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Associations of long-term exposure to air pollution and greenness with incidence of chronic obstructive pulmonary disease in Northern Europe: The Life-GAP project

Shanshan Xu [a,*], Alessandro Marcon [b], Randi Jacobsen Bertelsen [c], Bryndis Benediktsdottir [d,e], Jørgen Brandt [f], Lise Marie Frohn [f], Camilla Geels [f], Thorarinn Gislason [d,e], Joachim Heinrich [g,h], Mathias Holm [i], Christer Janson [j], Iana Markevych [k,l,m], Lars Modig [n], Hans Orru [o], Vivi Schlünssen [p], Torben Sigsgaard [p], Ane Johannessen [q]

[a] Centre for International Health, Department of Global Public Health and Primary Care, University of Bergen, Bergen, Norway
[b] Unit of Epidemiology and Medical Statistics, Department of Diagnostics and Public Health, University of Verona, Verona, Italy
[c] Department of Clinical Science, University of Bergen, Bergen, Norway
[d] Department of Respiratory Medicine and Sleep, Landspitali – the National University Hospital of Iceland, Reykjavik, Iceland
[e] University of Iceland, Medical Faculty, Iceland
[f] Department of Environmental Science, Aarhus University, Roskilde, Denmark
[g] Institute and Clinic for Occupational, Social and Environmental Medicine, University Hospital, Ludwig Maximilian University of Munich, Munich, Germany
[h] Allergy and Lung Health Unit, Melbourne School of Population and Global Health, University of Melbourne, Melbourne, Australia
[i] Occupational and Environmental Medicine, School of Public Health and Community Medicine, Institute of Medicine, Sahlgrenska Academy, University of Gothenburg, Gothenburg, Sweden
[j] Department of Medical Sciences: Respiratory, Allergy and Sleep Research, Uppsala University, Uppsala, Sweden
[k] Institute of Psychology, Jagiellonian University, Krakow, Poland
[l] Health and Quality of Life in a Green and Sustainable Environment", Strategic Research and Innovation Program for the Development of MU – Plovdiv, Medical University of Plovdiv, Plovdiv, Bulgaria
[m] Environmental Health Division, Research Institute at Medical University of Plovdiv, Medical University of Plovdiv, Plovdiv, Bulgaria
[n] Department of Public Health and Clinical Medicine, Section of Sustainable Health, Umeå University, United States
[o] Department of Public Health, Institute of Family Medicine and Public Health, Faculty of Medicine, University of Tartu, Tartu, Estonia
[p] Department of Public Health, Research unit for Environment Occupation and Health, Danish Ramazzini Center, Aarhus University, Aarhus, Denmark
[q] Department of Global Public Health and Primary Care, University of Bergen, Bergen, Norway

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ABSTRACT

Background: Prolonged exposure to air pollution has been linked to adverse respiratory health, yet the evidence concerning its association with chronic obstructive pulmonary disease (COPD) is inconsistent. The evidence of a greenness effect on chronic respiratory diseases is limited.

Objective: This study aimed to investigate the association between long-term exposure to particulate matter ($PM_{2.5}$ and PM_{10}), black carbon (BC), nitrogen dioxide (NO_2), ozone (O_3) and greenness (as measured by the normalized difference vegetation index - NDVI) and incidence of self-reported chronic bronchitis or COPD (CB/COPD).

Methods: We analyzed data from 5355 adults from 7 centers participating in the Respiratory Health in Northern Europe (RHINE) study. Mean exposures to air pollution and greenness were assessed at available residential addresses in 1990, 2000 and 2010 using air dispersion models and satellite data, respectively. Poisson regression with log person-time as an offset was employed to analyze the association between air pollution, greenness, and CB/COPD incidence, adjusting for confounders.

Results: Overall, there were 328 incident cases of CB/COPD during 2010–2023. Despite wide statistical uncertainty, we found a trend for a positive association between NO_2 exposure and CB/COPD incidence, with incidence rate ratios (IRRs) per 10 μg/m^3 difference ranging between 1.13 (95% CI: 0.90–1.41) in 1990 and 1.18 (95% CI: 0.96–1.45) in 2000. O_3 showed a tendency for inverse association with CB/COPD incidence (IRR from

* Corresponding author.
E-mail address: shanshan.xu@uib.no (S. Xu).

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0.84 (95% CI: 0.66–1.07) in 2000 to 0.88 (95% CI: 0.69–1.14) in 2010. No consistent association was found between PM, BC and greenness with CB/COPD incidence across different exposure time windows.
Conclusion: Consistent with prior research, our study suggests that individuals exposed to higher concentrations of NO_2 may face an elevated risk of developing COPD, although evidence remains inconclusive. Greenness was not associated with CB/COPD incidence, while O_3 showed a tendency for an inverse association with the outcome.

1. Introduction

Chronic obstructive pulmonary disease (COPD) is an important global public health threat. Globally, its prevalence in 2020 was estimated 10.6%, translating to approximately 480 million cases, and it is the third leading cause of death worldwide, accounting for over 3 million annual deaths (Boers et al., 2023; Safiri et al., 2022). In the Global Initiative for Chronic Obstructive Lung Disease (GOLD) 2024 report, the concept of "pre-COPD", characterized by respiratory symptoms without airflow obstruction is also introduced as a potential precursor for COPD GOLD (2024). Chronic bronchitis (CB), traditionally defined as chronic cough and sputum production for 3 months a year for at least 2 consecutive years (Kim and Criner, 2013), represents a key manifestation within this COPD spectrum, and interpreted as pre-COPD it warrants early intervention to prevent more severe COPD development (Han et al., 2021). While COPD can occur at any age, it is typically diagnosed in elderly patients. COPD presents sex-specific differences, with women potentially more susceptible due to smaller airways and hormonal variations, which may affect lung function and disease progression (Barnes, 2016).

Both active and passive cigarette smoking are major risk factors for both CB and COPD. Additionally, environmental factors such as ambient air pollution have been shown to play a role, and even low-level pollution may pose significant health risks in a long-term perspective (World Health, 2021). Pollutants like particulate matter (PM), ozone (O_3) and nitrogen dioxide (NO_2) can initiate inflammation and oxidative stress, impairing lung function and hastening airway damage, leading to COPD progression. Recent large cohort studies have shown that long-term exposure to PM and NO_2 were associated with an increased incidence of COPD (Guo et al., 2018; Liu et al., 2021), although some other studies report absence of such associations (Fisher et al., 2016; Schikowski et al., 2014).

Exposure to greenness is generally considered beneficial to health, fostering increased physical activity and social interactions, reducing stress, and lessening exposure to air pollution, noise, and excessive heat (James et al., 2015; Markevych et al., 2017). However, a recent review examining the relationship between greenness exposure and respiratory health outcomes reveals that its effects on COPD remain less investigated and unclear (Johannessen et al., 2023).

Given the inconsistent findings regarding the relationship between air pollution, greenness and obstructive lung disease, this study hypothesizes that long-term exposure to air pollution is associated with an increased incidence of CB/COPD, while exposure to greenness has a protective effect against the disease. We aim to examine the associations between long-term exposure to air pollution, greenness, and the incidence of CB/COPD, focusing on various exposure time windows within the three decades from 1990 to 2010. By integrating CB and COPD into a single outcome, we seek to capture a broader spectrum of COPD-related conditions, including its preliminary stages.

