, for BC, the fully adjusted HRs remained increased even below 1 $10^{-5}m^{-1}$ (Table 3). We did not find any evidence for a threshold for the associations between $PM_{2.5}$, NO_2, and BC and asthma incidence (Figure 2), with no evidence of deviation from linearity observed (data not shown), which is also supported by the threshold analyses (Table S6).

In two-pollutant models, the HRs for NO_2 and BC remained unchanged after adjusting for $PM_{2.5}$, whereas the HRs for $PM_{2.5}$ were attenuated to below unity when adjusting for NO_2 or BC (Table 4). In two-pollutant models with O_3, the HRs for $PM_{2.5}$, NO_2, or BC were essentially unaffected, while the negative association between O_3 and asthma incidence was attenuated to unity.

Observed associations were robust when time-varying concentrations were used controlling for time trends (Figure S2 and Table S7), and when restricting participants to subsets of cohorts (Table S9). However, effect estimates of air pollution exposure back-extrapolated to the baseline year were attenuated to unity for $PM_{2.5}$, and remained unchanged for NO_2 and BC (Table S8). The associations of $PM_{2.5}$, NO_2, and BC with asthma incidence were consistently stronger in previous smokers, unemployed and low-educated participants (Figure S3). O_3 also showed a borderline positive association in never smokers.

Discussion

In this pooled analysis of three cohorts, long-term exposures to $PM_{2.5}$, NO_2, and BC were associated with increased risks of asthma in 98,326 adults from Denmark and Sweden, even at levels below the current EU limit values. The concentration-response curves were steeper at the lower end of the exposure ranges, and showed no evidence of a threshold below which air pollution effects were null. The association of asthma with $PM_{2.5}$ was attenuated to unity in two-pollutant models, while the associations with NO_2 and BC remained robust.

Our results on $PM_{2.5}$ and asthma incidence are in line with those from two studies that also used objective asthma incidence definitions, based on a cohort of 1.1 million adults in Toronto (HR 1.02; 1.00–1.04, per 3.2 $\mu g/m^3$) [14] and 100,084 adults in Sydney, Australia (HR 1.08; 0.89–1.30, per 1 $\mu g/m^3$) [13], as well as with two studies with self-reported asthma, with 23,704 participants in six ESCAPE cohorts [odds ratio (OR) 1.04; 0.88–1.23, per 5 $\mu g/m^3$] [16], and 50,884 women from the US Sisters Cohort with an OR of 1.20 (0.99–1.46) per 3.6 $\mu g/m^3$ in $PM_{2.5}$ [17]. In contrast, the American Nurses' Health Study did not detect association between $PM_{2.5}$ and self-reported asthma (HR 0.90; 0.73–1.12, per 10 $\mu g/m^3$) [15]. Our findings of an association between NO_2 and asthma incidence are generally in line with existing evidence. In studies using objective asthma definitions, HRs ranged from 1.03

(0.88–1.19) per 5 μg/m^3 in the Sydney cohort [13], and 1.03 (1.02–1.05) per 4.1 ppb (around 7.7 μg/m^3) in NO_2 in a Toronto cohort [14], to 1.10 (1.01–1.20) per 5.8 μg/m^3 in the Danish Diet, Cancer, and Health Cohort [18]. Results for NO_2 from studies with self-reported asthma also suggest positive associations, with ORs of 1.10 (0.99–1.21) per 10 μg/m^3 in six ESCAPE cohorts [16], 1.12 (0.96–1.30) per 5.8 ppb (~10.9 μg/m^3) in the US Sisters Study [17], and 1.43 (1.02–2.01) per 10 μg/m^3 in the European Community Respiratory Health Survey study [21], and 1.54 (1.00–2.36) per 10 μg/m^3 in a Swedish cohort [19]. Additionally, our finding of an association between BC and asthma incidence is consistent with the ESCAPE finding [16]. We did not observe an association of O_3 with asthma, overall, but found that it might increase risks of asthma in non-smokers, which is in line with an earlier finding by McDonnel et al [22].

Our findings provided solid evidence that air pollution affects asthma below current limit values and guidelines. This study is based on cohorts from Denmark and Sweden, with some of the lowest air pollution levels in Europe. The findings of this study agreed with the majority of the literature on air pollution and adult-onset asthma, which came from areas with low to moderate $PM_{2.5}$ levels in Europe [16, 18-20], Canada [14], the United States [15, 17], and Australia [13] (Table S1).

Our findings of attenuated $PM_{2.5}$ effects in two-pollutant models with NO_2 or BC can be difficult to interpret and require further exploration. Differential measurement error may complicate the interpretation of two-pollutant models [29]. The pollutant with the lowest measurement error may show the most consistent association in two-pollutant models. After adjustment for NO_2, the significant single pollutant HR for $PM_{2.5}$ was reduced to unity, whereas the association with NO_2 remained robust after adjustment for $PM_{2.5}$. Given that the correlation between $PM_{2.5}$ and NO_2 was moderate and the width of the confidence interval was only modestly increased in the two-pollutant models, we did not interpret the reduction

of the HR for $PM_{2.5}$ as merely an artefact related to multi-collinearity. The association with NO_2 might reflect direct effects of NO_2 or related particles emitted at combustion, such as BC and ultrafine particles (UFPs; particulate matter with diameter < 0.1 µm). We did also not interpret the reduction of the $PM_{2.5}$ HR as implying that particles had no effect in our setting, as adjustment for NO_2 also adjusted for particles from the same sources with NO_2, including motorized traffic and other combustion sources. Only two studies to date examined two-pollutant models with $PM_{2.5}$ and NO_2. The Toronto cohort study found that the association with $PM_{2.5}$ was robust to additional adjustment for NO_2, though notably, associations with NO_2 were stronger, both in single and in two-pollutant models [14], suggesting independent effects of both pollutants. Furthermore, the Toronto study, as the first and only to have examined the role of UFPs on asthma incidence, found no association with UFPs, providing some support for a direct effect of NO_2 on asthma [14]. Our results are in line with the finding in the ESCAPE study, where, comparable to our $PM_{2.5}$ results, the HR for PM_{10} (highly correlated with $PM_{2.5}$) was attenuated to below unity with NO_2 included in a model [16].

Exact biological mechanisms of how exposures to air pollution promote the development of asthma in adults are not known. Current understanding suggests that NO_2, an airway irritant which has been linked to airway inflammation and airflow limitation in animal models [30], may both be a causal agent responsible for asthma development and a proxy for traffic-related $PM_{2.5}$ or UFPs, which can deposit in the respiratory tract and the lung alveoli causing oxidative stress, inflammation, and other biochemical changes related to asthma [31]. NO_2 is emitted together with traffic-related PM mainly in the ultrafine range, which contribute minimally to total $PM_{2.5}$ mass but could contribute significantly to the development of asthma with large particle number and surface area, through high pulmonary deposition, causing oxidative stress and inflammation in tracheobronchial and alveolar regions [32]. However,

the only previous cohort study with data on $PM_{2.5}$, UFPs, and NO_2 and adult-onset asthma reported the strongest associations with NO_2, and only weak with $PM_{2.5}$ and UFPs, and found that the significant positive association for UFPs attenuated to null in a two-pollutant model with NO_2, supporting the idea of the independent effect of NO_2 on asthma development [14]. We presented novel observations of enhanced HRs in previous smokers, unemployed and low-educated participants for $PM_{2.5}$, NO_2, and BC, as well as in never smokers for O_3. Earlier studies found little evidence for effect modification by education [13], smoking status [13, 15, 16, 18], age or BMI [13, 14, 16], although two studies reported associations between traffic-related PM_{10} [20] and O_3 [22] and asthma in never smokers only. These results suggest possibly higher susceptibility of non-smokers and participants with lower socio-economic status to the effects of air pollution on asthma.

Adult asthma is a chronic disease with complex phenotype and recurring symptoms that makes it difficult to diagnose and identify a precise time of onset. Asthma definitions based on self-reports from respiratory disease surveys are subject to recall bias, resulting in more loose definitions and likely an overestimation of true burden [33, 34]. In this study we benefited from objective definitions based on hospital discharge diagnoses from nationwide hospital registers in Denmark and Sweden. Asthma incidence rates defined by hospital discharge diagnoses may underestimate true asthma burden, as not all asthma patients require hospital contact, and thus, an asthma hospital discharge diagnosis typically represents a point of disease progression to a more severe stage or exacerbation. It is appealing as it presents a well characterized asthma definition, typically confirmed by objective measurements of lung function and reversible airflow obstruction, as standard procedures in Danish and Swedish hospitals. The specificity of asthma diagnoses in the Danish Hospital Discharge Register was found to be as high as 0.98, validating their use in epidemiological studies [35].

The main strengths of our study include pooled analyses of three large prospective cohorts with objective assessments of asthma incidence, detailed individual and area-level information on major confounders, standardized assessments of air pollution exposure, and long follow-up periods. We most likely have a low sensitivity but high specificity for adult-onset asthma by using hospital discharge diagnoses. A limitation of our study is that our exposure assessment methods solely relied on residential exposures with no information on work addresses, commuting habits or personal time-activity patterns. Finally, our study lacks data on familial histories of asthma and allergy, pet ownership, and environmental tobacco smoke, which may be confounders or effect modifiers.

Conclusions

Our results suggest that long-term exposure to air pollution, especially from fossil fuel combustion sources such as motorized traffic, is associated with the development of adult-onset asthma, even at levels below the current EU and US limit values, calling for stricter air quality regulation as an important tool for asthma prevention.

Acknowledgments

Research described in this article was conducted under contract to the Health Effects Institute (HEI), an organization jointly funded by the United States Environmental Protection Agency (EPA) (Assistance Award No. R-82811201) and certain motor vehicle and engine manufacturers. The contents of this article do not necessarily reflect the views of HEI, or its sponsors, nor do they necessarily reflect the views and policies of the EPA or motor vehicle and engine manufacturers. The authors would also like to thank all participants in the CEANS, DCH, and DNC cohort studies, and the respective study teams (the ELAPSE project) for their hard work and effort. Thanks Niklas Andersson for the work of harmonizing complicated data on covariates between the four sub-cohorts in CEANS.

Author contributions

Study was conceptualized and designed by Zorana Jovanovic Andersen, Gerard Hoek, Bert Brunekreef, Petter Ljungman, and Shuo Liu. Gerard Hoek and Bert Brunekreef are PI of the ELAPSE project. Statistical analysis and drafting of the manuscript was conducted by Shuo Liu. Zorana Jovanovic Andersen helped in drafting the manuscript. Jeanette Therming Jørgensen and Ulla Arthur Hvidtfeldt prepared the individual cohort data for the analyses. Gerard Hoek, Bert Brunekreef, Jie Chen, and Maciej Strak coordinated the ELAPSE project, helped in preparing pooled data for analyses and provided support with the access to pooled cohort data. Sophia P. Rodopoulou, Evangelia Samoli and Klea Katsouyanni contributed with the statistical analyses strategy and scripts for the statistical analyses. Kees de Hoogh worked for the exposure assessment. All authors have read and revised the manuscript for the important intellectual content, and contributed with the interpretation of the results. All authors have approved the final draft of the manuscript.

