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## Long-term exposure to low-level air pollution and incidence of chronic obstructive pulmonary disease: The ELAPSE project

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## ABSTRACT

**Background:** Air pollution has been suggested as a risk factor for chronic obstructive pulmonary disease (COPD), but evidence is sparse and inconsistent.

**Objectives:** We examined the association between long-term exposure to low-level air pollution and COPD incidence.

**Methods:** Within the 'Effects of Low-Level Air Pollution: A Study in Europe' (ELAPSE) study, we pooled data from three cohorts, from Denmark and Sweden, with information on COPD hospital discharge diagnoses. Hybrid land use regression models were used to estimate annual mean concentrations of particulate matter with a diameter < 2.5  $\mu\text{m}$  (PM<sub>2.5</sub>), nitrogen dioxide (NO<sub>2</sub>), and black carbon (BC) in 2010 at participants' baseline residential addresses, which were analysed in relation to COPD incidence using Cox proportional hazards models.

**Results:** Of 98,058 participants, 4,928 developed COPD during 16.6 years mean follow-up. The adjusted hazard ratios (HRs) and 95% confidence intervals for associations with COPD incidence were 1.17 (1.06, 1.29) per 5  $\mu\text{g}/\text{m}^3$  for PM<sub>2.5</sub>, 1.11 (1.06, 1.16) per 10  $\mu\text{g}/\text{m}^3$  for NO<sub>2</sub>, and 1.11 (1.06, 1.15) per 0.5  $10^{-5}\text{m}^{-1}$  for BC. Associations persisted in subset participants with PM<sub>2.5</sub> or NO<sub>2</sub> levels below current EU and US limit values and WHO guidelines, with no evidence for a threshold. HRs for NO<sub>2</sub> and BC remained unchanged in two-pollutant models with PM<sub>2.5</sub>, whereas the HR for PM<sub>2.5</sub> was attenuated to unity with NO<sub>2</sub> or BC.

**Conclusions:** Long-term exposure to low-level air pollution is associated with the development of COPD, even below current EU and US limit values and possibly WHO guidelines. Traffic-related pollutants NO<sub>2</sub> and BC may be the most relevant.

## 1. Introduction

Chronic Obstructive Pulmonary Disease (COPD) is a common chronic respiratory disease characterized by progressive irreversible airflow limitation related to chronic inflammation in the lung parenchyma (Mannino and Buist, 2007). COPD is a complex disease determined by interactions between genetic and environmental factors, with smoking as the most important risk factor (Vijayan, 2013). Still, approximately 25–45% of COPD cases occur in never-smokers (Salvi and Barnes, 2009), and other risk factors, such as air pollution, are increasingly believed to play important roles (Eisner et al., 2010).

Ambient air pollution is a major risk factor for mortality and morbidity. Globally, around 7.5% of total deaths were attributed to particulate matter with diameter < 2.5  $\mu\text{m}$  (PM<sub>2.5</sub>) in 2016 (GBD 2016 Risk Factors Collaborators, 2017). Although it is well accepted that air pollution exposure is linked to airway disease (Kelly and Fussell, 2011), direct epidemiological and mechanistic evidence linking long-term air pollution exposure to COPD onset is sparse and insufficient, as concluded by an official report by American Thoracic Society (Thurston et al., 2020). We provide detailed information on previous epidemiological studies in supplementary Table S1. Seven out of ten studies on long-term exposure to air pollution and COPD incidence documented positive associations with at least one pollutant under investigation (Andersen et al., 2011; Atkinson et al., 2015; Danesh Yazdi et al., 2019; Gan et al., 2013; Guo et al., 2018; Schikowski et al., 2014; Weichenthal et al., 2017), and three reported null associations with all pollutants under study (Carey et al., 2016; Fisher et al., 2016; Salimi et al., 2018). Some studies lack adjustment for the most relevant confounders, such as smoking (Danesh Yazdi et al., 2019; Gan et al., 2013; Weichenthal et al., 2017). Additionally, only few studies explored the shape of the concentration response curve between long-term exposure to air pollution and COPD incidence (Danesh Yazdi et al., 2019; Gan et al., 2013; Guo et al., 2018), or presented mutually adjusted associations in two pollutant models (Atkinson et al., 2015; Carey et al., 2016; Gan et al., 2013; Weichenthal et al., 2017). Several studies investigated the associations of long-term air pollution exposure with lung function in adults (Guo et al., 2018; Lepeule et al., 2014; Rice et al., 2015; Wang et al., 2019), which is a main feature of COPD development.

The decrease in ambient air pollution level in Europe calls for new epidemiological studies to examine the health effects of air pollution at low levels, below current EU and US limit values or WHO guidelines (EEA, 2019). The 'Effects of Low-Level Air Pollution: A Study in Europe' (ELAPSE) project, which pooled data from 11 European cohorts with detailed individual information and seven large nationwide cohorts

across Europe (<http://www.elapseproject.eu/>), was conducted to investigate the health effects of long-term exposure to low-level ambient air pollution among adults.

Within the ELAPSE project, we aimed to investigate the associations of long-term exposures to PM<sub>2.5</sub>, nitrogen dioxide (NO<sub>2</sub>), black carbon (BC), and ozone (O<sub>3</sub>) and the development of COPD, particularly below current EU and US limit values and WHO guidelines. We further assessed the concentration response relationships and estimated the mutually adjusted associations.

## 2. Methods

### 2.1. Study population

We used data from three cohorts within the ELAPSE project with available information on COPD hospital discharge diagnoses: 1) the Swedish Cardiovascular Effects of Air Pollution and Noise (CEANS) study (Beelen et al., 2014; Korek et al., 2015), which pooled data from four sub-cohorts: the Stockholm Diabetes Prevention Program (SDPP), the Stockholm 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 (Tjønneland et al., 2007); and 3) the Danish Nurse Cohort (DNC) study with two sub-cohorts from baseline rounds in 1993 and 1999 (Hundrup et al., 2012). Covariate data were collected by questionnaires at the cohort baseline, between 1992 and 2004. More detail information on these cohorts are in online supplement S1 and Table S2. The study was undertaken in accordance with the Declaration of Helsinki. All three cohorts were approved by the local ethics committees in accordance with the national regulations.