2. Material and methods

2.1. Study population

Our study includes data from the Respiratory Health in Northern Europe (RHINE) study, with seven study centers located in Reykjavik, Iceland; Umea, Uppsala, and Gothenburg in Sweden; Bergen in Norway; Aarhus in Denmark; and Tartu in Estonia (Fig. 1). Initiated between 1990 and 1994 (RHINE I), the RHINE study is a prospective cohort study that longitudinally examines respiratory symptoms, diseases and environmental exposures. The study has undergone several follow-up phases: 1999–2001 (RHINE II), 2010–2012 (RHINE III), and the most recent from 2020 to 2023 (RHINE IV). Comprehensive descriptions of the cohort have been provided on RHINE websites and in earlier publications (Janson et al., 2018; Johannessen et al., 2014; RHINE Study Homepage, 2022; Xu et al., 2023).

Complete data on covariates for the purpose of our study were not available at RHINE I and II. Consequently, we considered the participants in RHINE III (2010–2012) as our baseline population. Our longitudinal analysis comprises 5355 adults aged 40–65 years who reported no history of CB or COPD at RHINE III, with environmental exposure data calculated from residential addresses spanning RHINE I, II, and III, as well as covariates in RHINE III, and with outcome data on CB and COPD incidence at RHINE IV. The participant selection process is depicted in Fig. 2.

The study received approval from the regional ethics committees at each study center, in accordance with national legislations (RHINE Study Homepage, 2022), and all participants provided written informed consent before entering the study.

2.2. Air pollution exposure assessment

During the first three data collection phases (RHINE I, II, and III), we geocoded the residential addresses of all participants and linked these addresses with estimates of various air pollutants. These pollutants included $PM_{2.5}$, PM_{10}, black carbon (BC), NO_2 and ground-level O_3, covering the years 1990, 2000 and 2010. Except for Tartu, the assessment of air pollution exposures utilized a combined approach involving two models. This approach integrated the Danish Eulerian Hemispheric Model (DEHM), which simulates regional-scale air pollution transport and processes across the Northern Hemisphere, and the Urban Background Model (UBM), which focuses on the local scale with a spatial resolution of 1 km × 1 km to model local-scale air pollution concentrations (Brandt et al., 2001a, 2001b, 2003, 2012). In this study, we used the outputs from the combined DEHM/UBM model, drawing from the NordicWelfAir project's findings that cover Iceland, Norway, Sweden, Finland, and Denmark from 1979 to 2018 (Frohn et al., 2022; Paunu et al., 2021). The performance of the DEHM/UBM model has previously been evaluated by comparing its estimates against the actual measurement for $PM_{2.5}$, NO_2 and O_3. The evaluation revealed that the DEHM/UBM model demonstrated a range of effectiveness from moderate to high, depending on the specific pollutant and country. Specifically, for the period from 1990 to 2016, the correlations between the model's results and monitoring stations data ranged from 0.43 (for $PM_{2.5}$ in Denmark) to 0.96 (for $PM_{2.5}$ in Sweden). Supplementary Table S1 presents detailed correlation coefficients for Norway, Sweden, and Denmark. For a comprehensive discussion of these evaluations, refer to Frohn et al. (2022).

In the Tartu center, BC and O_3 were unavailable in this study. Instead, the annual mean levels of $PM_{2.5}$, PM_{10}, and NO_2 were estimated using the Eulerian air quality dispersion model, within the Airviro Air Quality Management System and with a 1 km × 1 km spatial grid across Estonia (AirViro 2011).

2.3. Greenness exposure assessment

Exposure to greenness was quantified using the Normalized Difference Vegetation Index (NDVI), derived from cloud-free satellite imagery captured by Landsat 4–5 Thematic Mapper (TM) and Landsat 8 Operational Land Imager (OLI). The NDVI values, which varying between −1 and 1, serve as indicators of vegetation density, with values closer to 1 signifying more dense vegetation. NDVI value below zero were recoded to zero, following established practices in this field (Fan et al., 2020). The study selected RHINE I, II, and III as the periods for satellite imagery analysis (Supplementary Table S2). The years corresponding with the air pollution exposure years (1990, 2000 and 2010) were selected as the greenness exposure years. In this study, greenness exposure was calculated based on the annual average NDVI value for those years, using a 300-m circular buffer zone surrounding each participant's home as the measurement area (WHO, 2016).

2.4. Exposure time windows

Participants were allocated annual average levels of air pollution and greenness across three distinct exposure periods: 1) the year 1990, 2) the year 2000, and 3) the year 2010. These years were chosen as they were the only years with geocoded residential address information for all RHINE participants.

2.5. Definitions of CB/COPD

The standard RHINE questionnaire was used to assess respiratory symptoms and diseases. Self-reported CB/COPD was defined by either: a positive response to the question, "Has a doctor ever told you that you have chronic obstructive pulmonary disease (COPD)?" OR affirmative responses to all three of these sequential questions related to CB: a) "Do you usually bring up phlegm or do you have phlegm in your lungs which you have difficulty bringing up?" b) "Do you bring up phlegm in this way almost every day for at least three months every year?" c) "Have you had periods of this kind for at least two years in a row?" Incident CB/COPD was defined by initially negative responses to all three CB and COPD questions in the RHINE III survey, followed by a positive answer to either COPD or CB in the RHINE IV survey.

2.6. Statistical analysis

We conducted descriptive statistics for general characteristics of the participants with and without CB/COPD, as well as to analyze the characteristics of those included in and excluded from the main analysis. We used the Mann-Whitney *U* test for continuous variables and the Chi-square test for categorical variables to compare characteristics across these groups. Spearman correlation coefficients (ρ) were used to estimate the correlation between various air pollutants and greenness variables measured at different time points. Incidence rates were estimated as the ratio between the number of new cases of CB/COPD at RHINE IV and person-years at risk (per 1000). Exact 95% confidence intervals of incidence rate were computed using the Poisson distribution.

We used Poisson regression models to examine the association of exposure to air pollution and greenness in different time windows with CB/COPD incidence, with log person-years as an offset. We calculated the person-years by accounting for the time interval between the completion dates of the RHINE III and RHINE IV questionnaires. Since the exact diagnosis date for CB/COPD was unknown, we estimated the incidence time for those who developed the condition by using the midpoint between the RHINE III and IV questionnaire dates. The associations between air pollutants and greenness and CB/COPD were evaluated using three progressively adjusted models. Covariates for adjustment were chosen based on knowledge from existing literature