Support statement

This work is supported by the Health Effects Institute #4954-RFA14-3/16-5-3 and a grant from the China Scholarship Council No. 201806010406. SALT and TwinGene are sub-studies of The Swedish Twin Registry (STR) which is managed by Karolinska Institutet and receives additional funding through the Swedish Research Council under the grant No. 2017-00641.

Conflict of interest

There are no competing interests for any author.

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Table 1. Characteristics of participants at baseline (1992–2004) and air pollutants for the year 2010 by adult-onset asthma status.

Characteristic	Total (N=98,326)	No asthma (N=96,361)	Asthma (N=1,965)
Population			
Baseline period	1992–2004	1992–2004	1992–2004
End of follow-up	2011, 2015	2011, 2015	2011, 2015
Person-years at risk	1,634,458	1,601,795	32,664
Follow-up time, years (Mean ± SD)	16.6 ± 5.2	16.8 ± 5.0	8.9 ± 5.8
Age, years (Mean ± SD)	55.8 ± 7.5	55.8 ± 7.5	55.4 ± 6.7
Age < 65 years old, N (%)	91,318 (93)	89,462 (93)	1,856 (94)
Female, N (%)	64,492 (66)	63,073 (65)	1,419 (72)
BMI, kg/m^2 (Mean ± SD)	25.3 ± 4.0	25.3 ± 4.0	25.9 ± 4.4
Normal weight, N (%)*****	49,901 (51)	49,007 (51)	894 (45)
Smoking duration, years (Mean ± SD)	17.1 ± 16.5	17.1 ± 16.5	16.1 ± 16.0
Smoking intensity, n/day (Mean ± SD)	9.2 ± 10.4	9.2 ± 10.4	8.9 ± 10.3
Never smoker, N (%)	36,395 (37)	35,635 (37)	760 (39)
Married or living with partner, N (%)	70,137 (71)	68,790 (71)	1,347 (69)
Employed, N (%)	75,111 (76)	73,616 (76)	1,495 (76)
High educational level, N (%)*****	43,310 (44)	42,485 (44)	825 (42)
COPD, N (%)	485 (0.5)	474 (0.5)	11 (1)
Mean year income, €ϕ	20991.8	20994.5	20857.3
Air pollution at residence†			
$PM_{2.5}$, $\mu g/m^3$ (Mean ± SD)	12.12 ± 2.48	12.11 ± 2.48	12.43 ± 2.35
NO_2, $\mu g/m^3$ (Mean ± SD)	25.10 ± 7.97	25.08 ± 7.97	26.25 ± 7.79

BC, $10^{-5}m^{-1}$ (Mean ± SD)	1.17 ± 0.41	1.17 ± 0.41	1.23 ± 0.41
O_3, $\mu g/m^3$ (Mean ± SD)	78.12 ± 4.62	78.13 ± 4.61	77.95 ± 4.81

BMI, body mass index; SD, standard deviation; $PM_{2.5}$, particulate matter with diameter < 2.5 μm; NO_2, nitrogen dioxide; BC, black carbon; O_3, ozone; COPD, chronic obstructive pulmonary disease.

*: Normal weight means BMI values from 18.5 to 24.9 according to the World Health Organization (WHO) categories; High educational level means university degree and more.

ϕ: Mean year income is a continuous variable in euros, which is at municipality level in 2001 for DCH and DNC and at neighbourhood level in 1994 for CEANS.

†: The annual average concentrations of $PM_{2.5}$, NO_2, BC and O_3 were estimated for the year 2010 at 100 m resolution. O_3 was estimated during the warm season from April 1 through September 30.

Table 2. Associations between long-term air pollution exposure and adult-onset asthma.

	Model 1	Model 2	Model 3
	HR (95%CI)		
N	98,326	98,326	98,326
$PM_{2.5}$	1.24 (1.06–1.45)	1.20 (1.03–1.41)	1.22 (1.04–1.43)
NO_2	1.19 (1.11–1.26)	1.18 (1.10–1.25)	1.17 (1.10–1.25)
BC	1.17 (1.10–1.25)	1.16 (1.08–1.24)	1.15 (1.08–1.23)
O_3	0.89 (0.81–0.98)	0.91 (0.83–1.01)	0.90 (0.81–0.99)

Model 1 included age (time axis), sex (strata), study (strata), and calendar year of baseline;

Model 2 further adjusted for smoking (status, duration, intensity, and intensity*intensity), BMI (category), marital status, employment status and education levels;

Model 3 further adjusted for area-level mean income, which is at municipality level in 2001 for DCH and DNC or at neighbourhood level in 1994 for CEANS.

Results are presented as hazard ratio (HR) and 95% confidence interval (CI) [HR (95%CI)] for the following increases: 5 $\mu g/m^3$ for $PM_{2.5}$, 10 $\mu g/m^3$ for NO_2, 0.5 10^{-5} m^{-1} for BC and 10 $\mu g/m^3$ for O_3.

Table 3. Associations between long-term air pollution exposure and adult-onset asthma below various cut-off values based on Model 3.

Pollutants	Concentration levels	Number of observations	HR (95%CI)
$PM_{2.5}$			
	All levels	98,326	1.22 (1.04–1.43)
	< 25 μg/m^3	98,326	1.22 (1.04–1.43)
	< 20 μg/m^3	98,326	1.22 (1.04–1.43)
	< 15 μg/m^3	86,295	1.23 (0.97–1.57)
	< 12 μg/m^3	35,662	1.53 (0.90–2.60)
	< 10 μg/m^3	20,857	1.49 (0.76–2.94)
NO_2			
	All levels	98,326	1.17 (1.10–1.25)
	< 40 μg/m^3	96,481	1.21 (1.13–1.29)
	< 30 μg/m^3	69,877	1.29 (1.15–1.45)
	< 20 μg/m^3	28,114	1.24 (0.92–1.67)
BC			
	All levels	98,326	1.15 (1.08–1.23)
	< 3 10^{-5}m^{-1}	98,319	1.15 (1.08–1.23)
	< 2.5 10^{-5}m^{-1}	98,240	1.15 (1.08–1.23)
	< 2 10^{-5}m^{-1}	97,001	1.15 (1.08–1.23)
	< 1.5 10^{-5}m^{-1}	74,838	1.17 (1.09–1.26)
	< 1 10^{-5}m^{-1}	34,693	1.33 (1.02–1.74)
	< 0.5 10^{-5}m^{-1}	4,906	0.77 (0.15–3.97)

O_3			
	All levels	98,326	0.90 (0.81–0.99)
	< 80 μg/m^3	57,897	0.91 (0.78–1.06)
	< 60 μg/m^3	58	—

Results are presented as hazard ratio (HR) and 95% confidence interval (CI) [HR (95%CI)] for the following increases: 5 μg/m^3 for $PM_{2.5}$, 10 μg/m^3 for NO_2, 0.5 10^{-5} m^{-1} for BC and 10 μg/m^3 for O_3.

Table 4. Two-pollutant models for association between long-term air pollution exposure and adult-onset asthma based on Model 3 (N=98,326).

Pollutants	Single-pollutant model	Two-pollutant model (Adjusted for pollutants below)			
		$PM_{2.5}$	**NO_2**	**BC**	**O_3**
$PM_{2.5}$	1.22 (1.04–1.43)	—	0.88 (0.70–1.09)	0.95 (0.77–1.18)	1.16 (0.97–1.39)
NO_2	1.17 (1.10–1.25)	1.21 (1.11–1.32)	—	1.19 (1.02–1.37)*	1.19 (1.10–1.28)
BC	1.15 (1.08–1.23)	1.17 (1.07–1.27)	0.98 (0.85–1.15)*	—	1.16 (1.07–1.25)
O_3	0.90 (0.81–0.99)	0.94 (0.84–1.05)	1.05 (0.93–1.18)	1.01 (0.90–1.14)	—

Results are presented as hazard ratio and 95% confidence interval [HR (95%CI)] for the following increases: 5 $\mu g/m^3$ for $PM_{2.5}$, 10 $\mu g/m^3$ for NO_2, 0.5 10^{-5} m^{-1} for BC and 10 $\mu g/m^3$ for O_3.

*: Two-pollutant result for NO_2 and BC are difficult to interpret because of their high correlation.

Figure legends

Figure 1. Distribution of the annual average of air pollution concentrations by sub-cohorts for the year 2010.

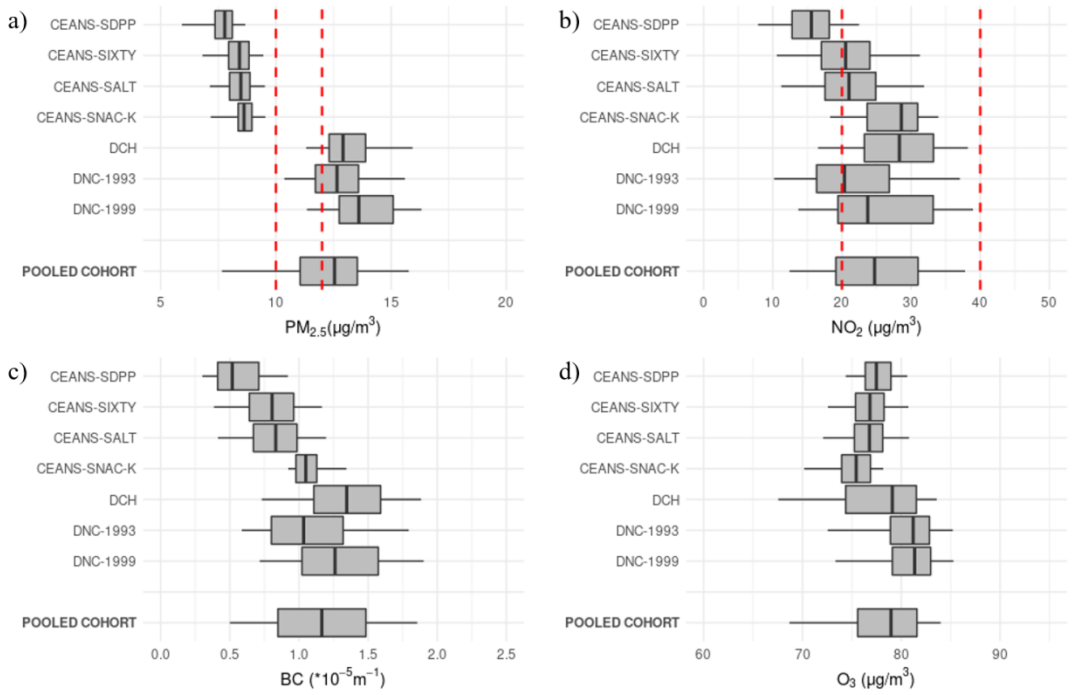
Red long dash lines indicate different limited/guideline values in EU, US, and WHO for $PM_{2.5}$ and NO_2.