### 2.2. Exposure assessment

Annual mean concentrations of PM<sub>2.5</sub>, NO<sub>2</sub>, BC, and warm season O<sub>3</sub> (April to September) for 2010 were estimated at the study participants' baseline residential addresses, at a 100 × 100 m spatial resolution, using standardized Europe-wide hybrid land use regression (LUR) models (de Hoogh et al., 2018). The LUR model utilized routine monitoring data from the European Environment Agency (EEA) AirBase for PM<sub>2.5</sub>, NO<sub>2</sub>, and O<sub>3</sub>, and ESCAPE monitoring data for BC as the dependent variable. BC was measured by the reflectance of PM<sub>2.5</sub> filters and expressed in absorbance units. The mean concentrations of O<sub>3</sub> were estimated as the average of daily maximum 8-hour means. Satellite data, dispersion model estimates, land use, and traffic variables were predictors to

develop models to estimate annual mean air pollution concentrations. The models performed well in five-fold hold-out validation explaining 72%, 59%, 54%, and 69% of spatial variability of the measured concentrations for PM<sub>2.5</sub>, NO<sub>2</sub>, BC, and O<sub>3</sub>, respectively (de Hoogh et al., 2018). Predictions from the 2010 model correlated highly with models developed for 2000 and 2005 models for (NO<sub>2</sub> and O<sub>3</sub>) and 2013 model for PM<sub>2.5</sub> at the overall European scale, with squared correlations (R<sup>2</sup>) larger than 76% (de Hoogh et al., 2018).

Additionally, we estimated pollutant concentrations for each year from baseline to the end of follow-up using back-extrapolation to 1990. We applied back-extrapolation by using monthly average concentrations from a chemical transport and dispersion model based on emission and meteorological data, the Danish Eulerian Hemispheric Model (DEHM), across Europe at 26 × 26 km spatial resolution back to at least 1990 (Brandt et al., 2012). 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 AirBase monitoring data were less consistent, not available for BC and only available from about 2008 for PM<sub>2.5</sub>, which does not give us a solid base to perform a harmonious back-extrapolation across cohort areas. Residential history addresses for each year of follow-up 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 NUTS-1 spatial scale (Nomenclature of territorial units for statistics), allowing different spatial trends within Europe. The NUTS classification is a hierarchical system for dividing up the economic territory of the EU and the UK for the purpose of the collection, development and harmonization of European regional statistics. NUTS 1 reflect major socio-economic regions and may be an entire (small) country or parts of a country (e.g. four regions in the Netherlands and 14 regions in France). We compared temporal patterns of predicted DEHM and measured AirBase concentrations for countries (Sweden were not included) with available measurements, and trends are fairly similar for modeled and measured data, better for NO<sub>2</sub> than for PM<sub>2.5</sub> (data not shown).

For our study based on three cohorts in Denmark and Sweden within ELAPSE project, we back-extrapolated concentrations for all pollutants for CEANS and DCH cohorts with available historical address information, using both an absolute difference and a ratio method with 2010 as the reference year. 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.

### 2.3. Outcome definition

We defined incidence of COPD as the first-ever hospital discharge diagnosis for COPD after baseline, which was defined as emergency room visits, inpatient hospitalizations, or outpatient visits in the Danish cohorts (DCH and DNC), and inpatient hospitalization in CEANS, following the principal diagnosis of International Classification of Diseases, 9th Revision (ICD-9) codes 490–492, and 494–496, or ICD-10 codes J40–44.

### 2.4. Statistical analysis

We used stratified Cox proportional hazards models, to examine the associations of long-term exposure to air pollution with COPD incidence, with censoring at the time of death, diagnosis of asthma (principal diagnosis of ICD-9 codes 493 or ICD-10 codes J45–46), emigration, or the end of follow-up in 2011 (CEANS) or 2015 (DCH and DNC),

whichever came first. Air pollution exposure was entered first as a linear term. Age was the underlying time scale due to the evidence of better adjustment for potential confounders by age (Thiebaut and Benichou, 2004). The associations between air pollutants and COPD were examined using three models 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 (1992–2004). Model 2 additionally adjusted for smoking status (never, former, current), smoking duration (years), smoking intensity (linear and squared term; cigarettes/day), body-mass index (BMI, categorical: <18.5, 18.5–24.9, 25.0–29.9, ≥30 kg/m<sup>2</sup>), 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). Model 3 (main model), additionally adjusted for area-level annual year income (in euros): at municipality-level in 2001 for DCH and DNC, and at neighbourhood level in 1994 for CEANS. Participants with complete information for all variables in Model 3 were included in the analyses, and participants with COPD hospital diagnoses before baseline were excluded.

We examined whether associations persisted at low concentrations by excluding participants with exposure to a priori defined cut-off values, including existing EU and US limit values and WHO guidelines (25, 20, 15, 12, 10 µg/m<sup>3</sup> for PM<sub>2.5</sub>; 40, 30, 20 µg/m<sup>3</sup> for NO<sub>2</sub>; 3, 2.5, 2, 1.5, 1, 0.5 10<sup>-5</sup>m<sup>-1</sup> for BC; and 80, 60 µg/m<sup>3</sup> for O<sub>3</sub>). To further evaluate the shape of the concentration response curves between air pollution exposure and COPD incidence, we used natural cubic splines with three degrees of freedom in Model 3 and tested for the deviation of linearity from the linear model using likelihood ratio test. In an attempt to account for mutual correlation and estimate independent effect of each pollutant on COPD development, we fitted two-pollutant models in Model 3 and did collinearity test for pollutants.