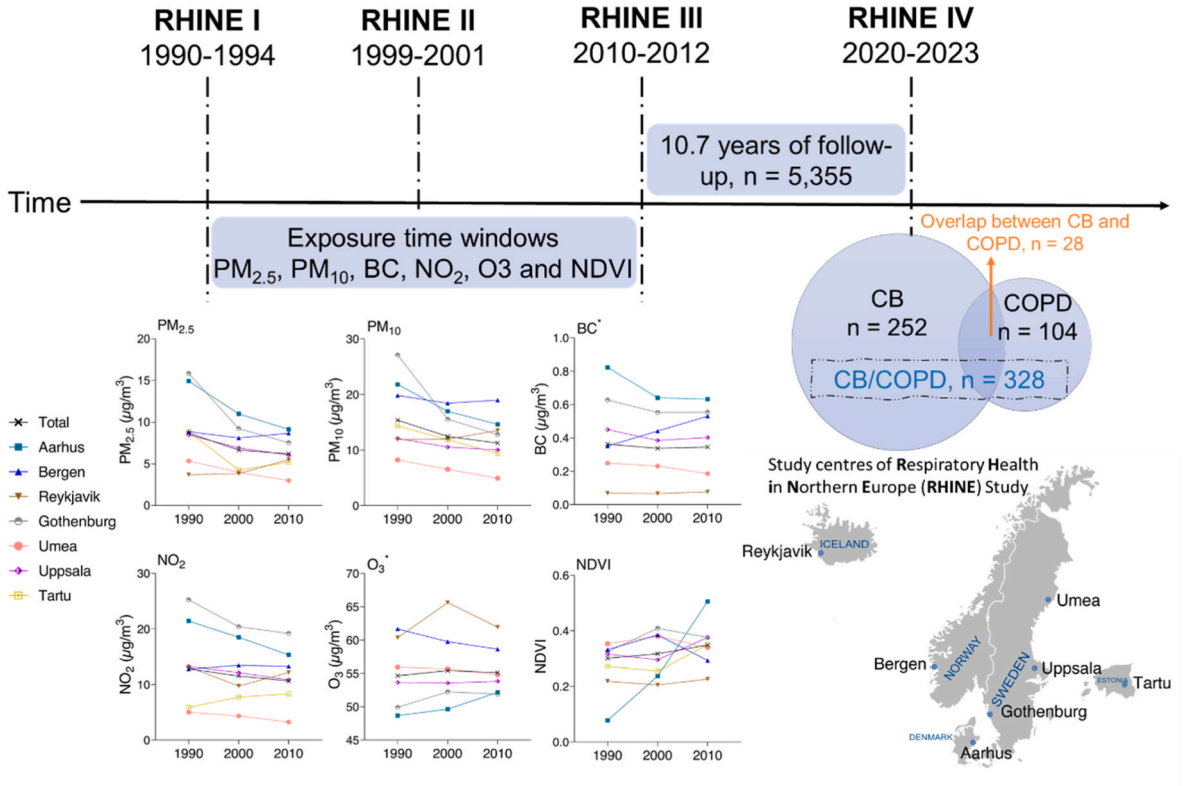

Fig. 1. This illustration features (in clockwise direction): the study timeline; a Venn diagram showing the incidence and overlap of self-reported CB and COPD cases; a geographical representation of the study center locations involved in Northern Europe (RHINE) Study; graphics showing the temporal trends of environmental exposures by study center.
* Data on BC and O_3 were unavailable at the Tartu center.

(Liu et al., 2021; Marchetti et al., 2023). Model 1 adjusted for sex, age, and the location of the study center. Model 2 (main analysis) expanded on this by additionally adjusting for body mass index (BMI, kg/m^2), education level (primary school, secondary school, college/university), smoking status (never, former, current), smoking duration (years) and smoking intensity (cigarettes/day). We centered the data for smoking duration and intensity by subtracting the mean values of smoking years and cigarettes per day from each smoker's records, while maintaining zero for those who never smoked. This approach facilitates the comparison of smoking effects between ever smoking and non-smokers (Leffondré et al., 2002).

To evaluate the robustness of our findings, we conducted several sensitivity analyses. First, we used two-exposure models that performed simultaneous adjustments for individual NDVI and air pollutants across identical exposure periods (Model 3). Additionally, we examined the impact of employing a distinct air pollution evaluation model for Tartu by repeating the main analysis (Model 2) while excluding data from Tartu. Furthermore, within the same Model 2 framework, we further adjusted for 'serious respiratory infections before the age of 5′ as an additional covariate. This adjustment aimed to determine whether early-life respiratory health could influence the observed associations between long-term environmental exposures and CB/COPD incidence. Moreover, to account for uncertainties regarding the exact diagnosis dates for CB/COPD, we conducted a sensitivity analysis assuming diagnosis at the end of the follow-up period.

Using Model 2, we assessed the potential effect modification in the association between air pollution, greenness and CB/COPD incidence by conducting stratified analysis by age at baseline (divided into <50 and ≥50 years), sex (males and females), smoking status (categorized as never and ever smokers), and education level (basic education including primary and secondary, and higher education including college and university). We also tested effect modification by including interaction terms into Model 2. Furthermore, we evaluated the effect modification of greenness on the air pollution-CB/COPD relationship by categorizing NDVI values into tertiles and including the interaction between NDVI tertiles and air pollution in Model 2.

The associations were reported as incidence rate ratio (IRR) with 95% confidence intervals per predefined increment: 5 μg/m^3 for $PM_{2.5}$, 10 μg/m^3 for PM_{10}, NO_2 and O_3, 0.4 μg/m^3 for BC, and 0.1 unit for NDVI. Risk estimates were interpreted focusing on effect sizes and confidence intervals rather than p-values, and evaluating consistency across different time windows, exposure metrics, and alternative analyses, in line with the American Statistical Association (ASA) statement (Wasserstein and Lazar, 2016; Wasserstein et al., 2019). This allowed us to interpret a consistent pattern of confidence intervals marginally including 1 as tendencies of associations, reflecting both statistical and clinical significance. Also following the ASA statement, interaction analyses were interpreted with the aid of *p*-values. Data analyses were performed using Stata statistical software (version 18.0, Stata Corporation, College Station, Texas, USA)

3. Results

Among the 10,914 RHINE III participants with complete assessments of air pollution and greenness exposure for the years 1990, 2000 and 2010, we excluded those without baseline (RHINE III) covariates