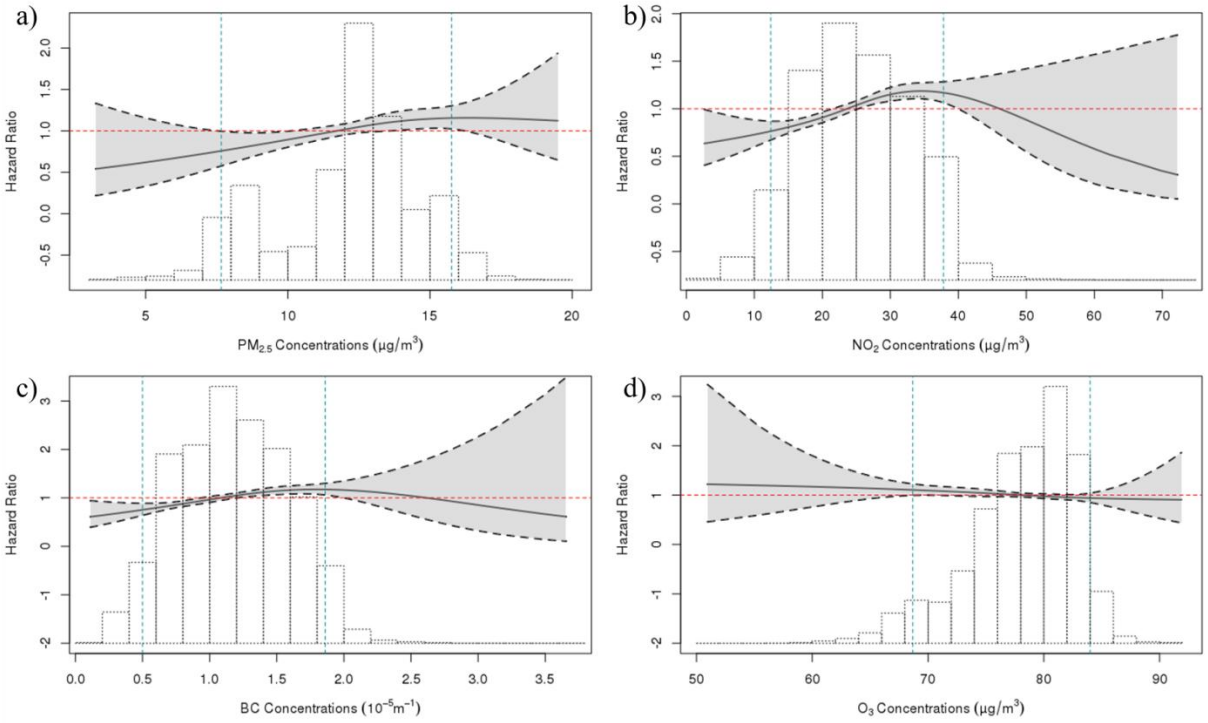
The bold lines in the middle of the box indicate the median values (50^{th} percentiles). The lower and upper hinges correspond to the 25^{th} and 75^{th} percentiles. The lower and upper whisker extends to 5^{th} and 95^{th} percentiles.

Figure 2. Estimated concentration-response curves for effects of long-term air pollution exposure on adult-onset asthma.

Natural cubic splines with three degrees of freedom were fit for air pollutants to evaluate the shape of the associations based on the main model - Model 3.

Solid lines indicate hazard ratio values and black dashed lines indicate their 95% confidence intervals. Red dashed lines is the HRs equal to 1 indicating no risk attributed to air pollution exposure. Green dashed lines indicate the 5^{th} and 95^{th} percentiles of air pollutants' concentrations.


a)
CEANS-SDPP
CEANS-SIXTY
CEANS-SALT
CEANS-SNAC-K
DCH
DNC-1993
DNC-1999
POOLED COHORT
5
10
15
20
PM2.5(µg/m3)
b)
CEANS-SDPP
CEANS-SIXTY
CEANS-SALT
CEANS-SNAC-K
DCH
DNC-1993
DNC-1999
POOLED COHORT
0
10
20
30
40
50
NO2 (µg/m3)
c)
CEANS-SDPP
CEANS-SIXTY
CEANS-SALT
CEANS-SNAC-K
DCH
DNC-1993
DNC-1999
POOLED COHORT
0.0
0.5
1.0
1.5
2.0
2.5
BC (*10−5m−1)
d)
CEANS-SDPP
CEANS-SIXTY
CEANS-SALT
CEANS-SNAC-K
DCH
DNC-1993
DNC-1999
POOLED COHORT
60
70
80
90
O3 (µg/m3)


a)
Hazard Ratio
PM2.5 Concentrations (μg/m3)
b)
Hazard Ratio
NO2 Concentrations (μg/m3)
c)
Hazard Ratio
BC Concentrations (10−5m−1)
d)
Hazard Ratio
O3 Concentrations (μg/m3)

Supplement material

Long-term exposure to low-level air pollution and incidence of asthma: the ELAPSE project

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1. Description of the Three Study Cohorts.

We included three out of 11 pooled ELAPSE large prospective cohorts into our analyses. One of the cohorts, the CEANS cohort, is composed of four individual Swedish cohorts. The other two study cohorts, the DCH cohort and the DNC cohort, are from Denmark. The DNC cohort includes two parts of participants who were recruited in 1993 or 1999.

1) CEANS, Cardiovascular Effects of Air Pollution and Noise, Sweden: including SDPP, SIXTY, SALT, and SNAC-K.

SDPP, the Stockholm Diabetes Preventive Program (SDPP), Sweden

The Stockholm diabetes prevention program was a population-based prospective study and aimed at investigating the etiology of type 2 diabetes and developing prevention strategies for type 2 diabetes [1]. An initial survey included all men and women in the targeted age group in Stockholm County; for men in four municipalities (Värmdö, Upplands Bro, Tyresö and Sigtuna), and for women these four plus a fifth municipality (Upplands Väsby). All were screened by a questionnaire regarding presence of own diabetes and diabetes in relatives. Subjects with family history of diabetes (FHD) and randomly selected subjects without FHD, all without previously diagnosed diabetes, were invited to a health examination. This baseline study, 1992–1994 for men and 1996–1998 for women, comprised 7,949 subjects, aged 35–56 years, and about 50% had FHD. In the follow-up study 8–10 years later, 2,383 men (2002–2004) and 3,329 women (2004–2006) participated. At the health examinations, both at baseline and follow-up, an extensive questionnaire (information on lifestyle factors, such as physical activity, dietary habits, tobacco use, alcohol consumption, health status, socioeconomic status and psychosocial conditions) was completed. Diabetes heredity was confirmed and measurements of weight, height, hip and waist circumference as well as blood pressure were performed. In addition, an oral glucose tolerance test (OGTT) was made, and blood was sampled at fasting state

and 2 hour after glucose intake. Outcomes based on the Swedish nationwide health registries (such as the myocardial infarction and stroke registries, the cause-of death register, and the national patient register) have been used.

SIXTY, the Cohort of 60-year-olds, Sweden

The Cohort of 60-year-olds is a study aiming to identify biological and socio-economic risk factors and predictors for cardiovascular diseases [2]. Recruitment took place between August 1997 and March 1999. A random sample of every third man and woman living in Stockholm County, who was born between 1 July 1937 and 30 June 1938, was invited to participate. In total, 4,232 subjects were included. Height, weight, BMI, Waist/Hip ratio and resting ECD, blood pressure and fasting blood samples were taken during a physical examination, while a comprehensive questionnaire was completed, including information on socioeconomic, medical and life-style factors. Outcomes based on the Swedish nationwide health registries (such as the myocardial infarction and stroke registries, the cause-of-death register and the national patient register) have been used.

SALT, the Stockholm Screening Across the Lifespan Twin study, Sweden

Participants come from two sub-studies of the Swedish Twin Registry (STR) [3]. The Screening Across the Lifespan Twin study (SALT) [4] & TwinGene [5] was set-up to screen all twins born in Sweden before 1958 for the most common complex diseases with a focus on cardiovascular diseases. TwinGene is a sub-study establishing a biobank with DNA and serum from SALT participants. SALT is based on a telephone interview and recruitment took place between 1998 and 2002. Information concerning birth order and weight, zygosity, contact with twin partner and family constellation, diseases, use of medication, occupation, education, life style habits, gender- and age specific (hormone replacement therapy) and memory problems (age > 65) was collected. In TwinGene, twins born before 1958 were contacted 2004-2008. Health and medication data were collected

from questionnaires. Blood sampling material was mailed to study subjects, who contacted a local health care center for blood sampling. Information about COPD come from linkages to Swedish nationwide health registries. This investigation on air pollution is restricted to participants living in Stockholm County.

SNAC-K, The Swedish National study of Aging and Care in Kungsholmen, Sweden

SNAC-K is an ongoing longitudinal study aiming to investigate the ageing process and identify possible preventive strategies to improve health and care in elderly adults [6]. The study population consists of randomly sampled individuals >=60 years old and in a central area of Stockholm (Kungsholmen) between March 2001 and June 2004. The sample was stratified for age and year of assessment giving sub-cohorts with 60, 66, 72, 78, 81, 84, 87, 90, 93, 96, and 99+ year olds. Information was collected through social interviews, assessment of physical functioning, clinical examination (incl. geriatric, neurological and physical assessments) as well as cognitive assessment. At baseline, information regarding events prior to the study period was gathered. The follow-up interval is six years for the younger age cohorts, and three years for the older age cohorts (81+). During the follow-up intervals, medical events of all participants are registered through linkage with primary care registry and hospital discharge registry (available for all subjects in Sweden). In case of death, hospital and cause of death registries provide the clinical information, and informant interviews are carried out. The same protocol as for the baseline data collection is used during the follow-up, though only concerning the follow-up period. Website of study: https://www.snac-k.se. Any outcomes based on the Swedish nationwide health registries (such as the myocardial infarction and stroke registries, the cause-of-death register and the national patient register) have been used.