We conducted several sensitivity analyses. First, to examine the robustness of using 2010 as the reference year for air pollution exposure assignment, we re-ran Model 3 with 1) back-extrapolated annual average concentrations in baseline year, using the difference and ratio between 2010 and the baseline year; 2) time-varying air pollution concentrations, using back-extrapolated annual averages for cohorts with complete residential history addresses from baseline until the end of follow-up (available for CEANS, DCH), with 1-year or 5-year strata to account for time trends in COPD incidence and air pollution. Secondly, we estimated associations in Model 3 by separately including each of the three cohorts or by excluding one cohort each time.

We assessed potential effect modification of the association between air pollution and COPD incidence by age at baseline (<65, ≥65 years), BMI, smoking status, marital status, employment status, educational level, and asthma status at baseline, by introducing an interaction term into Model 3 and using the Wald test.

The results are presented as hazard ratios (HRs) and 95% confidence intervals (CIs) for an increase of 5 µg/m<sup>3</sup> for PM<sub>2.5</sub>, 10 µg/m<sup>3</sup> for NO<sub>2</sub>, 0.5 10<sup>-5</sup> m<sup>-1</sup> for BC, and 10 µg/m<sup>3</sup> for O<sub>3</sub>. All analyses were performed in R software (version 3.4.0).

## 3. Results

From a total of 106,727 participants with complete air pollution exposure data (21,986 from CEANS, 56,308 from DCH, and 28,433 from DNC), we excluded 633 participants with COPD at baseline and 7,586 participants with missing information on confounders. Of the remaining 98,508 participants in the main analyses, recruited between 1992 and 2004 (cohort baseline), 4,928 developed COPD during a mean follow-up of 16.6 years (Table 1). Mean age at baseline was 55.8 years. Participants who developed COPD were older, less likely to be married, employed, or highly educated, smoked more, and had higher levels of PM<sub>2.5</sub>, NO<sub>2</sub>, and BC compared to those without COPD. 667 (1%) participants were asthma patients at baseline and 180 developed COPD during follow-up (Table 1). More details on cohorts and sub-cohorts are

**Table 1**

Characteristics of participants at baseline and residential air pollutants for the year 2010 by first-ever COPD hospitalization status.

Characteristic	Total (N = 98,508)	No COPD (N = 93,580)	COPD (N = 4,928)
<b>Population</b>			
Baseline period, years	1992–2004	—	—
End of follow-up, years	2011, 2015	—	—
Person-years at risk, person years	1,637,916	1,584,771	53,145
Follow-up time, years (mean ± SD)	16.6 ± 4.7	16.9 ± 4.9	10.8 ± 5.8
Age, years (mean ± SD)	55.8 ± 7.5	55.6 ± 7.5	58.3 ± 5.9
Age < 65 years old, n (%)	91,529 (93)	86,983 (93)	4,546 (92)
<b>Individual level variables#</b>			
Female, n (%)	64,689 (66)	61,563 (66)	3,126 (63)
BMI, kg/m <sup>2</sup> (mean ± SD)	25.3 ± 4.0	25.3 ± 4.0	25.3 ± 4.4
Normal weight, n (%)	50,004 (51)	47,549 (51)	2,455 (50)
Smoking duration, years (mean ± SD)	17.0 ± 16.5	16.2 ± 16.2	33.2 ± 13.3
Smoking intensity, n/day (mean ± SD)	9.2 ± 10.4	8.8 ± 10.2	16.2 ± 10.5
Never smoker, n (%)	36,571 (37)	36,173 (39)	398 (8)
Married or living with partner, n (%)	70,287 (71)	67,264 (72)	3,023 (61)
Employed, n (%)	75,323 (76)	72,202 (77)	3,121 (63)
High educational level, n (%)	43,435 (44)	41,785 (45)	1,650 (33)
Asthma patients, n (%)	667 (1)	487 (1)	180 (4)
<b>Area-level variable</b>			
Mean year income, €φ	20990.9	21046.1	19942.2
<b>Air pollutants*</b>			
PM <sub>2.5</sub> , µg/m <sup>3</sup> (mean ± SD)	12.12 ± 2.48	12.07 ± 2.50	13.04 ± 1.86
NO <sub>2</sub> , µg/m <sup>3</sup> (mean ± SD)	25.11 ± 7.97	24.98 ± 7.97	27.53 ± 7.51
BC, 10 <sup>-5</sup> m <sup>-1</sup> (mean ± SD)	1.17 ± 0.41	1.17 ± 0.41	1.32 ± 0.38
O <sub>3</sub> , µg/m <sup>3</sup> (mean ± SD)	78.13 ± 4.62	78.17 ± 4.59	77.41 ± 5.07

BMI: body mass index; SD: standard deviation; SES: socio-economic status; COPD: chronic obstructive pulmonary disease; PM<sub>2.5</sub>: particulate matters with aerodynamic diameters of <2.5 µm; NO<sub>2</sub>: nitrogen dioxide; BC: black carbon; O<sub>3</sub>: ozone.

\*: The annual average concentrations of PM<sub>2.5</sub>, NO<sub>2</sub>, BC, and O<sub>3</sub> were estimated for the year 2010 at 100 m resolution. O<sub>3</sub> was estimated during the warm season from April 1 through September 30.

#: Normal weight means BMI values from 18.5 to 24.9 according to the World Health Organization (WHO) categories; High education 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.

in supplementary Table S2.

Mean air pollution levels in 2010 were 12.1 µg/m<sup>3</sup> for PM<sub>2.5</sub>, 25.1 µg/m<sup>3</sup> for NO<sub>2</sub>, 1.2 10<sup>-5</sup>m<sup>-1</sup> for BC, and 78.1 µg/m<sup>3</sup> for O<sub>3</sub> (Table 1). In all three cohorts, some participants exceeded the EU limit value and the WHO guideline of 40 µg/m<sup>3</sup> for NO<sub>2</sub>, while all participants complied with the EU limit value for PM<sub>2.5</sub> of 25 µg/m<sup>3</sup>, and the PM<sub>2.5</sub> levels in CEANS complied even with the WHO guideline of 10 µg/m<sup>3</sup> (Fig. 1 and Table S3). We observed that air pollution levels were decreasing during follow-up time (Figure S1). The Pearson correlation coefficients were strongest between BC and NO<sub>2</sub> (overall r = 0.91, ranging 0.43–0.93 by sub-cohorts), followed by BC and PM<sub>2.5</sub> (overall r = 0.74, ranging 0.29–0.70 by sub-cohorts). PM<sub>2.5</sub> was moderately correlated with NO<sub>2</sub> (overall r = 0.63, ranging 0.60–0.75 by sub-cohorts), while O<sub>3</sub> was negatively correlated with all other pollutants (Table S4).