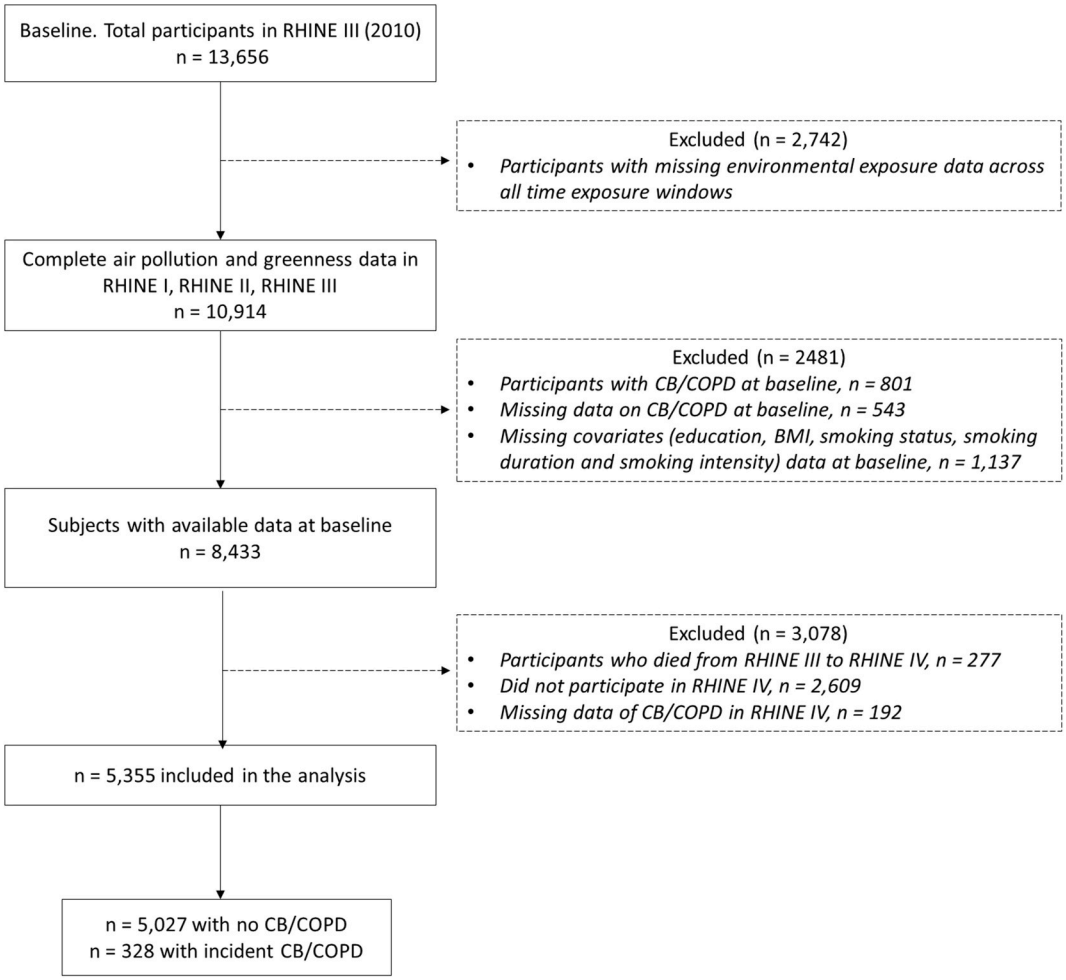

Fig. 2. Flowchart of the study population.

Table 1
Characteristics of participants at baseline (RHINE III) and residential air pollutants and greenness values across different exposure time points by CB/COPD status.

Characteristic		Total (n = 5355)	No CB/COPD (n = 5027)	Incident CB/COPD (n = 328)	P value[†]
Study center, n (%)					
Aarhus		1007 (18.8)	959 (19.1)	48 (14.6)	0.045
Bergen		842 (15.7)	789 (15.7)	53 (16.2)	
Gothenburg		789 (14.7)	730 (14.5)	59 (18.0)	
Umea		794 (14.8)	739 (14.7)	55 (16.8)	
Uppsala		1060 (20.0)	986 (19.6)	74 (22.6)	
Reykjavik		617 (11.5)	586 (11.7)	31 (9.5)	
Tartu		246 (4.6)	238 (4.7)	8 (2.4)	
Age (years), mean ± SD		51.5 ± 7.0	51.3 ± 7.0	53.4 ± 6.7	<0.001
Age ≥50 years old, n (%)		3131 (58.5)	2904 (57.8)	227 (69.2)	<0.001
Sex, n (%)					
Male		2528 (47.2)	2364 (47.0)	164 (50.0)	0.296
Female		2827 (52.8)	2663 (53.0)	164 (50.0)	
Body mass index (kg/m^2), mean ± SD		25.7 ± 4.1	25.7 ± 4.1	26.2 ± 4.1	0.004
Education, n (%)					
Primary school		430 (8.0)	395 (7.9)	35 (10.7)	0.003
Secondary school		2196 (41.0)	2041 (40.6)	155 (47.3)	
College or university		2729 (51.0)	2591 (51.5)	138 (42.1)	
Smoking status, n (%)					
Never		2955 (55.2)	2829 (56.3)	126 (39.4)	<0.001
Former		1813 (33.9)	1687 (33.6)	126 (38.4)	
Current		587 (11.0)	511 (10.2)	76 (23.2)	
Smoking duration (years), mean ± SD		9.4 ± 12.9	8.9 ± 12.6	16.0 ± 15.8	<0.001
Smoking intensity (n/day), mean ± SD		5.7 ± 8.3	5.5 ± 8.1	8.5 ± 9.6	<0.001
Exposure in 1990	$PM_{2.5}$, μg/m^3, mean ± SD	9.95 ± 4.51	9.95 ± 4.51	9.94 ± 4.55	0.955
	PM_{10}, μg/m^3, mean ± SD	17.11 ± 7.15	17.11 ± 7.11	17.11 ± 7.63	0.647
	BC, μg/m^3, mean ± SD*	0.48 ± 0.29	0.48 ± 0.29	0.47 ± 0.26	0.689
	NO_2, μg/m^3, mean ± SD	15.69 ± 7.77	15.68 ± 7.74	15.91 ± 8.33	0.828
	O_3, μg/m^3, mean ± SD*	54.76 ± 6.60	54.77 ± 6.59	54.64 ± 6.73	0.914
	NDVI, mean ± SD	0.27 ± 0.16	0.27 ± 0.16	0.29 ± 0.16	0.006
Exposure in 2000	$PM_{2.5}$, μg/m^3, mean ± SD	7.41 ± 2.79	7.41 ± 2.79	7.39 ± 2.77	0.648
	PM_{10}, μg/m^3, mean ± SD	13.59 ± 4.69	13.60 ± 4.68	13.44 ± 4.86	0.819
	BC, μg/m^3, mean ± SD*	0.44 ± 0.24	0.43 ± 0.24	0.43 ± 0.23	0.825
	NO_2, μg/m^3, mean ± SD	14.02 ± 7.18	14.00 ± 7.14	14.42 ± 7.76	0.345
	O_3, μg/m^3, mean ± SD*	55.56 ± 6.55	55.58 ± 6.55	55.21 ± 6.56	0.436
	NDVI, mean ± SD	0.33 ± 0.15	0.33 ± 0.15	0.34 ± 0.15	0.263
Exposure in 2010	$PM_{2.5}$, μg/m^3, mean ± SD	6.89 ± 2.60	6.89 ± 2.60	6.81 ± 2.67	0.449
	PM_{10}, μg/m^3, mean ± SD	12.72 ± 5.53	12.73 ± 5.51	12.59 ± 5.88	0.670
	BC, μg/m^3, mean ± SD*	0.45 ± 0.26	0.44 ± 0.25	0.45 ± 0.27	0.924
	NO_2, μg/m^3, mean ± SD	13.38 ± 7.60	13.35 ± 7.51	13.89 ± 8.80	0.617
	O_3, μg/m^3, mean ± SD*	55.26 ± 5.35	55.29 ± 5.32	54.91 ± 5.74	0.351
	NDVI, mean ± SD	0.38 ± 0.13	0.38 ± 0.13	0.38 ± 0.13	0.894

Abbreviation: $PM_{2.5}$ = particulate matter with an aerodynamic diameter less than 2.5 μm (μm); PM_{10} = particulate matter with an aerodynamic diameter less than 10 μm (μm); BC = black carbon; NO_2 = nitrogen dioxide; O_3 = ozone; NDVI = normalized difference vegetation index.
[†]Mann-Whitney *U* test for continuous variables and Chi-squared test for categorical variables.
*Data on BC and O_3 were unavailable at the Tartu center. A total of 5109 participants had data available for BC and O_3. Of these, 4789 were without CB/COPD, and 320 involved incident cases of CB/COPD.