2) DCH, Danish Diet, Cancer and Health study, Denmark

The primary aim of the DCH study is to investigate diet and lifestyle in relation to incidence of cancer and other chronic diseases [7]. Historical residential history of the study participants is available, which facilitate studies of air pollution and noise. The study enrolled participants in two areas, Copenhagen and Aarhus, Denmark. 160,725 individuals aged 50–64 years were invited to participate between December 1993 and May 1997. Out of the 160,725 people invited, 57,053 were enrolled. On enrolment, each participant completed self-administered questionnaires (in Danish) that included questions on dietary habits, health status, family history of cancer, social factors, reproductive factors, smoking, environmental smoking, and lifestyle habits. Anthropometric measurements including blood pressure and blood samples were also obtained. The DCH cohort is followed up regularly by use of complete nationwide registers hence the loss to follow-up is virtually nil. Data on asthma incidence from the Danish National Patient Registry were used.

3) DNC, Danish Nurse Cohort study, Denmark

The Danish Nurse Cohort was established in 1993 and includes a total of 28,731 female members of the Danish Nurse Organization who were 44 years of age or older at recruitment in 1993 or 1999 [8]. Inspired by the American Nurses' Health Study, the Danish Nurse Cohort aimed to provide the basis for research into the potential health effects related to use of hormone replacement therapy (HRT) in a European population. In 1993, the cohort was initiated by sending a questionnaire to 23,170 female members of the Danish Nurse Organization who were at least 44 years old at the time. The Danish Nurse Organization includes 95% of all nurses in Denmark. In total, 19,898 nurses accepted an invitation and answered a comprehensive questionnaire on lifestyle (smoking, alcohol consumption, leisure time physical activity, diet, BMI, etc.), occupational characteristics (shift work, work environment, etc.), health, reproductive factors, and other factors. The

cohort was reinvestigated in 1999, adding 8,833 nurses (8,344 new nurses who turned 44 in the period 1993–1999 and 489 non-responders from the 1993 who were re-invited).

2. Air Pollution Exposure Assessment

Annual average concentrations of $PM_{2.5}$, NO_2, BC, and warm season O_3 (April through September; the maximum running 8-hour averages) for 2010 were estimated at the study participants' baseline residential addresses with the use of standardized Europe-wide hybrid land use regression (LUR) models [9, 10]. The LUR models incorporated the European Environment Agency (EEA) AirBase routine monitoring data for $PM_{2.5}$, NO_2, and O_3 and ESCAPE monitoring data for BC. BC was measured by the reflectance of $PM_{2.5}$ filters and expressed in absorbance units [9]. Satellite and chemical transport model air pollution estimates, land use, and traffic data were predictors to develop models for annual mean air pollution concentrations. The developed hybrid LUR models were used to create exposure surfaces at a 100 × 100 m spatial scale for exposure assignments to the cohorts. The exposure models performed well in five-fold hold-out validation, explaining a large fraction of spatial variability for $PM_{2.5}$ (72%), NO_2 (59%), BC (54%), and O_3 (69%) in the measured annual mean concentrations [9]. Additionally, predictions from the 2010 model correlated highly with models developed for 2000 and 2005 models for (NO_2 and O_3) and 2013 model for $PM_{2.5}$ at the overall European scale, with squared correlations (R^2) larger than 76% [9].

We also estimated pollutant concentrations for each year from recruitment to the end of follow-up using back-extrapolation to 1990. We back-extrapolated by using a chemical transport and dispersion model, the Danish Eulerian Hemispheric Model (DEHM) [11], which calculated monthly average concentrations across Europe at 26 × 26 km resolution.

The rationale to use DEHM for back-extrapolation is the consistent availability of estimates across Europe for the full study period for all pollutants. In contrast, routine monitoring data were less consistent, not available for BC and only available from about 2008 for $PM_{2.5}$. Residential address histories for each year were incorporated in the back-extrapolation, such that both changes in air pollution spatial patterns and moving residential address were accounted for. For application to the cohorts, we calculated population weighted average concentrations at the study area level, allowing different spatial trends within Europe. We back-extrapolated concentrations for all pollutants using both an absolute difference and a ratio method with 2010 as the reference. With the absolute difference method the concentration difference between a year and 2010 from the DEHM model is added to all cohort exposures for that year in the same NUTS-1 area. With the ratio method the concentration ratio between a year and 2010 from the DEHM model is used to multiply all cohort exposure for that year in the same NUTS-1 area. In case of higher concentrations in the past, the ratio method therefore increases the contrast in cohort exposures.

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Table S1. Overview of studies on air pollution and asthma incidence in adults.

Author, year	Cohort/Study	Sample Size (N)	Asthma incidence defintion	Pollutant (mean levels)	Effect estimates
McDonnell et al., 1999 [12]	The Ahsmog Study, California, USA,	3,091 non-smokers	Self-reported asthma diagnosed by a doctor	O_3 (46.5 ppb)	RR (95% CI): M: 2.09 (1.03–4.16) per 27 ppb F: 0.86 (0.58–1.26) per 27 ppb
Jacquemin et al., 2009 [13]	European Respiratory Health Survey (ECRHS), 17 European cities	4,185	Self-reported ever asthma diagnosed by a doctor	NO_2 (median: 27.7 $\mu g/m^3$)	OR (95% CI): 1.43 (1.02–2.01) per 10 $\mu g/m^3$
Künzli et al., 2009 [14]	The SAPALDIA cohort, Switzerland	2,725 never-smokers	Self-reported doctor-diagnosed asthma	$dTPM_{10}$ (-0.59 $\mu g/m^3$)	HR (95% CI): 1.30 (1.05–1.61) per 1 $\mu g/m^3$
Modig et al., 2009 [15]	The Respiratory Health in Northern Europe (RHINE) cohort, Sweden	3,609	Self-reported asthma with questionnaire	NO_2 (17.9 $\mu g/m^3$)	OR (95% CI): 1.54 (1.00–2.36) per 10 $\mu g/m^3$
Andersen et al., 2012 [16]	The Diet, Cancer and Health cohort, Denmark	57,053	Hospital contact (in-, outpatient, or emergency) primary discharge diagnoses ICD-10: J45–46	NO_2 (median: 15.2 $\mu g/m^3$)	HR (95% CI): 1.10 (1.01–1.20) per 5.8 $\mu g/m^3$
Young et al., 2014 [17]	The Sister Study, USA	50,884 women (sisters with breast	Self-reported doctor diagnosed asthma	NO_2 (median: 9.3 ppb) $PM_{2.5}$ (median 10.8	OR (95% CI): 1.12 (0.96–1.30) per 5.8 ppb

		cancer)		$\mu g/m^3$)	1.20 (0.99–1.46) per 3.6 $\mu g/m^3$
Jacquemin et al., 2015 [18]	The European Study of Cohorts for Air Pollution Effects (ESCAPE), six cohorts	23,704 adults	Self-reported ever asthma diagnosed by a doctor, breathless while wheezing, asthma attacks, or asthma medication	NO_2 (mean range 22–31 $\mu g/m^3$ by cohort) $PM_{2.5}$ (mean range 10–18 $\mu g/m^3$ by cohort) $PM_{2.5absorbance}$ (mean range 1.0–2.1 $10^{-5}m^{-1}$ by cohort)	OR (95% CI): 1.10 (0.99–1.21) per 10 $\mu g/m^3$ 1.04 (0.88–1.23) per 5 $\mu g/m^3$ 1.06 (0.95–1.19) per 1 $10^{-5}m^{-1}$
Fisher et al., 2016 [19]	The Nurses' Health Study, USA	121,701 female nurses	Self-reported physician-diagnosed asthma and use of asthma medication	$PM_{2.5}$ (14.2 $\mu g/m^3$)	HR (95% CI): 0.90 (0.73–1.12) per 10 $\mu g/m^3$
Weichenthal et al., 2017 [20]	The Ontario Population Health and Environment Cohort (ONPHEC), Toronto Canada,	1,100,000	Ontario Asthma Surveillance System (physician insurance claims, hospital admissions and medication data): ICD-9: 493	NO_2 (21.4 ppb) $PM_{2.5}$ (10.9 $\mu g/m^3$) UFPs (28,473 count/cm^3)	HR (95% CI): 1.03 (1.02–1.05) per 4.1 ppb 1.02 (1.00–1.04) per 3.2 $\mu g/m^3$ 1.00 (1.00–1.01) per 10,097 count/cm^3

Salimi et al., 2018 [21]	The Sax Institute's 45 and Up Study, Sydney, Australia	100,084	Primary diagnosis of hospitalization ICD-10: J45–46	NO_2 (17.5 μg/m^3) $PM_{2.5}$ (4.5 μg/m^3)	HR (95% CI): 1.03 (0.88–1.19) per 5 μg/m^3 1.08 (0.89–1.30) per 1 μg/m^3

$PM_{2.5}$, particulate matter with diameter < 2.5 μm; $dTPM_{10}$, the difference in traffic-related particulate matter with diameter < 10 μm; NO_2, nitrogen dioxide; BC, black carbon; O_3, ozone; HR, hazard ratio; OR, odds ratio; CI, confidence interval; SAPALDIA, The Swiss Cohort Study on Air Pollution and Lung Diseases in Adults;

Unit conversion for pollutant concentration, for NO_2: 1 ppb = 1.88 μg/m^3; for O_3: 1 ppb = 2.00 μg/m^3.