In single-pollutant models (Table 2), long-term exposures to PM<sub>2.5</sub>, NO<sub>2</sub>, and BC were positively associated with COPD incidence in all three models, with substantial reduction in HR from Model 1 to Model 2 (mainly explained by smoking), and no change in estimates from Model 2 to Model 3. The fully adjusted HRs (95% CIs) in Model 3 were 1.17 (1.06, 1.29) per 5 µg/m<sup>3</sup> increase for PM<sub>2.5</sub>, 1.11 (1.06, 1.16) per 10 µg/

m<sup>3</sup> increase for NO<sub>2</sub>, 1.11 (1.06, 1.15) per 0.5 10<sup>-5</sup>m<sup>-1</sup> increase for BC, and 0.99 (0.93, 1.05) per 10 µg/m<sup>3</sup> increase for O<sub>3</sub>.

In two-pollutant models (Table 2), the HRs for NO<sub>2</sub> and BC remained unchanged from single-pollutant models after adjusting for PM<sub>2.5</sub> and were somewhat higher after adjustment for O<sub>3</sub>, whereas the HR for PM<sub>2.5</sub> was attenuated to unity after adjusting for either NO<sub>2</sub> or BC. For NO<sub>2</sub> and BC, the HRs for NO<sub>2</sub> and BC were attenuated slightly and changed to non-significant after adjusting for each other. However, because of the high correlation between NO<sub>2</sub> and BC, it was difficult to interpret this two-pollutant model even though no collinearity was detected for the two pollutants in two-pollutant model [variance inflation factors (VIFs) are around 6]. In two-pollutant models with O<sub>3</sub>, the HRs for PM<sub>2.5</sub>, NO<sub>2</sub>, or BC were essentially unaffected, while the negative association between O<sub>3</sub> and COPD incidence changed to positive after adjustment for PM<sub>2.5</sub>, NO<sub>2</sub>, or BC, partially explained by the negative correlations for O<sub>3</sub> with other pollutants (Table S4).

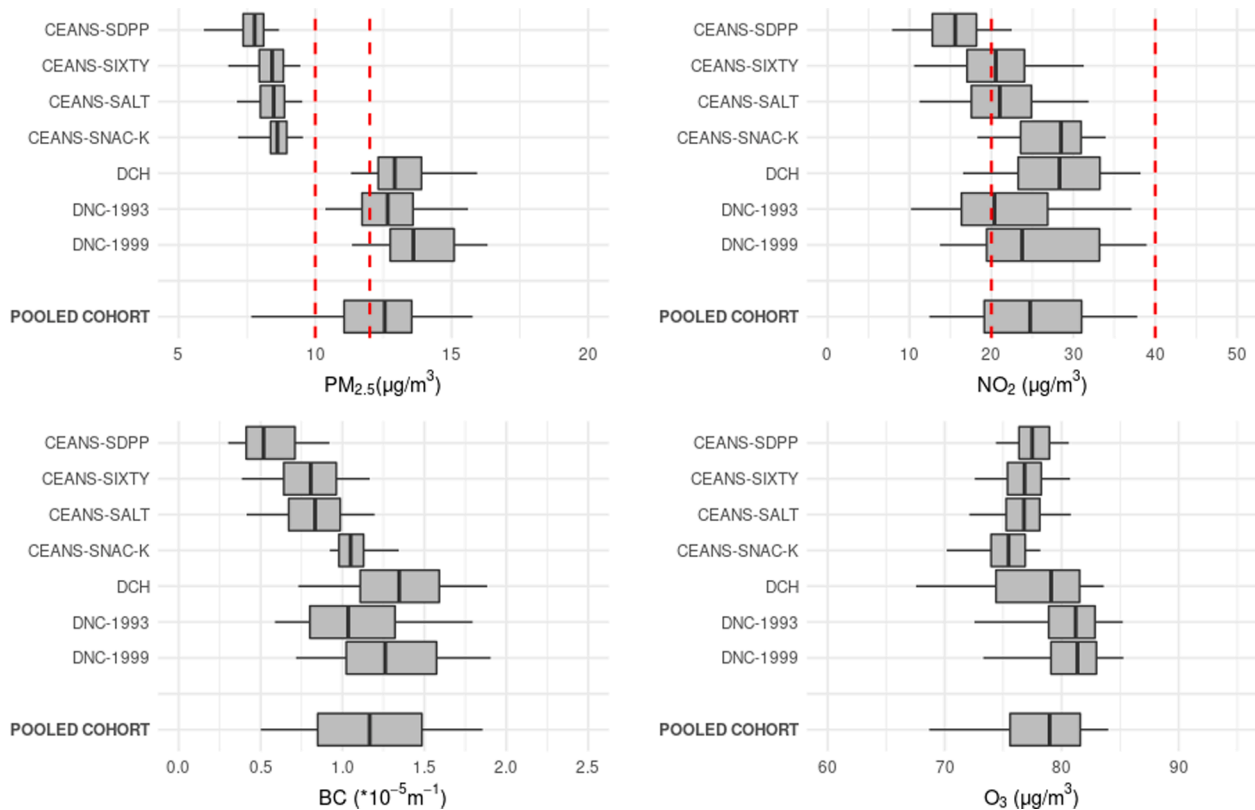
The HRs were generally higher in sub-populations with lower air pollution levels, with slightly larger CIs (Table 3). There was no significant deviation from linearity for any pollutants except for NO<sub>2</sub> (p = 0.04). The concentration response curves showed linear associations at concentrations between 5th and 95th percentiles (green lines in the Fig. 2) for PM<sub>2.5</sub>, NO<sub>2</sub>, and BC, with somewhat steeper curves at the lowest levels, levelling off at higher levels, with no evidence of a threshold (Fig. 2).