(Fig. 2). This resulted in 8433 participants with complete baseline data. Of these, 277 had died by 2021, 2609 did not participate in the RHINE IV survey, and 192 in RHINE IV had missing CB/COPD data, leaving 5355 participants for the main analysis (Fig. 2). Supplementary Table S3 outlines the characteristics of participants included in the main analysis versus those who were excluded. Those excluded tended to have lower education levels, and were more often smokers with longer smoking durations and higher smoking intensities ($p < 0.001$). The average age at baseline was 51.5 years, with approximately 59% over 50 years old (Table 1). There were 252 reported incidents of CB, 104 reported incidents of COPD, and 28 instances where participants reported incidents of both CB and COPD. This results in a total of 328 incident cases of either CB or COPD included in the main analysis (Fig. 1). Those who developed CB/COPD tended to be older, had lower education levels, and smoked more. Over a mean follow-up of 10.7 years, the crude incidence rate of CB/COPD was 5.74 per 1000 person-years (95% CI: 5.15–6.40). Air pollution and NDVI levels were comparable across the 1990, 2000, and 2010 exposure time windows in both the non-CB/COPD and incident CB/COPD groups (Table 1). Fig. 1 shows the study center-specific trends of air pollutants and NDVI from 1990 to 2010. In general, a decrease in air pollution was noted across most centers. However, the Bergen center showed an increasing trend in BC levels, and Reykjavik observed an increase in PM and NO_2 during 2000–2010. Additionally, Aarhus experienced an increase in greenness levels throughout 1990–2010. Within the exposure in 1990, 2000 and 2010, $PM_{2.5}$, PM_{10}, NO_2 and BC showed strong correlations with one another (Supplementary Fig. S1). Notably, strong positive correlations were observed between $PM_{2.5}$ and PM_{10} ($\rho = 0.90$) in 2010 exposure, $PM_{2.5}$ and BC ($\rho = 0.93$) in 2000 exposure, and $PM_{2.5}$ and BC ($\rho = 0.90$) in 1990 exposure. O_3 showed a moderate to high negative correlation with the other pollutants. The weakest correlation was seen in 2010 exposure, with a $\rho = -0.26$ for the correlation between O_3 and PM_{10} in 2010. NDVI generally showed negative correlation with $PM_{2.5}$, PM_{10}, BC, and NO_2 within the same exposure time windows.

In the main analysis of the association between air pollutants and CB/COPD incidence, NO_2 showed a consistent positive association with CB/COPD risk across all exposure time windows. The adjusted IRR shows a 13% increased risk of CB/COPD (IRR = 1.13, 95% CI: 0.90–1.41) per 10 μg/m^3 for increase in NO_2 in the 1990 exposure. In 2000 exposure, this increased risk rose to 18% (IRR = 1.18, 95% CI: 0.96–1.45), and then slightly decreased to 14% in 2010 exposure (IRR = 1.14, 95% CI: 0.96–1.35) for every 10 μg/m^3 increase in NO_2 (Table 2).

Table 2
Incidence rate ratio (IRR) and 95% CI for the association between air pollutants and greenness and CB/COPD incidence in all subjects (n = 5355).

CB/COPD	Exposure in 1990		Exposure in 2000		Exposure in 2010	
	Model 1	Model 2	Model 1	Model 2	Model 1	Model 2
$PM_{2.5}$	1.00 (0.71–1.40)	0.97 (0.70–1.35)	1.05 (0.66–1.69)	1.12 (0.70–1.79)	1.05 (0.75–1.48)	1.07 (0.76–1.51)
PM10	1.01 (0.76–1.37)	1.00 (0.74–1.34)	1.06 (0.71–1.60)	1.11 (0.74–1.67)	1.05 (0.77–1.42)	1.07 (0.79–1.45)
BC*	0.96 (0.76–1.24)	0.97 (0.75–1.24)	1.04 (0.79–1.36)	1.08 (0.82–1.40)	1.12 (0 86–1.47)	1.16 (0.88–1.51)
NO_2	1.12 (0.90–1.41)	1.13 (0.90–1.41)	1.15 (0.94–1.42)	1.18 (0.96–1.45)	1.13 (0.95–1.34)	1.14 (0.96–1.35)
O_3*	0.88 (0.70–1.11)	0.87 (0.69–1.10)	0.86 (0.67–1.10)	0.84 (0.66–1.07)	0.89 (0 69–1.14)	0.88 (0.69–1.14)
NDVI	1.02 (0.91–1.14)	1.01 (0.90–1.13)	0.97 (0.89–1.06)	0.96 (0.88–1.05)	1.00 (0.91–1.10)	1.00 (0.90–1.10)

Abbreviation: $PM_{2.5}$ = particulate matter with an aerodynamic diameter less than 2.5 μm (μm); PM_{10} = particulate matter with an aerodynamic diameter less than 10 μm (μm); BC = black carbon; NO_2 = nitrogen dioxide; O_3 = ozone; NDVI = normalized difference vegetation index.
The exposure increments are defined as follows: $PM_{2.5}$ by 5 μg/m^3, PM_{10}, NO_2 and O_3 by 10 μg/m^3, BC by 0.4 μg/m^3, and NDVI by 0.1 unit.
Model 1 adjusted for sex, age and study center. Model 2 further adjusted for education, body mass index, smoking status, smoking duration (centered) and smoking intensity (centered).
*Data on BC and O_3 were unavailable at the Tartu center. A total of 5109 paticipants had data available for BC and O_3. Of these, 4789 were without CB/COPD, and 320 involved incident cases of CB/COPD.

Table 3
Incidence rate ratio (IRR) and 95% CI for the relationship between air pollution and greenness with CB/COPD incidence, derived from **a two-exposure model**.

Exposure		Exposure in 1990	Exposure in 2000	Exposure in 2010
		IRR (95% CI)	IRR (95% CI)	IRR (95% CI)
$PM_{2.5}$	+ NDVI	0.98 (0.69–1.39)	1.07 (0.66–1.75)	1.08 (0.75–1.56)
PM_{10}	+ NDVI	1.00 (0.74–1.37)	1.07 (0.70–1.64)	1.08 (0.78–1.50)
BC*	+ NDVI	0.97 (0.74–1.27)	1.04 (0.78–1.39)	1.20 (0.89–1.61)
NO_2	+ NDVI	1.18 (0.90–1.55)	1.17 (0.93–1.46)	1.17 (0.96–1.42)
O_3*	+ NDVI	0.82 (0.62–1.08)	0.86 (0.66–1.12)	0.85 (0.64–1.12)
NDVI	+ $PM_{2.5}$	1.00 (0.89–1.13)	0.97 (0.88–1.06)	1.00 (0.90–1.12)
NDVI	+ PM_{10}	1.01 (0.90–1.13)	0.97 (0.88–1.06)	1.01 (0.90–1.12)
NDVI	+ BC*	1.00 (0.89–1.13)	0.97 (0.88–1.06)	1.04 (0.93–1.15)
NDVI	+ NO_2	1.05 (0.92–1.9)	0.99 (0.90–1.09)	1.04 (0.93–1.16)
NDVI	+ O_3*	1.06 (0.93–1.20)	0.98 (0.89–1.08)	1.04 (0.93–1.16)

Abbreviation: $PM_{2.5}$ = paticulate matter with an aerodynamic diameter less than 2.5 μm (μm); PM_{10} = particulate matter with an aerodynamic diameter less than 10 μm (μm); BC = black carbon; NO_2 = nitrogen dioxide; O_3 = ozone; NDVI = normalized difference vegetation index.
The exposure increments are defined as follows: $PM_{2.5}$ by 5 μg/m^3, PM_{10}, NO_2 and O_3 by 10 μg/m^3, BC by 0.4 μg/m^3, and NDVI by 0.1 unit.
Models include each pollutant + NDVI in the same exposure time windows and were adjusted for sex, age, study center, education, body mass index, smoking status, smoking duration (centered) and smoking intensity (centered).
*Data on BC and O_3 were unavailable at the Tartu center. A total of 5109 paticipants had data available for BC and O_3. Of these, 4789 were without CB/COPD, and 320 involved incident cases of CB/COPD.