Table S2. Characteristics of participants by cohorts and adult-onset asthma status at baseline based on the number of observations in Model 3

Characteristic at baseline*	All cohorts (N=98,326)			DCH (N=52,961)			DNC (N=24,978)					
							1993 (N=16,937)			1999 (N=8,041)		
	Total	No asthma	Asthma	Total	No asthma	Asthma	Total	No asthma	Asthma	Total	No asthma	Asthma
Baseline period	1992–2004			1993–1997			1993			1999		
End of follow-up	2011, 2015			2015			2015			2015		
Person-years at risk, N	1,634,458	1,601,795	32,664	928,404	918,007	10,397	327,563	324,095	3,468	126,658	125,361	1,298
Follow-up time, years (Mean ± SD)	16.6±5.2	16.8±5.0	8.9±5.8	17.5±4.7	17.7±4.5	9.1±5.9	19.3±5.6	19.5±5.4	9.9±6.6	15.8±2.4	15.9±2.1	8.7±5.0
Number of observations	98,326	96,361	1,965	52,961	51,813	1,148	16,937	16,585	352	8,041	7,892	149
Asthma incidence rate		2.0%			2.2%			2.1%			1.9%	
Age, years (Mean ± SD)	55.8±7.5	55.8±7.5	55.4±6.7	56.6±4.4	56.6±4.4	56.8±4.4	56.2±8.4	56.2±8.4	54.2±7.6	47.9±4.2	47.9±4.2	47.9±3.7
Age categories, N (%)												
< 65 years old	91,318 (93)	89,462 (93)	1,856 (94)	52,335 (99)	51,203 (99)	1,132 (99)	14,318 (85)	14,002 (84)	316 (90)	7,914 (98)	7,767 (98)	147 (99)
≥ 65 years old	7,008 (7)	6,899 (7)	109 (6)	626 (1)	610 (1)	16 (1)	2,619 (15)	2,583 (16)	36 (10)	127 (2)	125 (2)	2 (1)

Female, N (%)	64,492 (66)	63,073 (65)	1,419 (72)	27,732 (52)	27,023 (52)	709 (62)	16,937 (100)	16,585 (100)	352 (100)	8,041 (100)	7,892 (100)	149 (100)
BMI, kg/m^2 (Mean ± SD)	25.3±4.0	25.3±4.0	25.9±4.4	26.0±4.1	26.0±4.1	26.4±4.3	23.6±3.5	23.6±3.4	24.3±4.2	23.9±3.6	23.9±3.6	24.6±3.9
BMI, WHO categories, N (%)												
<18.5	1,298 (1)	1,273 (1)	25 (1)	416 (1)	404 (1)	12 (1)	495 (3)	484 (3)	11 (3)	139 (2)	138 (2)	1 (1)
18.5–24.9	49,901 (51)	49,007 (51)	894 (45)	22,893 (43)	22,436 (43)	457 (40)	11,688 (69)	11,467 (69)	221 (63)	5,492 (68)	5,400 (68)	92 (62)
25.0–29.9	35,604 (36)	34,867 (36)	737 (38)	22,013 (42)	21,536 (42)	477 (42)	3,875 (23)	3,790 (23)	85 (24)	1,875 (23)	1,832 (23)	43 (29)
≥30.0	11,523 (12)	11,214 (12)	309 (16)	7,639 (14)	7,437 (14)	202 (18)	879 (5)	844 (5)	35 (10)	535 (7)	522 (7)	13 (9)
Smoking status, N (%)												
Current smoker	32,398 (33)	31,842 (33)	556 (28)	19,218 (36)	18,869 (36)	349 (30)	6,357 (38)	6,247 (38)	110 (31)	2,303 (29)	2,263 (29)	40 (27)
Previous smoker	29,533 (30)	28,884 (30)	649 (33)	14,728 (28)	14,371 (28)	357 (31)	4,824 (28)	4,711 (28)	113 (32)	2,619 (33)	2,567 (33)	52 (35)
Never smoker	36,395	35,635	760 (39)	19,045	18,573	442 (39)	5,756	5,627	129 (37)	3,119	3,062	57 (38)

	(37)	(37)		(36)	(36)		(34)	(34)		(39)	(39)	
Smoking duration, years (Mean ± SD)	17.1±16.5	17.1±16.5	16.1±16.0	19.1±17.2	19.1±17.2	17.7±16.7	16.5±15.8	16.5±15.8	14.6±15.1	12.5±12.7	12.5±12.7	12.8±12.9
Smoking intensity, n/day (Mean ± SD)	9.2±10.4	9.2±10.4	8.9±10.3	10.4±11.2	10.5±11.3	9.4±10.6	8.4±9.3	8.4±9.3	7.8±9.3	7.5±8.4	7.5±8.3	9.5±11.1
Marital status, N (%)												
Single	8,450 (9)	8,298 (9)	152 (8)	3,194 (6)	3,138 (6)	56 (5)	1,782 (11)	1,757 (11)	25 (7)	749 (9)	735 (9)	14 (9)
Married or living with partner	70,137 (71)	68,790 (71)	1,347 (69)	37,928 (72)	37,130 (72)	798 (70)	11,471 (68)	11,235 (68)	236 (67)	6,105 (76)	6,001 (76)	104 (70)
Divorced/Separated	13,755 (14)	13,413 (14)	342 (17)	8,917 (17)	8,694 (17)	223 (19)	2,098 (12)	2,039 (12)	59 (17)	1,024 (13)	997 (13)	27 (18)
Widowed	5,984 (6)	5,860 (6)	124 (6)	2,922 (6)	2,851 (6)	71 (6)	1,586 (9)	1,554 (9)	32 (9)	163 (2)	159 (2)	4 (3)
Employment status, N (%)												
Employed	75,111 (76)	73,616 (76)	1,495 (76)	41,519 (78)	40,650 (78)	869 (76)	11,877 (70)	11,609 (70)	268 (76)	7,621 (95)	7,477 (95)	144 (97)
Others	23,215 (24)	22,745 (24)	470 (24)	11,442 (22)	11,163 (22)	279 (24)	5,060 (30)	4,976 (30)	84 (24)	420 (5)	415 (5)	5 (3)

Educational levels, N (%)*												
Low level	14,102 (14)	13,845 (14)	257 (13)	7,819 (15)	7,644 (15)	175 (15)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)
Medium level	40,914 (42)	40,031 (42)	883 (45)	33,404 (63)	32,644 (63)	760 (66)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)
High level	43,310 (44)	42,485 (44)	825 (42)	11,738 (22)	11,525 (22)	213 (19)	16,937 (100)	16,585 (100)	352 (100)	8,041 (100)	7,892 (100)	149 (100)
COPD, N (%)#	485 (0.5)	474 (0.5)	11 (1)	365 (1)	320 (1)	45 (4)	60 (0.4)	53 (0.3)	7 (2)	14 (0.2)	14 (0.2)	0 (0)
Area-level mean year incomeϕ	20991.8	20994.5	20857.3	20199.0	20193.7	20436.8	19229.3	19226.4	19366.9	18983.3	18980.8	19113.6

Table S2 continued.

Characteristic at baseline*	**CEANS (N=20,387)**											
	SDPP (N=7,520)			**SIXTY (N=3,931)**			**SALT (N=6,128)**			**SNAC-K (N=2,808)**		
	Total	**No asthma**	**Asthma**	**Total**	**No asthma**	**Asthma**	**Total**	**No asthma**	**Asthma**	**Total**	**No asthma**	**Asthma**
Enrollment period	1992–1998			1997–1999			1998–2002			2001–2004		

End of follow-up		2011			2011			2011			2011	
Person-years at risk, N	118,408	117,103	1,305	50,027	49,552	475	62,880	62,464	416	20,519	20,339	180
Follow-up time, years (Mean ± SD)	15.7±2.6	15.9±2.4	9.8±4.2	12.7±2.6	12.8±2.5	6.7±3.8	10.3±2.5	10.3±2.4	5.3±3.3	7.3±2.9	7.3±2.9	5.5±2.5
Number of observations	7,520	7,387	133	3,931	3,860	71	6,128	6,049	79	2,808	2,775	33
Asthma incidence rate		1.8%			1.8%			1.3%			1.2%	
Age, years (Mean ± SD)	47.1±4.9	47.1±4.9	47.3±5.1	60.0±0	60.0±0	60.0±0	57.8±10.6	57.8±10.6	58.2±9.7	72.9±10.4	72.9±10.4	71.1±7.6
Age categories, N (%)												
< 65 years old	7,520 (100)	7,387 (100)	133 (100)	3,931 (100)	3,860 (100)	71 (100)	4,621 (75)	4,567 (76)	54 (68)	679 (24)	676 (24)	3 (9)
≥ 65 years old	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	1,507 (25)	1,482 (24)	25 (32)	2,129 (76)	2,099 (76)	30 (91)
Female, N (%)	4,590 (61)	4,493 (61)	97 (73)	2,049 (52)	2,007 (52)	42 (59)	3,391 (55)	3,339 (55)	52 (66)	1,752 (62)	1,734 (62)	18 (55)
BMI, kg/m^2 (Mean ± SD)	25.7±4.0	25.7±4.0	26.6±4.4	26.8±4.2	26.8±4.2	27.8±5.3	24.6±3.4	24.5±3.4	25.7±3.4	25.6±4.3	25.6±4.3	25.8±4.2
BMI, WHO categories, N (%)												

<18.5	51 (1)	51 (1)	0 (0)	26 (1)	26 (1)	0 (0)	94 (2)	93 (2)	1 (1)	77 (3)	77 (3)	0 (0)
18.5–24.9	3,596 (48)	3,544 (48)	52 (39)	1,392 (35)	1,368 (35)	24 (34)	3,597 (59)	3,564 (59)	33 (42)	1,243 (44)	1,228 (44)	15 (45)
25.0–29.9	2,927 (39)	2,874 (39)	53 (40)	1,752 (45)	1,723 (45)	29 (41)	2,036 (33)	1,999 (33)	37 (47)	1,126 (40)	1,113 (40)	13 (39)
≥30.0	946 (13)	918 (12)	28 (21)	761 (19)	743 (19)	18 (25)	401 (7)	393 (6)	8 (10)	362 (13)	357 (13)	5 (15)
Smoking status, N (%)												
Current smoker	1,982 (26)	1,947 (26)	35 (26)	833 (21)	824 (21)	9 (13)	1,303 (36)	1,295 (21)	8 (10)	402 (14)	397 (14)	5 (15)
Previous smoker	2,737 (36)	2,682 (36)	55 (41)	1,514 (39)	1,484 (38)	30 (42)	2,039 (33)	2,011 (33)	28 (35)	1,072 (38)	1,058 (38)	14 (42)
Never smoker	2,801 (37)	2,758 (37)	43 (32)	1,584 (40)	1,552 (40)	32 (45)	2,786 (45)	2,743 (45)	43 (54)	1,334 (48)	1,320 (48)	14 (42)
Smoking duration, years (Mean ± SD)	12.7±13.0	12.7±13.0	13.6±13.3	15.5±16.3	15.5±16.3	15.3±16.3	14.7±17.0	14.8±17.0	10.3±14.1	15.6±19.2	15.6±19.2	18.1±20.4
Smoking intensity, n/day (Mean ± SD)	8.5±8.8	8.5±8.8	8.7±8.5	8.0±9.2	8.0±9.2	8.1±9.3	7.6±9.9	7.6±9.9	7.7±12.1	4.0 ±6.1	3.9±6.1	4.8±6.3
Marital status, N (%)												