Associations for PM<sub>2.5</sub> were attenuated to unity when using back-extrapolated exposure at baseline with both ratio and difference methods, and were only slightly attenuated (ratio method) or remained unchanged (difference method) for NO<sub>2</sub> and BC exposures (Table S5). Observed associations were robust to applying time-varying exposure analyses (Figure S2 and Table S6) or restricting participants to subsets of cohorts (Table S7). In effect modification analyses (Figure S3), the associations of PM<sub>2.5</sub> were consistently stronger in participants aged < 65 years, obese participants, current smokers, married/divorced participants, and people with low education, with significant interaction though observed only for PM<sub>2.5</sub> with age, as well as PM<sub>2.5</sub>, NO<sub>2</sub>, and BC with marital status. We did not find any significant modification by asthma status at baseline, with significant positive associations in nurses without asthma and positive associations but with very wide CIs in nurses with asthma (small population of 667 nurses with asthma).

#### 4. Discussion

In this analysis of 98,508 adults from Denmark and Sweden, we observed that long-term exposures to PM<sub>2.5</sub>, NO<sub>2</sub>, and BC were associated with increased risks of COPD, even at levels below current EU and US limit values and possibly WHO guidelines. The concentration response curves and subset analyses showed no evidence of a threshold. PM<sub>2.5</sub> was not associated with COPD in two-pollutant models with adjustment for NO<sub>2</sub> or BC, while associations with NO<sub>2</sub> and BC remained robust after adjusting for PM<sub>2.5</sub>. The robust associations with NO<sub>2</sub> and BC might reflect direct effects of NO<sub>2</sub> or correlated particles emitted from combustion sources, such as BC and ultrafine particles (UFPs; particulate matter with diameter < 0.1 µm).

Our results are in line with findings from several studies on long-term exposure to air pollution and COPD incidence (Andersen et al., 2011; Atkinson et al., 2015; Danesh Yazdi et al., 2019; Gan et al., 2013; Guo et al., 2018; Schikowski et al., et al., 2014; Weichenthal et al., 2017). In a study of 11,084,660 Medicare beneficiaries, Danesh Yazdi et al. linked long-term exposure to PM<sub>2.5</sub> with first hospital admission for COPD with a HR of 1.051 (1.050–1.052) per 1 µg/m<sup>3</sup>, which persisted in a subset of cohort with PM<sub>2.5</sub> values below 12 µg/m<sup>3</sup>, the US limit value (Danesh Yazdi et al., 2019). In a cohort of 91,709 participants from Taiwan, Guo et al. reported a significant association of PM<sub>2.5</sub> with COPD with a HR of 1.08 (1.04–1.11) per 5 µg/m<sup>3</sup> (Guo et al., 2018). However, neither of these studies had data on NO<sub>2</sub> and BC and could not evaluate whether the association with PM<sub>2.5</sub> was confounded by these two pollutants, as



**Fig. 1.** Distribution of the annual average of air pollution concentrations by sub-cohorts for the year 2010. 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. For  $PM_{2.5}$ , red dotted lines indicate the annual average limited/guideline values of WHO ( $10 \mu g/m^3$ ), U.S. ( $12 \mu g/m^3$ ), and EU ( $25 \mu g/m^3$ , exceed the maximum concentration of our study). For  $NO_2$ , red dotted lines indicate the annual average limited/guideline values of WHO/EU ( $40 \mu g/m^3$ ), and WHO HRAPIE (health risks of air pollution in Europe) ( $20 \mu g/m^3$ ). 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. (For interpretation of the references to colour in this figure legend, the reader is referred to the web version of this article.)

observed in our study. In a Canadian cohort of 1.1 million Toronto residents, Weichenthal et al. reported significant associations of COPD with both  $PM_{2.5}$  and  $NO_2$ , with HRs of 1.06 (1.04–1.08) per  $3.2 \mu g/m^3$  and 1.11 (1.07–1.15) per 4.1 ppb, respectively, which persisted in mutually adjusted model (Weichenthal et al., 2017). Andersen et al. reported an association between  $NO_2$  and first hospital diagnosis for COPD in the DCH cohort, with a HR of 1.08 (1.02–1.14) per  $5.8 \mu g/m^3$ , but with no data on  $PM_{2.5}$  or BC (Andersen et al., 2011). However, the two large cohorts from US and Canada did not adjust for smoking habits, which is an important confounder of an association between air pollution and COPD (Danesh Yazdi et al., 2019; Weichenthal et al., 2017). Additionally, three other studies, Gan et al. in a Canadian study of 467,994 Vancouver residents (Gan et al., 2013), Atkinson et al. in a national cohort in UK with 812,063 subjects (Atkinson et al., 2015), and Schikowski et al. in 6,550 participants from ESCAPE cohorts (Schikowski et al., 2014), found non-significant positive associations with COPD incidence (Table S1). Our study findings disagree with three studies that reported null associations (Carey et al., 2016; Fisher et al., 2016; Salimi et al., 2018). An Australian study of 100,084 Sydney residents observed negative associations of  $PM_{2.5}$  and  $NO_2$  with first hospitalization of COPD (Salimi et al., 2018). In a study of 211,016 London residents, Carey et al. observed null associations of  $PM_{2.5}$  and  $NO_2$  with COPD incidence [general practitioner (GP) visit or hospital admission] (Carey et al., 2016), as did Fisher et al. between  $PM_{2.5}$  and COPD incidence (self-reported physician-diagnosed COPD with subsequently reported COPD diagnostic tests) in 121,701 female nurses from the US Nurses' Health Study (Fisher et al., 2016).

