**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 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.

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**Abstract**

**Background:** Long-term exposure to ambient air pollution has been linked to childhood-onset asthma, while evidence on adult-onset asthma 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 (PM2.5), nitrogen dioxide (NO2), 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 μg/m3 for PM2.5, 1.17 (1.10−1.25) per 10 µg/m3 for NO2, and 1.15 (1.08−1.23) per 0.5 10-5m-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 PM2.5 and NO2. NO2 and BC estimates remained unchanged in two-pollutant models with PM2.5, whereas PM2.5 estimates were attenuated to unity. The concentration response curves showed no evidence of a threshold.

**Conclusions:** Long-term exposure to air pollution, especially from 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 (PM2.5) [5]. While PM2.5 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 (NO2), PM2.5, particulate matter with diameter < 10 µm (PM10), 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 NO2 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 PM2.5 suggested positive associations. Two studies reported positive associations between air pollution and asthma incidence in non-smokers only, one with traffic-related PM10 [20] and the other with ozone (O3) [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 (PM2.5, NO2, BC, and O3) 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 PM2.5, NO2, BC, and warm season O3 (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/m2), 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 PM2.5, NO2, and BC at the residence than asthma-free participants. For NO2, 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 PM2.5 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 NO2 concentrations are shown in Table S2, Table S3, and Table S4, respectively. We found that participants living in the highest quintiles of exposure to NO2 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 NO2 levels (Table S4). We show that air pollution levels were decreasing during follow-up time (Figure S1). PM2.5, NO2, and BC were generally moderate-to-highly correlated with each other (Pearson correlation coefficients > 0.6), while O3 was negatively correlated with the other pollutants (Table S5). NO2 and BC were highly correlated in all (0.67−0.93) sub-cohorts except for SNAC-K (0.43).

We observed positive associations between PM2.5, NO2, 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 PM2.5 levels below 15, 12, and 10 µg/m3 (Table 3). HRs for NO2 were also slightly higher when only including participants with concentrations below 40, 30, and 20 µg/m3. Likewise, for BC, the fully adjusted HRs remained increased even below 1 10-5m-1 (Table 3). We did not find any evidence for a threshold for the associations between PM2.5, NO2, 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 NO2 and BC remained unchanged after adjusting for PM2.5, whereas the HRs for PM2.5 were attenuated to below unity when adjusting for NO2 or BC (Table 4). In two-pollutant models with O3, the HRs for PM2.5, NO2, or BC were essentially unaffected, while the negative association between O3 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 PM2.5, and remained unchanged for NO2 and BC (Table S8). The associations of PM2.5, NO2, and BC with asthma incidence were consistently stronger in previous smokers, unemployed and low-educated participants (Figure S3). O3 also showed a borderline positive association in never smokers.

**Discussion**

In this pooled analysis of three cohorts, long-term exposures to PM2.5, NO2, 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 PM2.5 was attenuated to unity in two-pollutant models, while the associations with NO2 and BC remained robust.

Our results on PM2.5 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 µg/m3) [14] and 100,084 adults in Sydney, Australia (HR 1.08; 0.89−1.30, per 1 μg/m3) [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 μg/m3] [16], and 50,884 women from the US Sisters Cohort with an OR of 1.20 (0.99–1.46) per 3.6 μg/m3 in PM2.5 [17]. In contrast, the American Nurses' Health Study did not detect association between PM2.5 and self-reported asthma (HR 0.90; 0.73–1.12, per 10 μg/m3) [15]. Our findings of an association between NO2 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/m3 in the Sydney cohort [13], and 1.03 (1.02−1.05) per 4.1 ppb (around 7.7 μg/m3) in NO2 in a Toronto cohort [14], to 1.10 (1.01−1.20) per 5.8 μg/m3 in the Danish Diet, Cancer, and Health Cohort [18]. Results for NO2 from studies with self-reported asthma also suggest positive associations, with ORs of 1.10 (0.99–1.21) per 10 μg/m3 in six ESCAPE cohorts [16], 1.12 (0.96–1.30) per 5.8 ppb (~10.9 μg/m3) in the US Sisters Study [17], and 1.43 (1.02−2.01) per 10 μg/m3 in the European Community Respiratory Health Survey study [21], and 1.54 (1.00–2.36) per 10 μg/m3 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 O3 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 PM2.5 levels in Europe [16, 18-20], Canada [14], the United States [15, 17], and Australia [13] (Table S1).