Single	1,234 (16)	1,209 (16)	25 (19)	181 (5)	175 (5)	6 (8)	855 (14)	837 (14)	18 (23)	455 (16)	447 (16)	8 (24)
Married or living with partner	6,286 (84)	6,178 (84)	108 (81)	2,907 (74)	2,866 (74)	41 (58)	4,150 (68)	4,107 (68)	43 (54)	1,290 (46)	1,273 (46)	17 (52)
Divorced/Separated	0 (0)	0 (0)	0 (0)	642 (16)	624 (16)	18 (25)	688 (11)	676 (11)	12 (15)	386 (14)	383 (14)	3 (9)
Widowed	0 (0)	0 (0)	0 (0)	201 (5)	195 (5)	6 (8)	435 (7)	429 (7)	6 (8)	677 (24)	672 (24)	5 (15)
Employment status, N (%)												
Employed	6,826 (91)	6,705 (91)	121 (91)	2,669 (68)	2,623 (68)	46 (65)	3,948 (64)	3,905 (65)	43 (54)	651 (23)	647 (23)	4 (12)
Others	694 (9)	682 (9)	12 (9)	1,262 (32)	1,237 (32)	25 (35)	2,180 (36)	2,144 (35)	36 (46)	2,157 (77)	2,128 (77)	29 (88)
Educational levels, N (%)*												
Low level	2,370 (32)	2,338 (32)	32 (24)	1,570 (40)	1,547 (40)	23 (32)	1,635 (27)	1,615 (27)	20 (25)	708 (25)	701 (25)	7 (21)
Medium level	2,889 (38)	2,834 (38)	55 (41)	1,267 (32)	1,234 (32)	24 (34)	2,230 (36)	2,198 (36)	32 (41)	1,124 (40)	1,112 (40)	12 (36)
High level	2,261 (30)	2,215 (30)	46 (35)	1,094 (28)	1,070 (28)	24 (34)	2,263 (37)	2,236 (37)	27 (34)	976 (35)	962 (35)	14 (42)
COPD, N (%)#	0 (0)	0 (0)	0 (0)	4 (0.1)	4 (0.1)	0 (0)	17 (0.3)	16 (0.3)	1 (1)	25 (1)	24 (1)	1 (3)

Area-level mean year incomeϕ	24,340.7	24340.6	24341.9	24762.8	24769.3	24410.6	25305.5	25315.1	24576.2	28665.6	28665.6	28664.0

BMI, body mass index; SD, standard deviation; WHO, world health organization; COPD, chronic obstructive pulmonary disease.

*: Low educational level means primary school or less; Medium educational level means up to secondary school or equivalent; High educational level means university degree and more.

#: the prevalence of COPD among participants at baseline.

ϕ: Area-level mean year income is a continuous variable in euros, which is at municipality-level in 2001 for DCH and DNC and at neighbourhood level in 1994 for CEANS.

Table S3. Description of air pollutants by sub-cohorts and adult-onset asthma status for the year 2010.

Pollutants	Cohorts	Number of observations	Total			No Asthma			Asthma		
			Mean ± SD	Range	IQR	Mean ± SD	Range	IQR	Mean ± SD	Range	IQR
$PM_{2.5}$, µg/m^3											
	All	98,326	12.12±2.48	3.24–19.49	2.48	12.11±2.48	3.24–19.49	2.50	12.43±2.35	3.75–18.30	2.07
	SDPP	7,520	7.63±0.92	3.79–10.96	0.75	7.63±0.92	3.79–10.96	0.75	7.70±0.90	4.30–10.70	0.68
CEANS	SIXTY	3,931	8.31±0.92	3.24–11.01	0.88	8.30±0.92	3.24–11.01	0.89	8.63±0.56	7.12–10.11	0.59
	SALT	6,128	8.38±0.84	3.47–11.37	0.88	8.38±0.84	3.47–11.37	0.88	8.31±0.93	3.75–9.96	0.98
	SNAC-K	2,808	8.56±0.83	5.16–11.37	0.59	8.56±0.83	5.16–11.37	0.59	8.54±1.00	5.53–9.89	0.53
DCH	DCH	52,961	13.20±1.43	7.29–19.49	1.58	13.20±1.43	7.29–19.49	1.58	13.29±1.43	7.70–18.30	1.85
DNC	1993	16,937	12.74±1.54	6.48–19.14	1.87	12.74±1.54	6.48–19.14	1.86	12.91±1.54	9.55–16.93	1.93
	1999	8,041	13.80±1.51	6.89–19.49	2.34	13.80±1.51	6.89–19.49	2.34	13.66±1.61	9.58–16.81	2.54
NO_2, µg/m^3											
	All	98,326	25.10±7.97	2.68–72.23	11.88	25.08±7.97	2.68–72.23	11.88	26.25±7.79	5.68–62.36	11.80
	SDPP	7,520	15.47±4.29	2.96–37.09	5.39	15.47±4.29	2.96–37.09	5.38	15.78±4.46	6.24–26.10	5.85
CEANS	SIXTY	3,931	20.67±6.14	2.68–47.88	7.01	20.62±6.15	2.68–47.88	7.04	22.98±5.24	10.36–38.20	6.03

	SALT	6,128	21.29±6.18	2.98–50.32	7.34	21.29±6.19	2.98–50.23	7.33	21.30±5.79	5.68–39.79	7.39
	SNAC-K	2,808	27.41±5.08	11.62–42.61	7.31	27.40±5.08	11.62–42.61	7.38	27.79±7.86	16.44–35.02	6.19
DCH	DCH	52,961	28.03±6.83	6.40–72.23	9.98	28.01±6.84	6.40–72.23	10.00	28.96±6.42	9.50–62.36	9.32
DNC	1993	16,937	21.89±8.00	4.54–72.23	10.51	21.87±8.00	4.54–72.23	10.53	22.74±7.94	6.75–51.92	10.51
	1999	8,041	25.83±8.47	6.42–54.26	13.77	25.81±8.46	6.42–54.26	13.74	26.79±8.96	8.59–47.52	15.58
BC, $10^{-5}m^{-1}$											
	All	98,326	1.17±0.41	0.11–3.66	0.64	1.17±0.41	0.11–3.66	0.64	1.23±0.41	0.22–3.18	0.62
	SDPP	7,520	0.56±0.19	0.14–1.39	0.30	0.56±0.19	0.14–1.39	0.30	0.58±0.21	0.22–1.15	0.33
CEANS	SIXTY	3,931	0.80±0.25	0.11–2.10	0.32	0.80±0.25	0.11–2.10	0.32	0.90±0.25	0.28–1.50	0.31
	SALT	6,128	0.83±0.25	0.16–2.43	0.31	0.83±0.25	0.16–2.43	0.31	0.82±0.25	0.29–2.07	0.31
	SNAC-K	2,808	1.08±0.15	0.43–1.74	0.15	1.08±0.15	0.43–1.74	0.15	1.09±0.13	0.86–1.44	0.11
DCH	DCH	52,961	1.34±0.35	0.35–3.66	0.48	1.34±0.35	0.35–3.66	0.48	1.38±0.33	0.49–3.18	0.47
DNC	1993	16,937	1.09±0.37	0.13–3.66	0.52	1.09±0.37	0.13–3.66	1.52	1.12±0.37	0.34–2.49	0.52
	1999	8,041	1.30±0.38	0.36–2.74	0.55	1.29±0.38	0.36–2.74	0.55	1.35±0.40	0.56–2.30	0.74
O_3, $\mu g/m^3$											
	All	98,326	78.12±4.62	50.96–91.87	6.00	78.13±4.61	50.96–91.87	6.00	77.95±4.81	59.58–90.24	6.09

	SDPP	7,520	77.55±1.92	68.37–85.01	2.59	77.55±1.92	68.37–85.01	2.59	77.59±1.98	71.55–82.10	2.81
CEANS	SIXTY	3,931	76.70±2.52	63.15–83.79	2.88	76.72±2.52	63.15–83.79	2.90	75.82±2.50	68.60–81.28	2.96
	SALT	6,128	76.57±2.73	57.17–84.87	2.87	76.56±2.73	57.17–84.87	2.88	76.80±2.42	64.54–82.58	2.27
	SNAC-K	2,808	75.11±2.65	58.63–82.50	2.91	75.11±2.66	58.63–82.50	2.91	74.87±2.11	69.21–77.96	2.58
DCH	DCH	52,961	77.54±5.10	50.96–87.79	7.15	77.54±5.10	50.96–87.79	7.15	77.38±5.17	59.58–86.96	7.37
DNC	1993	16,937	80.41±4.00	50.96–91.87	3.95	80.42±3.99	50.96–91.87	3.95	79.99±4.57	61.37–90.06	4.25
	1999	8,041	80.62±3.83	57.02–91.83	3.88	80.63±3.83	57.02–91.83	3.87	80.19±4.16	61.85–90.24	4.34

$PM_{2.5}$, particulate matter with diameter < 2.5 μm; NO_2, nitrogen dioxide; BC, black carbon; O_3, ozone.

The annual average concentrations of $PM_{2.5}$, NO_2, BC and O_3 were estimated for the year 2010 at 100 m resolution. O_3 was estimated during the warm season from April 1 through September 30.

Table S4. Characteristics of participants at baseline (1992–2004) and air pollutants for the year 2010 by the quintiles of NO_2 concentrations.

Characteristic	NO_2 quintiles				
	1st	2nd	3rd	4th	5th
NO_2, $\mu g/m^3$ (Range)	2.68–17.87	17.87–22.51	22.51–27.31	27.31–32.59	32.59–72.23
No of participants, N	19,665	19,664	19,666	19,665	19,666
Age, years (Mean ± SD)	53.43 ± 7.85	55.52 ± 7.83	56.52 ± 7.35	57.57 ± 7.28	55.89 ± 6.50
Female, N (%)	13,762 (70)	13,528 (69)	12,641 (64)	11,866 (60)	12,695 (65)
BMI, kg/m^2 (Mean ± SD)	25.10 ± 3.92	25.04 ± 3.86	25.34 ± 4.00	25.74 ± 4.16	25.47 ± 4.17
Normal weight, N (%)*	10,487 (53)	10,507 (53)	10,015 (51)	9,113 (46)	9,779 (50)
Smoking duration	14.80 ± 15.31	15.87 ± 16.12	17.13 ± 16.77	18.09 ± 17.16	19.58 ± 16.77
Smoking intensity	8.50 ± 9.87	8.61 ± 9.96	9.11 ± 10.44	9.44 ± 10.68	10.50 ± 10.76
Never smoker, N (%)	7,607 (39)	7,670 (39)	7,497 (38)	7,346 (37)	6,275 (32)
Married or living with partner, N (%)	16,050 (82)	15,032 (76)	14,042 (71)	13,278 (68)	11,743 (60)
Employed, N (%)	15,573 (79)	14,840 (75)	14,593 (74)	14,351 (73)	15,754 (80)
High educational level, N (%)	10,578 (54)	9,791 (50)	8,160 (41)	6,684 (34)	8,097 (41)
Mean year income, €ϕ	21154.41	20985.80	21083.05	21213.40	20522.29

$PM_{2.5}$, $\mu g/m^3$ (Mean ± SD)	9.93 ± 2.38	11.16 ± 2.09	12.16 ± 1.81	13.00 ± 1.74	14.33 ± 1.74
BC, $10^{-5}m^{-1}$ (Mean ± SD)	0.66 ± 0.19	0.94 ± 0.19	1.16 ± 0.16	1.41 ± 0.21	1.70 ± 0.22
O_3, $\mu g/m^3$ (Mean ± SD)	80.43 ± 2.71	79.35 ± 2.97	78.80 ± 4.07	78.43 ± 3.70	73.60 ± 5.67

*: Normal weight means BMI values from 18.5 to 24.9 according to the World Health Organization (WHO) categories; High educational level means university degree and more.