Our finding of a significant association of BC with COPD

development is in agreement with the result by Gan et al. in the Canadian study (Gan et al., 2013), which found a significant association of 5-year average exposure to BC with first COPD hospitalization (HR 1.06; 1.02–1.09 per  $0.97 \cdot 10^{-5} m^{-1}$ ), which remained unchanged after adjusting for  $PM_{2.5}$  and  $NO_2$ . On the contrary, in the ESCAPE cohorts, Schikowski et al. found positive or negative, but not significant, associations for BC using two different COPD definitions (Schikowski et al., 2014).

Only two studies investigated associations between long-term exposure to  $O_3$  and COPD incidence (Atkinson et al., 2015; Danesh Yazdi et al., 2019). In the national UK cohort, Atkinson et al. reported negative associations with COPD incidence, with HRs of 0.94 (0.89–1.00) and 0.96 (0.90–1.02) per  $3 \mu g/m^3$  increase in  $O_3$ , based on GP records or hospital admissions, respectively (Atkinson et al., 2015). In contrast, in the South-western US, Danesh Yazdi et al. reported a positive association between annual average  $O_3$  and first COPD hospital admission, with a HR of 1.024 (1.023–1.025) per 1 ppb increase (Danesh Yazdi et al., 2019). In our study, we observed negative correlations between  $O_3$  and  $PM_{2.5}/NO_2/BC$ , related to the fine spatial scale model we used in a relatively small area. We also observed the null associations with  $O_3$  in single-pollutant models became significantly positive in two-pollutant models with  $NO_2$  or BC. Overall, our findings strengthen the evidence base by adding new results to support the notion that long-term exposure to air pollution may lead to the development of COPD. Traffic-related pollutants  $NO_2$  and BC may be the most relevant for COPD development. Results for the associations of BC and  $O_3$  exposures are much less investigated and inconclusive, calling for future studies on the potential roles of BC and  $O_3$  in COPD.

**Table 2**

Results of single- and two-pollutant models for the associations between long-term air pollution exposure and first-ever COPD hospitalization (N = 98,508).

	Single-pollutant models			Two-pollutant models – based on Model 3 (Adjusted for pollutants below)			
	Model 1	Model 2	Model 3	PM <sub>2.5</sub>	NO <sub>2</sub>	BC	O <sub>3</sub>
PM <sub>2.5</sub>	1.53 (1.39, 1.69)	1.17 (1.06, 1.29)	1.17 (1.06, 1.29)	—	0.97 (0.85, 1.11)	1.00 (0.88, 1.14)	1.21 (1.08, 1.35)
NO <sub>2</sub>	1.21 (1.17, 1.26)	1.10 (1.06, 1.15)	1.11 (1.06, 1.16)	1.12 (1.06, 1.18)	—	1.06 (0.97, 1.17)*	1.16 (1.11, 1.23)
BC	1.22 (1.17, 1.27)	1.10 (1.06, 1.15)	1.11 (1.06, 1.15)	1.11 (1.05, 1.17)	1.05 (0.95, 1.15)*	—	1.15 (1.09, 1.20)
O <sub>3</sub>	0.79 (0.75, 0.84)	0.98 (0.93, 1.04)	0.99 (0.93, 1.05)	1.05 (0.98, 1.12)	1.13 (1.05, 1.22)	1.10 (1.02, 1.18)	—

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<sup>2</sup>), BMI (category), marital status, employment status and education levels; Model 3 further adjusted for area-level mean year income, which is at municipality-level in 2001 for DCH and DNC and at neighbourhood level in 1994 for CEANS.

\*: Two-pollutant result for NO<sub>2</sub> and BC are difficult to interpret because of their high correlation.

Results are presented as hazard ratio and 95% confidence interval [HR (95%CI)] for the following increments: 5 µg/m<sup>3</sup> for PM<sub>2.5</sub>, 10 µg/m<sup>3</sup> for NO<sub>2</sub>, 0.5 10<sup>-5</sup> m<sup>-1</sup> for BC and 10 µg/m<sup>3</sup> for O<sub>3</sub>.

**Table 3**

Results for the associations between long-term air pollution exposure and first-ever COPD hospitalization below various cut-off values in Model 3.

Pollutants	Concentration levels	Number of observations	HR (95%CI)
PM <sub>2.5</sub>	All levels	98,508	1.17 (1.06, 1.29)
	<25 µg/m <sup>3</sup>	98,508	1.17 (1.06, 1.29)
	<20 µg/m <sup>3</sup>	98,508	1.17 (1.06, 1.29)
	<15 µg/m <sup>3</sup>	86,433	1.23 (1.05, 1.44)
	<12 µg/m <sup>3</sup>	35,661	1.10 (0.71, 1.69)
	<10 µg/m <sup>3</sup>	20,842	1.46 (0.71, 3.01)
NO <sub>2</sub>	All levels	98,508	1.11 (1.06, 1.16)
	<40 µg/m <sup>3</sup>	96,657	1.12 (1.07, 1.17)
	<30 µg/m <sup>3</sup>	69,973	1.20 (1.11, 1.30)
	<20 µg/m <sup>3</sup>	28,144	1.06 (0.85, 1.33)
BC	All levels	98,508	1.11 (1.06, 1.15)
	<3 10 <sup>-5</sup> m <sup>-1</sup>	98,501	1.11 (1.06, 1.15)
	<2.5 10 <sup>-5</sup> m <sup>-1</sup>	98,423	1.11 (1.06, 1.16)
	<2 10 <sup>-5</sup> m <sup>-1</sup>	97,179	1.11 (1.07, 1.16)
	<1.5 10 <sup>-5</sup> m <sup>-1</sup>	74,929	1.16 (1.08, 1.25)
	<1 10 <sup>-5</sup> m <sup>-1</sup>	34,707	1.19 (0.95, 1.51)
	<0.5 10 <sup>-5</sup> m <sup>-1</sup>	4,904	3.81 (0.42, 34.95)
O <sub>3</sub>	All levels	98,508	0.99 (0.93, 1.05)
	<80 µg/m <sup>3</sup>	57,952	1.04 (0.95, 1.13)
	<60 µg/m <sup>3</sup>	60	—