However, these trends lacked precision, and the elevated risk did not reach statistical significance. O_3 showed a similar consistent, but negative, association with CB/COPD incidence over different time periods. The adjusted IRRs indicated minor variations in effect size over time. For a 10 μg/m^3 increment in O_3, the adjusted IRRs indicated a reduction in risk by 13% in 1990 exposure (IRR = 0.87, 95% CI: 0.69–1.10), 16% in 2000 exposure (IRR = 0.84, 95% CI: 0.66–1.07), and 12% in 2010 exposure (IRR = 0.88, 95% CI: 0.69–1.14) (Table 2). $PM_{2.5}$, PM_{10}, and BC did not show a consistent pattern of association with CB/COPD incidence across different time points, except a tendency for positive association between BC exposure in year 2010 and CB/COPD (IRR = 1.16, 95% CI: 0.88–1.51). Results from the two-exposure models were similar to results from single exposure models. Notably, the associations with PM and BC exposure in 2000 were slightly reduced after adjusting for NDVI (Table 3). No association was found between NDVI and CB/COPD (Tables 2 and 3).

We observed no significant interaction (***p* value for the interaction > 0.05**) between air pollutant and greenness with sex, smoking status or education (Fig. 3). Interaction with age, however, was found for $PM_{2.5}$, PM_{10} and NO_2. Specifically, for participants aged ≥50 years, the risk of CB/COPD incidence increased by 40% (IRR = 1.40, 95% CI: 1.07–1.82) with NO_2 exposure in 1990 (***p* value for interaction = 0.015**), and by 35% (IRR = 1.35, 95% CI: 1.03–1.78) with exposure in 2000 (***p* value for interaction = 0.072**) (Fig. 3-A). We did not identify any significant interactions between air pollution and NDVI tertiles on CB/COPD incidence (Supplementary Table S4). Sensitivity analyses excluding participants from Tartu supported the consistency of the main findings (Supplementary Table S5). Additional sensitivity analyses including adjustment for early-life respiratory infections and assuming incidence time at the end of the follow-up period also confirmed the robustness of our primary results (Supplementary Tables S6 and S7).

4. Discussion

This study explored the association between air pollution, greenness, and the incidence of CB/COPD across three exposure periods (1990, 2000, and 2010). Despite wide statistical uncertainty, we observed an indication for an adverse effect of NO_2 exposure and incidence of CB/COPD. In contrast, O_3 showed a tendency for an inverse association with CB/COPD. No association was found between $PM_{2.5}$, PM_{10}, BC, NDVI and CB/COPD.

The concept of "pre-COPD" has been introduced recently to identify early symptoms and signs of the disease, facilitating early diagnosis and intervention (Han et al., 2021). In our study, we use a broad definition for COPD to include both symptomatic individuals, potentially at the pre-COPD stage as indicated by chronic bronchitis symptoms, and those with a clinical COPD diagnosis. This inclusive approach helps identify early-stage COPD symptoms, such as chronic bronchitis, which is characterized by chronic cough and sputum production (Kim and Criner, 2013).

Direct comparisons with previous studies on air pollution and CB/COPD are challenging due to variations in study design, exposure assessment, and disease definitions. Despite wide statistical uncertainty, our findings suggest that NO_2 exposure has stronger associations with the risk of CB/COPD compared to the other pollutant metrics considered. This finding aligns with a recent study in Italy which used a similar disease definition. Considering 4111 participants, Marchetti et al. (2023) found that exposure to NO_2 was linked to a 16% increase in the odds of having CB/COPD, whereas exposures to $PM_{2.5}$, PM_{10}, and summer O_3 showed no such associations.

Several studies agree on a likely role of air pollution exposure on COPD incidence, although the associations vary depending on the specific pollutants examined. A large study involving 98,598 adults from Denmark and Sweden, with an average age of 56, found significant associations between $PM_{2.5}$, NO_2, and BC and the incidence of COPD, even at levels below EU limits, with traffic-related pollutants NO_2 and BC being particularly linked to COPD development (Liu et al., 2021).