Our findings of attenuated PM2.5 effects in two-pollutant models with NO2 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 NO2, the significant single pollutant HR for PM2.5 was reduced to unity, whereas the association with NO2 remained robust after adjustment for PM2.5. Given that the correlation between PM2.5 and NO2 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 PM2.5 as merely an artefact related to multi-collinearity. The association with NO2 might reflect direct effects of NO2 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 PM2.5 HR as implying that particles had no effect in our setting, as adjustment for NO2 also adjusted for particles from the same sources with NO2, including motorized traffic and other combustion sources. Only two studies to date examined two-pollutant models with PM2.5 and NO2. The Toronto cohort study found that the association with PM2.5 was robust to additional adjustment for NO2, though notably, associations with NO2 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 NO2 on asthma [14]. Our results are in line with the finding in the ESCAPE study, where, comparable to our PM2.5 results, the HR for PM10 (highly correlated with PM2.5) was attenuated to below unity with NO2 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 NO2, 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 PM2.5 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]. NO2 is emitted together with traffic-related PM mainly in the ultrafine range, which contribute minimally to total PM2.5 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 PM2.5, UFPs, and NO2 and adult-onset asthma reported the strongest associations with NO2, and only weak with PM2.5 and UFPs, and found that the significant positive association for UFPs attenuated to null in a two-pollutant model with NO2, supporting the idea of the independent effect of NO2 on asthma development [14]. We presented novel observations of enhanced HRs in previous smokers, unemployed and low-educated participants for PM2.5, NO2, and BC, as well as in never smokers for O3. 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 PM10 [20] and O3 [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 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.

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**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.

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**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/m2 (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†** |  |  |  |
|  PM2.5, µg/m3 (Mean ± SD) | 12.12 ± 2.48 | 12.11 ± 2.48 | 12.43 ± 2.35 |
|  NO2, µg/m3 (Mean ± SD) | 25.10 ± 7.97 | 25.08 ± 7.97 | 26.25 ± 7.79 |
|  BC, 10-5m-1 (Mean ± SD) | 1.17 ± 0.41 | 1.17 ± 0.41 | 1.23 ± 0.41 |
|  O3, µg/m3 (Mean ± SD) | 78.12 ± 4.62 | 78.13 ± 4.61 | 77.95 ± 4.81 |

BMI, body mass index; SD, standard deviation; PM2.5, particulate matter with diameter < 2.5 μm; NO2, nitrogen dioxide; BC, black carbon; O3, 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 PM2.5, NO2, BC and O3 were estimated for the year 2010 at 100 m resolution. O3 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 |
| **PM2.5** | 1.24 (1.06−1.45) | 1.20 (1.03−1.41) | 1.22 (1.04−1.43) |
| **NO2** | 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) |
| **O3** | 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 µg/m3 for PM2.5, 10 µg/m3 for NO2, 0.5 10-5 m-1 for BC and 10 µg/m3 for O3.

**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)** |
| PM2.5 |  |  |  |
|  | All levels | 98,326 | 1.22 (1.04−1.43) |
|  | < 25 µg/m3 | 98,326 | 1.22 (1.04−1.43) |
|  | < 20 µg/m3 | 98,326 | 1.22 (1.04−1.43) |
|  | < 15 µg/m3 | 86,295 | 1.23 (0.97−1.57) |
|  | < 12 µg/m3 | 35,662 | 1.53 (0.90−2.60) |
|  | < 10 µg/m3 | 20,857 | 1.49 (0.76−2.94) |
| NO2 |  |  |  |
|  | All levels | 98,326 | 1.17 (1.10−1.25) |
|  | < 40 µg/m3 | 96,481 | 1.21 (1.13−1.29) |
|  | < 30 µg/m3 | 69,877 | 1.29 (1.15−1.45) |
|  | < 20 µg/m3 | 28,114 | 1.24 (0.92−1.67) |
| BC |  |  |  |
|  | All levels | 98,326 | 1.15 (1.08−1.23) |
|  | < 3 10-5m-1 | 98,319 | 1.15 (1.08−1.23) |
|  | < 2.5 10-5m-1 | 98,240 | 1.15 (1.08−1.23) |
|  | < 2 10-5m-1 | 97,001 | 1.15 (1.08−1.23) |
|  | < 1.5 10-5m-1 | 74,838 | 1.17 (1.09−1.26) |
|  | < 1 10-5m-1 | 34,693 | 1.33 (1.02−1.74) |
|  | < 0.5 10-5m-1 | 4,906 | 0.77 (0.15−3.97) |
| O3 |  |  |  |
|  | All levels | 98,326 | 0.90 (0.81−0.99) |
|  | < 80 µg/m3 | 57,897 | 0.91 (0.78−1.06) |
|  | < 60 µg/m3 | 58 | ⎯ |

Results are presented as hazard ratio (HR) and 95% confidence interval (CI) [HR (95%CI)] for the following increases: 5 µg/m3 for PM2.5, 10 µg/m3 for NO2, 0.5 10-5 m-1 for BC and 10 µg/m3 for O3.

**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)** |
| **PM2.5** | **NO2** | **BC** | **O3** |
| **PM2.5** | 1.22 (1.04−1.43) | ⎯ | 0.88 (0.70−1.09) | 0.95 (0.77−1.18) | 1.16 (0.97−1.39) |
| **NO2** | 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) |
| **O3** | 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 µg/m3 for PM2.5, 10 µg/m3 for NO2, 0.5 10-5 m-1 for BC and 10 µg/m3 for O3.

\*: Two-pollutant result for NO2 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 PM2.5 and NO2.

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