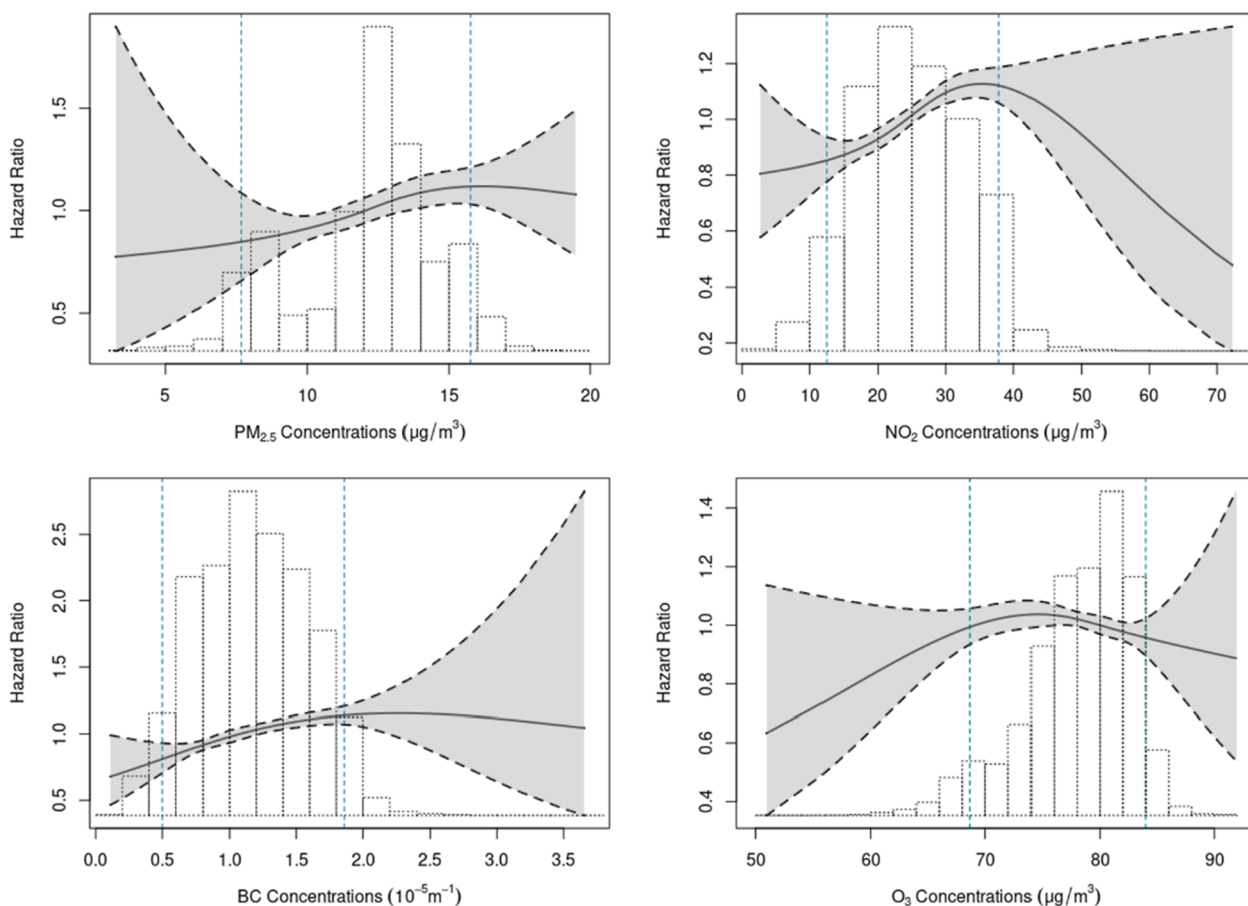
Results are presented for the following increments: 5 µg/m<sup>3</sup> for PM<sub>2.5</sub>, 10 µg/m<sup>3</sup> for NO<sub>2</sub>, 0.5 10<sup>-5</sup> m<sup>-1</sup> for BC and 10 µg/m<sup>3</sup> for O<sub>3</sub>.

Our findings of attenuated PM<sub>2.5</sub> associations in the two-pollutant models with NO<sub>2</sub> or BC, whereas the associations with NO<sub>2</sub> and BC remained robust after adjustment for PM<sub>2.5</sub>, can be difficult to interpret and call for more research. Differential measurement error may complicate the interpretation of two-pollutant models (Butland et al., 2019), as the pollutant with the lowest measurement error may show the

most consistent association in two-pollutant models. Given that the correlation between PM<sub>2.5</sub> and NO<sub>2</sub> was moderate and the width of the confidence interval was only slightly increased in the two-pollutant models, we did not interpret the reduction of the HR for PM<sub>2.5</sub> as merely an artefact related to multi-collinearity. The association with NO<sub>2</sub> might reflect direct effects of NO<sub>2</sub> or related particles emitted at combustion sources, such as BC and UFPs. Similarly, we did not interpret the reduction of the PM<sub>2.5</sub> HR as implying that particles had no effect, as adjustment for NO<sub>2</sub> also adjusted for particles from sources shared with NO<sub>2</sub>, including motorized traffic and other combustion sources. More data are needed to discern which air pollutants and sources are the most relevant for the development of COPD: total particle mass, combustion-related particles, or NO<sub>2</sub>.