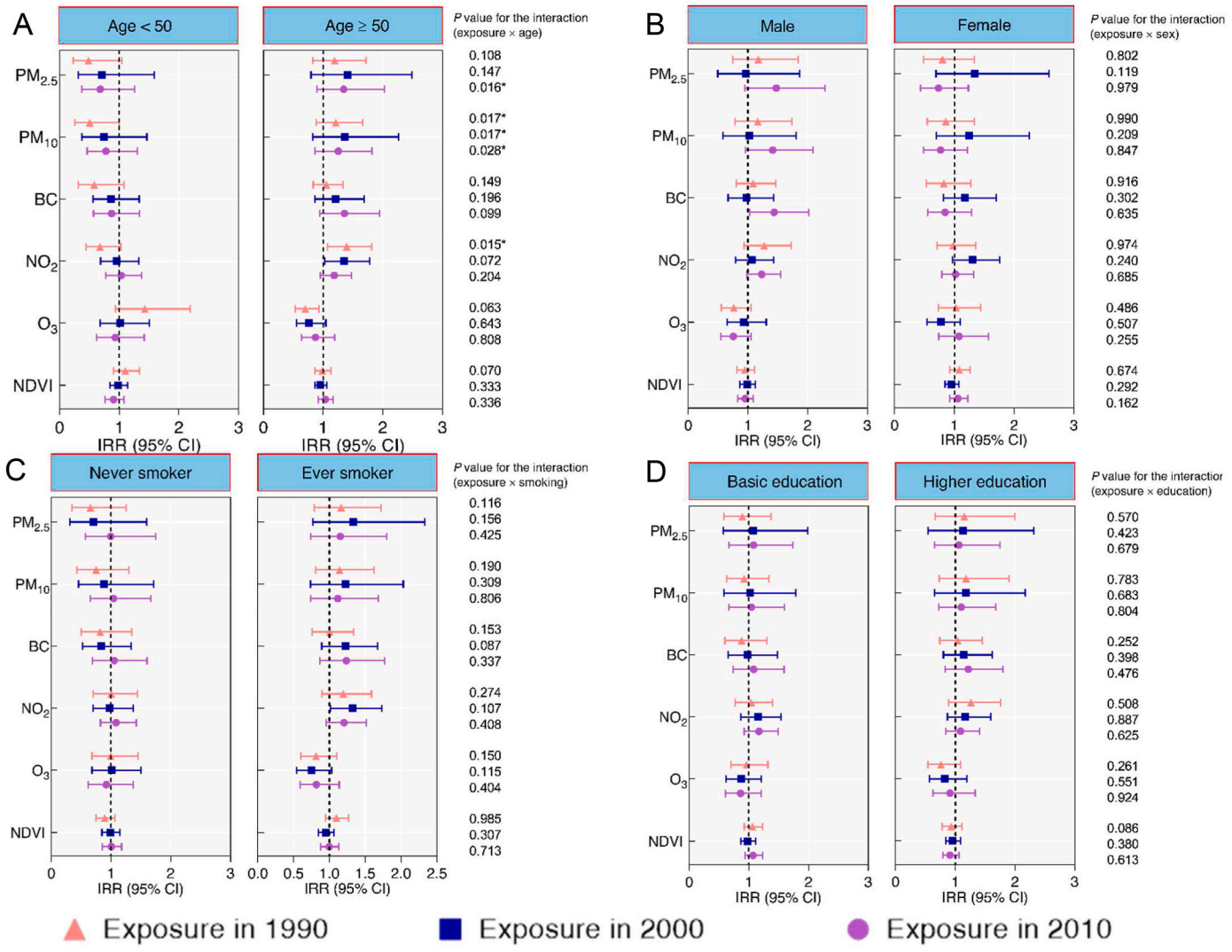

Fig. 3. Results of the adjusted stratified analysis by age, sex, smoking status and education. Within each specific stratum, model adjusted for sex, age, study center, education, BMI, smoking status, centered smoking duration and centered smoking intensity, where relevant.
Note that within each stratum, the variable used for stratification is not included as an adjustment variable.
The increment of the exposure is as follows: 5 μg/m^3 for $PM_{2.5}$, 10 μg/m^3 for PM_{10}, NO_2 and O_3, 0.4 μg/m^3 for BC, and 0.1 unit for NDVI.

Another research from the UK Biobank included 452,762 subjects also indicated that increased exposure to PM and NO_2 associated with higher COPD risks (Wang et al., 2022). Likewise, a cohort study from the Netherlands involving 65,009 participants identified an association between NO_2 and BC exposure and increased odds of chronic bronchitis incidence (Doiron et al., 2021). However, some other authors found less consistent associations. Schikowski et al. (2014) observed a trend towards increased incidence of COPD with higher levels of $PM_{2.5}$, PM_{10} and NO_2 in 6550 participants from the ESCAPE project. Similarly, in a study involving 103,838 female nurses in the United States, Fisher et al. (2016) reported inconsistent findings on the link between PM exposure and COPD incidence, with varying trends in their results. Another English cohort study of 812,063 participants, Atkinson et al. (2015) initially found that positive associations between PM and NO_2 exposure and COPD, but these associations were nullified after adjusting for smoking, BMI and neighborhood-level factors.

The pathogenic effects of air pollution on COPD remain unclear, but several plausible mechanisms are suggested. These include oxidative stress caused by free radicals from air pollutants, which can lead to lung inflammation, genotoxic effects like chromosome damage and single-strand breaks, and changes in gene expression and epigenetic modifications, contributing to COPD progression (Duan et al., 2020; Marcon et al., 2014). Animal model studies further support these findings (Jones et al., 2017). For instance, exposure of rats to air pollutants demonstrated COPD-like changes including lung function reduction, mucus metaplasia, and both lung and systemic inflammation (He et al., 2017). In our study, the more consistent results for NO_2 in relation to CB/COPD are interesting. NO_2, primarily emitted from combustion processes including traffic, is known to irritate the airways and cause inflammation, contributing to airway epithelial barrier dysfunction. This dysfunction exacerbates inflammatory responses and airway remodeling, which are key features in the pathogenesis of COPD (Aghapour et al., 2022). While other respiratory diseases can be affected by airway irritation, COPD is distinct due to its progressive nature and the susceptibility of the airways to long-term pollutant exposure, leading to chronic and often progressive airflow limitation. However, recent meta-analyses suggest there is low to moderate evidence linking air pollutants with the incidence of COPD (Boogaard et al., 2022; Park et al., 2021). This discrepancy in the effects of various pollutants on COPD incidence suggests that we need further research to identify the specific air pollutants and their sources that are most relevant for onset of COPD.

In our study, we observed a consistent higher levels of O_3 were associated with a decreased risk of CB/COPD in the total population, the direction of the estimates is similar to the findings on all-cause mortality we reported earlier (Xu et al., 2023). While this inverse relationship has been noted in other studies (Atkinson et al., 2015; Liu et al., 2021), some research has shown a positive relationship between O_3 exposure and COPD (Shin et al., 2021). The observed inverse association between ground-level O_3 and incident CB/COPD may be partially explained by the negative correlation between O_3 and other pollutants. In urban areas, lower O_3 levels are typically observed due to higher emissions of nitrogen oxides (NO_x) from combustion processes. This reduction in O_3 is driven by atmospheric chemistry, where O_3 reacts with nitric oxide (NO) to form nitrogen dioxide (NO_2) and oxygen (O_2). Such reactions contribute to decreased O_3 levels in areas with increased NOx emissions. Interestingly, our observations indicate that the effect sizes of NO_2 and O_3 on COPD incidence are similar but in opposite directions, coupled with a strong inverse correlation between NO_2 and O_3 across different exposure time windows, illustrating a complex dynamic in their relationship. Furthermore, while our study used annual mean levels for air pollution exposure, it is important to note that the negative correlation between O_3 and other air pollutants may be subject to seasonal influences. Notably, O_3 tends to increase in the summer, driven by photochemical processes, while particulate matter levels concurrently decline, largely due to a decrease in residential wood combustion during these warmer months (Li et al., 2021). The seasonal fluctuations complicate the assessment of ozone's impact on COPD, as its effects may be masked by the concurrent variations in other pollutant levels.

Except for the Aarhus center, the observed greenness levels in other study centers remained relatively stable throughout the study period, showing minor variations over time. The substantial increase in greenness observed in Aarhus is intriguing, and aligns with findings from Samuelsson et al. (2020), where their study reported that numerous residential areas in Denmark have undergone both densification (an increase in population density) and greening (an increase in vegetation) since the mid-1990s.

Current evidence on relations between greenness and COPD is limited and inconsistent (Johannessen et al., 2023). In our study, we found the association between NDVI and CB/COPD incidence was non-existent. On the contrary, a recent UK Biobank cohort study showed that long-term exposure to residential greenness, measured by summer mean NDVI values, was associated with lower risk of COPD incidence among UK adults (Yu et al., 2023). Similarly, a cross-sectional study conducted in China reported that a 500 m buffer of NDVI was associated with improved lung function and 10% lower odds of COPD (Xiao et al., 2022). Conversely, Fan et al. (2020) found a positive association between neighborhood greenness and COPD prevalence in their cross-sectional study within the Chinese population. However, it is important to bear in mind that these cross-sectional studies are limited in establishing causality due to their study design. Differences in study results could arise from variations in study design, exposure assessment, population characteristics and definition of the outcomes. Moreover, treating greenness indexes as a homogenous environment type without considering the quality and duration of individual interactions with green spaces might also contribute to these discrepancies (Yu et al., 2023). While green space are recognized for their potential to reduce air pollution (Setälä et al., 2013), they also produce pollen, a known respiratory irritant, and emit volatile organic compounds (VOCs) (Stas et al., 2021; Yeager et al., 2020). Both pollen and VOCs can adversely affect lung function, especially in individuals with sensitivities or existing respiratory issues (Lambert et al., 2020; Yoon et al., 2010). In our study, the strengths and directions of results in two-exposure models, including single pollutants and NDVI, are similar to those in single exposure models. The synergistic effects of air pollutants and greenness on COPD incidence remain unclear. Yu et al. (2023) found significant mediating effects of air pollution in the relationship between NDVI and COPD incidence. Specifically, they found that 23.4% of the association between NDVI with a 500-m buffer and incident COPD is mediated by $PM_{2.5}$. This indicates that part of the impact of greenness on COPD incidence might be attributed to the levels of $PM_{2.5}$ in the area. Such findings suggest a complex interplay between greenness and air pollutants. Future research should explore the causal mechanisms in greenness-respiratory health relationships and unravel the intricate interactions between air pollution and greenness on respiratory diseases.