ϕ: Mean year income is a continuous variable in euros, which is at municipality level in 2001 for DCH and DNC and at neighbourhood level in 1994 for CEANS.

Figure S1. The temporal variations of annual mean air pollution concentrations back-extrapolated using the ratio (left) and the absolute difference (right) method during follow-up periods (1992-2011 for CEANS and 1993-2015 for DCH) in 71,311 participants of CEANS (N=19,320) and DCH (N=51,991) cohorts**.**

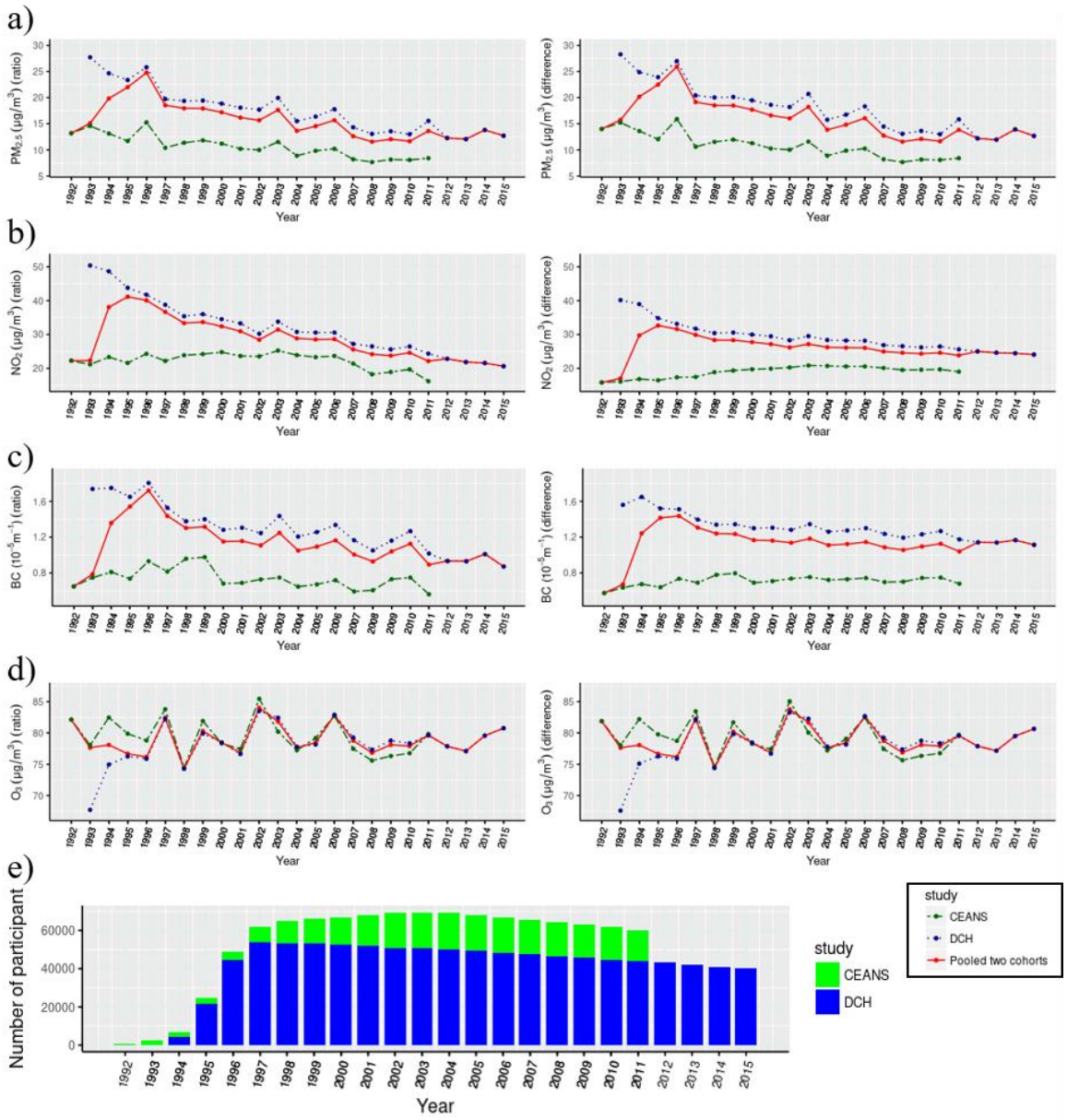


Table S5. Pearson correlations between air pollutants by sub-cohorts for the year 2010.

Cohorts	Number of observations	Pollutants	$PM_{2.5}$	NO_2	BC	O_3
All	98,326					
		$PM_{2.5}$	1.00			
		NO_2	0.63	1.00		
		BC	0.74	0.91	1.00	
		O_3	-0.13	-0.48	-0.37	1.00
CEANS- SDPP	7,520					
		$PM_{2.5}$	1.00			
		NO_2	0.60	1.00		
		BC	0.49	0.67	1.00	
		O_3	-0.18	-0.70	-0.33	1.00
CEANS- SIXTY	3,931					
		$PM_{2.5}$	1.00			
		NO_2	0.69	1.00		
		BC	0.59	0.84	1.00	
		O_3	-0.45	-0.71	-0.71	1.00
CEANS- SALT	6,128					
		$PM_{2.5}$	1.00			
		NO_2	0.67	1.00		
		BC	0.55	0.84	1.00	
		O_3	-0.47	-0.74	-0.76	1.00
CEANS- SNAC-K	2,808					
		$PM_{2.5}$	1.00			
		NO_2	0.75	1.00		
		BC	0.28	0.43	1.00	

		O_3	-0.49	-0.65	-0.74	1.00
DCH	52,961					
		$PM_{2.5}$	1.00			
		NO_2	0.72	1.00		
		BC	0.66	0.91	1.00	
		O_3	-0.56	-0.61	-0.57	1.00
DNC-1993	16,937					
		$PM_{2.5}$	1.00			
		NO_2	0.64	1.00		
		BC	0.69	0.92	1.00	
		O_3	-0.32	-0.42	-0.42	1.00
DNC-1999	8,041					
		$PM_{2.5}$	1.00			
		NO_2	0.61	1.00		
		BC	0.64	0.93	1.00	
		O_3	-0.16	-0.21	-0.20	1.00

Table S6. Results for threshold analyses of associations between long-term air pollution exposure and adult-onset asthma based on Model 3 (N=98,326).

Pollutants	Threshold	AIC	HR (95%CI)
$PM_{2.5}$	No threshold	36807.6	1.22 (1.04–1.43)
	5 μg/m^3	36807.61	1.22 (1.04–1.43)
	7.5 μg/m^3	36807.78	1.22 (1.04–1.43)
	10 μg/m^3	36808.71	1.20 (1.02–1.42)
NO_2	No threshold	36790.44	1.17 (1.10–1.25)
	10 μg/m^3	36790.73	1.17 (1.10–1.25)
	15 μg/m^3	36791.04	1.18 (1.10–1.26)
	20 μg/m^3	36796.19	1.17 (1.09–1.26)
BC	No threshold	36795.5	1.15 (1.08–1.23)
	0.5 $10^{-5}m^{-1}$	36795.68	1.15 (1.08–1.23)
	1 $10^{-5}m^{-1}$	36801.14	1.15(1.07–1.25)
	1.5 $10^{-5}m^{-1}$	36810.49	1.16 (0.98–1.37)
O_3	No threshold	36809.26	0.90 (0.81–0.99)
	40 μg/m^3	36809.26	0.90 (0.81–0.99)
	60 μg/m^3	36809.22	0.90 (0.81–0.99)
	80 μg/m^3	36811.37	0.78 (0.56–1.09)

AIC, Akaike Information Criterion. Results are presented as hazard ratio (HR) and 95% confidence interval (CI) [HR (95%CI)] for the following increases: 5 μg/m^3 for $PM_{2.5}$, 10 μg/m^3 for NO_2, 0.5 10^{-5} m^{-1} for BC and 10 μg/m^3 for O_3.

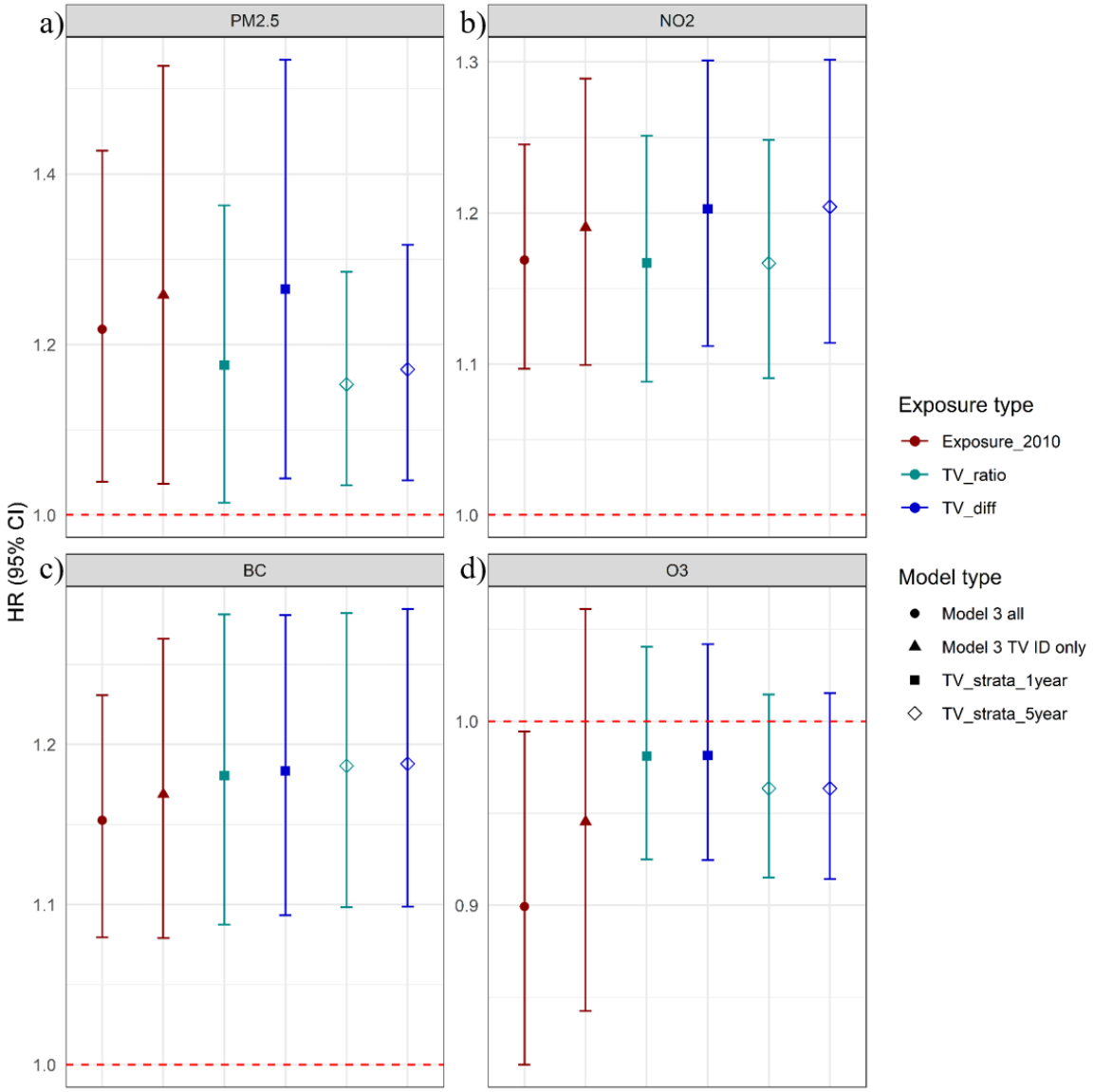
*: Lower AIC values represent improved prediction of models for the associations.