Limited representative toxicological studies provide mechanistic evidence for air pollution-related COPD development as most animal models replicate only a few COPD features and are time-consuming and technologically challenging (Huang et al., 2017; Jones et al., 2017). Air pollution induced oxidative stress and free radical reaction, which can trigger pulmonary and systemic inflammatory responses, are thought to be the plausible biological mechanisms behind the role of air pollution exposure in COPD development (Delfino et al., 2010; Hogg and van Eeden, 2009; Ling and van Eeden, 2009). Furthermore, airway remodelling related to repeated and intermittent air pollution exposures is likely a pathway to COPD development (Martinez, 2009); and a convincing number of studies on air pollution and accelerated decline in lung function can also shed light on the pathways (Guo et al., 2018; Lepeule et al., 2014; Rice et al., 2015; Wang et al., 2019). In effect modification, we observed slightly higher HRs with significant associations in current smokers, and no associations in never smokers. However, it should be noted that there was much smaller number of COPD cases in never smokers (398 out of 36,571) compared with current smokers (3,612 out of 32,295). Our observations of an enhanced association of PM<sub>2.5</sub>, NO<sub>2</sub>, and BC with COPD among participants < 65 years and married/divorced participants are novel. A study in Taiwan reported no effect modification by BMI or smoking (Guo et al., 2018). The DCH cohort study found no effect modification between NO<sub>2</sub> and COPD associations by BMI, smoking, or education (Andersen et al., 2011). The Toronto cohort reported a stronger association of NO<sub>2</sub> with COPD in participants < 60 years, in line with our results (Weichenthal et al., 2017), while the Vancouver cohort study did not observe effect modification by age for BC (Gan et al., 2013). Evidence therefore remains inconclusive on possible susceptibility of specific groups to the effects of air pollution on COPD development.

This study has several strengths and limitations. We benefited from a large cohort obtained by pooling data from three Nordic cohorts with low levels of air pollution, objective definition of COPD incidence as first hospital discharge diagnosis, detailed information on relevant confounders, harmonized well-established air pollution models with data on a multiple major air pollutants, available complete history residential addresses of two cohorts for time-varying exposure calculation, and a long follow-up period. We contributed to the very limited studies on long-term exposure measures of BC and O<sub>3</sub> in relation to COPD. The use of the first-ever hospital discharge diagnosis for COPD in hospital registers confers some degree of objective assessment, and studies have demonstrated the high specificity of COPD diagnoses using hospital registers in both Denmark (92% overall positive predictive rate) (Thomsen et al., 2011) and Sweden (<10% misclassification rate) (Inghammar et al., 2012), validating their use in epidemiology research. However, COPD is often undiagnosed for many years and not all patients with COPD are hospitalized, and therefore first-ever hospital discharge diagnoses may underrepresent the true COPD incidence. Additionally, it is difficult to separate COPD from asthma diagnosis and a part of COPD cases thus may in fact be asthma cases or mixed cases, which is another reason leading to underrepresentation of true COPD incidence. However, in our study, censoring occurred at the time of diagnoses of asthma, which could offset parts of the misclassification for first-ever



**Fig. 2.** Concentration-response curves for the association between long-term exposure to air pollution (PM<sub>2.5</sub>, NO<sub>2</sub>, BC, and O<sub>3</sub>) and first-ever COPD hospitalization. Natural cubic splines with three degrees of freedom were fit for air pollutants to evaluate the linearity of the associations based on Model 3. Solid lines indicate hazard ratio values and dashed lines indicate their 95% confidence intervals. Green dashed lines indicate 5th and 95th percentiles of air pollutants' concentrations. (For interpretation of the references to colour in this figure legend, the reader is referred to the web version of this article.)

COPD diagnoses. Rather, COPD hospital discharge diagnoses should not be regarded as onset of a disease but a hallmark of the progression of pre-existing COPD into a more severe stage. A Danish study found that the patients admitted acutely due to COPD exacerbation had a forced expiratory volume (FEV<sub>1</sub>) of approximately 30–40% of the predicted value, corresponding to the Global Initiative for Chronic Obstructive Lung Disease (GOLD) standard stages 3 and 4 (Eriksen et al., 2003). Thus, our study examines the onset of severe COPD, and likely represents older patients with a severe disease. One limitation of our study is the lack of lung function measurements and medical history in the cohorts for verifying COPD diagnoses. We observed that the HRs for PM<sub>2.5</sub>, NO<sub>2</sub>, and BC were attenuated largely after adjustment for individual confounders including smoking, one of the most important risk factors for COPD. Nonetheless, we cannot exclude the possibility of some residual confounding by smoking, since we did not have more detailed history data on smoking duration and intensity. Similar to many cohort studies some weaknesses of this study includes exposure misclassification, which is inherent when estimating air pollution levels at the residential address, and without information on air pollution levels at work, commuting habits, or personal time-activity patterns. Finally, our study lacked data on some potentially important confounders, such as physical activity, indoor air pollution and environmental tobacco smoking.

## 5. Conclusion

In this large study combining three European cohorts with access to data on hospital discharge diagnoses for COPD, long-term exposure to low levels of air pollution was associated with the development of

COPD, even at levels below current EU and US limit values and possibly WHO guidelines. Associations with the traffic related air pollutants NO<sub>2</sub> and BC were most consistent. These results provide supports to the available evidence suggesting that further reductions in air pollution could help prevent new cases of COPD.

## Declaration of Competing Interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

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## Author Contributions

**Zorana Jovanovic Andersen, Gerard Hoek, Bert Brunekreef, Petter Ljungman, and Shuo Liu:** Study conceptualization and design. **Gerard Hoek and Bert Brunekreef:** PI of the ELAPSE project. **Shuo Liu:** Statistical analysis and manuscript - original draft. **Zorana Jovanovic Andersen:** manuscript - review and editing. **Jeanette Thering Jørgensen and Ulla Arthur Hvidtfeldt:** individual cohort data preparation for the analyses. **Gerard Hoek, Bert Brunekreef, Jie Chen, and Maciej Strak:** ELAPSE project coordination, helping in preparing pooled data for analyses and providing support with the access to pooled cohort data. **Sophia P. Rodopoulou, Evangelia Samoli and Klea Katsouyanni:** contribution of statistical analyses strategy and scripts for the statistical analyses. **Kees de Hoogh:** 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.

## Data sharing

Requests for data can be made by contacting the corresponding author.

## Appendix A. Supplementary material

Supplementary data to this article can be found online at <https://doi.org/10.1016/j.envint.2020.106267>.

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