The effect modification analysis showed significant association among participants over 50 years old between NO_2 and O_3 and CB/COPD, which contrasts with an Italian study showing a stronger association in participants <50 years (Marchetti et al., 2023). Liu et al. (2021) found a more pronounced association between $PM_{2.5}$ exposure and COPD in participants under the age of 65. We found no significant effect modification by sex, smoking status, or education. Evidence on the role of sex in the association between air pollution and COPD (Doiron et al., 2019; Schikowski et al., 2014), as well as greenness and COPD (Fan et al., 2020; Xiao et al., 2022; Yu et al., 2023) remains inconclusive. Liu et al. (2021) noted a stronger link between $PM_{2.5}$ and COPD in current smokers. We did not observe effect modification by smoking status. Xiao et al. (2022) reported beneficial effects of greenness on respiratory health in nonsmokers but not in smokers. Overall, there is still uncertainty regarding specific groups' susceptibility to the effects of air pollution or greenness on COPD.

CB and COPD often result from a long and accumulating pathological process that evolves over years before diagnosis. Associations between environmental exposures and CB/COPD may vary depending on both the temporal onset of exposure and the latency period between exposure and disease. We found a stronger association of NO_2 and O_3 with CB/COPD in those over 50 years than those below 50 years, particularly with 1990 exposure data (Fig. 3-A). This mirrors our previous findings of a higher hazard ratio for all-cause mortality due to air pollution in 1990 in the overall population (Xu et al., 2023). Similarly, Andersen et al. (2011) observed the strongest COPD incidence was associated with the longest exposure duration. This pattern, similar to the effects of smoking, suggests that air pollution may have an extended latency period before it leads to observable disease. The observed effects in individuals over 50 years of age may be attributed to cumulative exposure. Additionally, changing air pollutant correlation coefficients over time could reflect varying emission sources and pollutant toxicity. It is also interesting to note that the impact of air pollutants on CB/COPD in 2000 was lessened in models adjusted for greenness. This observation highlights the need to consider variation across both space and time, as well as the interactions between air pollution and greenness, in studies exploring the effects of air pollution on respiratory health.

The main strength of this study is based on its foundation in a large, prospective cohort study in Northern Europe (RHINE). The RHINE study has an extensive follow-up period of over 30 years, providing invaluable data for our analysis. Additionally, access to the population registry allowed for precise geocoding based on exact addresses, enabling accurate exposure assessment. Furthermore, the use of state-of-the-art atmospheric chemical transport modeling allowed us to assess historical air pollution exposure. This retrospective approach facilitated an in-depth investigation of the varying effects of air pollution on CB/COPD incidence over different exposure time windows.

Nevertheless, our study has important limitations. First, COPD is a complex condition with recurring symptoms and is often underdiagnosed. The use of self-reported symptoms and diagnosis for CB/COPD in our study introduces the potential for recall and information bias, as well as outcome misclassification. These issues could affect the accuracy of our findings and suggest that results should be interpreted with caution. To capture the full spectrum of COPD more accurately, future epidemiological studies should combine clinically verified diagnoses with self-reported data. In addition, a significant limitation is censoring of data resulting from a considerable number of subjects not participating in the follow-up survey in RHINE IV, leading to their exclusion. This could potentially introduce selection bias, as the final

sample may not be fully representative of the target population. The absence of complete residential address history data restricts our ability to calculate time-varying exposure or cumulative exposure. We used education as a proxy for individual socioeconomic status, however, our study lacks detailed neighborhood-level socioeconomic data and other critical covariates such as household income, occupation, and detailed disease history data, which have been considered in previous studies (Atkinson et al., 2015; Fan et al., 2020; Liu et al., 2021). Lack of adjustment for these potential confounding factors might limit the validity of our findings and our understanding of disparities and inequities in respiratory health that are linked to environmental exposure. Furthermore, while our study identified consistent trends in the association between NO_2 and CB/COPD incidence across different exposure time windows, evidence remained statistically uncertain, probably due to a low study power. Acknowledging this is crucial as it underscores the need for cautious interpretation of our results. Further studies with larger sample sizes are needed to verify our conclusions. Lastly, we cannot rule out potential exposure misclassification, as we have focused on residential outdoor air pollution in three specific time points. However, even if we lack complete residential address histories for participants, confidence in our results is strengthened by findings from the ESCAPE project suggesting that bias arising from residential mobility was small (Oudin et al., 2012). Given that the determination of exposure was made independently of the outcome, any resulting misclassification is expected to be nondifferential, possibly biasing towards null.

5. Conclusions

In line with some previous research, our study indicates that exposure to NO_2 may play a more significant role in elevating the risk of chronic bronchitis and COPD compared to other pollutants. O_3 on the other hand showed a tendency for an inverse association with CB/COPD. However, because of the small number of incident cases, our findings should be interpreted with caution. We found no consistent evidence for an association between PM, BC and greenness with CB/COPD across different exposure time windows. Understanding the causal role of individual pollutants such as NO_2 and identifying susceptibility groups to air pollution are crucial for public health.

CRediT authorship contribution statement

Shanshan Xu: Writing – review & editing, Writing – original draft, Visualization, Methodology, Formal analysis, Conceptualization. **Alessandro Marcon:** Writing – review & editing, Validation, Supervision, Methodology, Conceptualization. **Randi Jacobsen Bertelsen:** Writing – review & editing, Supervision, Methodology, Conceptualization. **Bryndis Benediktsdottir:** Writing – review & editing. **Jørgen Brandt:** Writing – review & editing, Investigation. **Lise Marie Frohn:** Writing – review & editing, Investigation. **Camilla Geels:** Writing – review & editing, Investigation. **Thorarinn Gislason:** Writing – review & editing. **Joachim Heinrich:** Writing – review & editing. **Mathias Holm:** Writing – review & editing. **Christer Janson:** Writing – review & editing. **Iana Markevych:** Writing – review & editing. **Lars Modig:** Writing – review & editing. **Hans Orru:** Writing – review & editing. **Vivi Schlünssen:** Writing – review & editing. **Torben Sigsgaard:** Writing – review & editing. **Ane Johannessen:** Writing – review & editing, Supervision, Project administration, Methodology, Funding acquisition, Conceptualization.

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.

Data availability

The data presented in this paper are not readily available due to potential privacy violations, but can be obtained with justifiable request and with the consent of the national ethics committee.

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Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.envres.2024.119240.

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