Table S7. Results for Sensitivity Analysis by time-varying exposure analyses among two cohorts with available information (CEANS and DCH, N=71,311) based on Model 3.

Pollutants	Main model 3	Time-varying analyses			
	Reduced dataset (N=71,311)	Strata by per year of follow-up time		Strata by 5-years of follow-up time	
		Ratio method	Difference method	Ratio method	Difference method
$PM_{2.5}$	1.26 (1.04–1.53)	1.18 (1.01–1.36)	1.26 (1.04–1.53)	1.15 (1.03–1.29)	1.17 (1.04–1.32)
NO_2	1.19 (1.10–1.29)	1.17 (1.09–1.25)	1.20 (1.11–1.30)	1.17 (1.09–1.25)	1.20 (1.11–1.30)
BC	1.17 (1.08–1.27)	1.18 (1.09–1.28)	1.19 (1.09–1.28)	1.19 (1.10–1.28)	1.19 (1.10–1.28)
O_3	0.95 (0.84–1.06)	0.98 (0.92–1.04)	0.98 (0.92–1.04)	0.96 (0.92–1.01)	0.96 (0.91–1.02)

Results are presented as hazard ratio and 95% confidence interval [HR (95%CI)] for the following increases: 5 $\mu g/m^3$ for $PM_{2.5}$, 10 $\mu g/m^3$ for NO_2, 0.5 10^{-5} m^{-1} for BC, and 10 $\mu g/m^3$ for O_3.

Figure S2. Results for Sensitivity Analysis by time-varying exposure analyses among two cohorts with available information (CEANS and DCH, N=71,311) based on Model 3.



Three different exposure types were applied: Exposure_2010 indicates exposure in 2010; TV_ratio indicates time-varying exposure analysis with a ratio method; TV_ratio indicates time-varying exposure analysis with an absolute difference method.

Four different exposure types were applied: Model 3 all indicates using model 3 with all cohort participants; Model 3 TV ID only indicates using model 3 with time-varying exposure analysis available two cohort participants; TV_strata_1year indicates time-

varying exposure analysis with 1-year strata for the calendar time; TV_strata_5year indicates time-varying exposure analysis with 5-year strata for the calendar time.

Table S8. Back-extrapolated air pollution exposure at baseline and adult-onset asthma based on Model 3.

Pollutants	Main model 3	Baseline exposure analyses	
	(N=98,326)	Ratio method	Difference method
$PM_{2.5}$	1.22 (1.04–1.43)	1.04 (0.96–1.12)	0.98 (0.89–1.09)
NO_2	1.17 (1.10–1.25)	1.12 (1.07–1.17)	1.17 (1.10–1.25)
BC	1.15 (1.08–1.23)	1.11 (1.05–1.18)	1.15 (1.07–1.23)
O_3	0.90 (0.81–0.99)	0.95 (0.87–1.05)	0.95 (0.86–1.05)

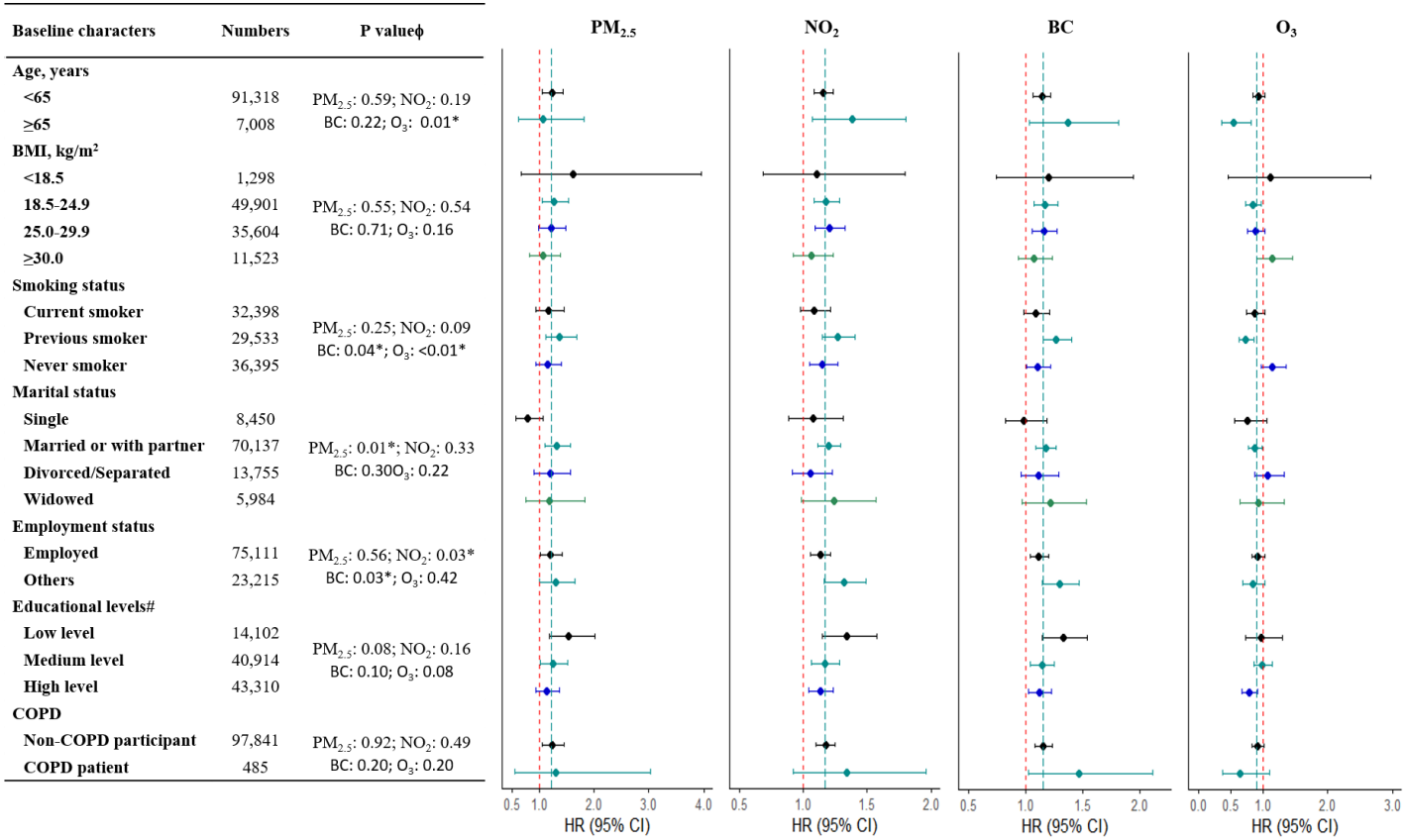
Results are presented as hazard ratio and 95% confidence interval [HR (95%CI)] for the following increases: 5 $\mu g/m^3$ for $PM_{2.5}$, 10 $\mu g/m^3$ for NO_2, 0.5 10^{-5} m^{-1} for BC, and 10 $\mu g/m^3$ for O_3.

Table S9. Results for Sensitivity Analysis by restricting participants to different cohorts in Model 3.

Cohorts	Number of observations	HR (95%CI)			
		$PM_{2.5}$	NO_2	BC	O_3
All cohorts	98,326	1.22 (1.04–1.43)	1.17 (1.10–1.25)	1.15 (1.08–1.23)	0.90 (0.81–0.99)
Exclude CEANS	77,939	1.24 (1.06–1.47)	1.17 (1.10–1.26)	1.15 (1.08–1.23)	0.87 (0.79–0.97)
Exclude DCH	45,365	1.18 (0.91–1.53)	1.14 (1.04–1.25)	1.15 (1.03–1.28)	0.79 (0.65–0.95)
Exclude DNC	73,348	1.25 (1.03–1.51)	1.19 (1.10–1.29)	1.17 (1.08–1.26)	0.95 (0.84–1.06)
Only CEANS	20,387	1.42 (0.74–2.71)	1.15 (0.93–1.41)	1.24 (0.97–1.59)	0.88 (0.55–1.39)
Only DCH	52,961	1.26 (1.02–1.57)	1.21 (1.10–1.33)	1.16 (1.06–1.27)	0.93 (0.82–1.06)
Only DNC	24,978	1.17 (0.88–1.56)	1.14 (1.02–1.27)	1.13 (1.01–1.28)	0.74 (0.60–0.92)

Results are presented as hazard ratio and 95% confidence interval [HR (95%CI)] for the following increases: 5 $\mu g/m^3$ for $PM_{2.5}$, 10 $\mu g/m^3$ for NO_2, 0.5 10^{-5} m^{-1} for BC and 10 $\mu g/m^3$ for O_3.

Figure S3. Effect modification on the association of long-term air pollution exposure with adult-onset asthma by baseline characters.



Effect modification analyses were conducted based on Model 3 and evaluated by introducing interaction terms. *P* values for whether there were statistical differences between strata were tested by the Wald test. Red long dash lines indicate the HRs equal to 1 and green long dash lines indicate the estimated HRs for all participants based on Model 3.

#: Low educational level means primary school or less; Medium educational level means up to secondary school or equivalent; High educational level means university degree and more.

*: A statistically significant *P* value (at 5% level) for effect modification analyses.