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Multiple myeloma risk in relation to long-term air pollution exposure - A pooled analysis of four European cohorts

Ulla Arthur Hvidtfeldt [a,*], Jie Chen [b], Sophia Rodopoulou [c], Maciej Strak [b,d], Kees de Hoogh [e,f], Zorana J. Andersen [g], Tom Bellander [h], Jørgen Brandt [i,j], Francesco Forastiere [k,l], Boel Brynedal [m], Ole Hertel [n], Barbara Hoffmann [o], Klea Katsouyanni [c,p], Matthias Ketzel [i,q], Karin Leander [h], Patrik K.E. Magnusson [r], Gabriele Nagel [s], Göran Pershagen [h], Debora Rizzuto [t,u], Evangelia Samoli [c], Rina So [g,v], Massimo Stafoggia [h,k], Anne Tjønneland [a,g], Gudrun Weinmayr [s], Kathrin Wolf [w], Emanuel Zitt [x,y], Bert Brunekreef [b], Gerard Hoek [b], Ole Raaschou-Nielsen [a,i]

[a] The Danish Cancer Institute, Copenhagen, Denmark
[b] Institute for Risk Assessment Sciences, Utrecht University, Utrecht, the Netherlands
[c] Department of Hygiene, Epidemiology and Medical Statistics, Medical School, National and Kapodistrian University of Athens, Athens, Greece
[d] National Institute for Public Health and the Environment, Bilthoven, the Netherlands
[e] Swiss Tropical and Public Health Institute, Allschwil, Switzerland
[f] University of Basel, Basel, Switzerland
[g] Department of Public Health, University of Copenhagen, Copenhagen, Denmark
[h] Institute of Environmental Medicine, Karolinska Institutet, Stockholm, Sweden
[i] Department of Environmental Science, Aarhus University, Roskilde, Denmark
[j] iClimate – interdisciplinary Centre for Climate Change, Aarhus University, Roskilde, Denmark
[k] Department of Epidemiology, Lazio Region Health Service/ASL Roma 1, Rome, Italy
[l] Environmental Research Group, School of Public Health, Faculty of Medicine, Imperial College, London, UK
[m] Department of Global Public Health, Karolinska Institutet, Stockholm, Sweden
[n] Departments of Ecoscience, Aarhus University, Roskilde, Denmark
[o] Institute for Occupational, Social and Environmental Medicine, Centre for Health and Society, Medical Faculty, Heinrich Heine University Düsseldorf, Düsseldorf, Germany
[p] MRC Centre for Environment and Health, School of Public Health, Imperial College London, London, UK
[q] Global Centre for Clean Air Research (GCARE), University of Surrey, Guildford, GU2 7XH, United Kingdom
[r] Department of Medical Epidemiology and Biostatistics, Karolinska Institutet, Stockholm, Sweden
[s] Institute of Epidemiology and Medical Biometry, Ulm University, Ulm, Germany
[t] Department of Neurobiology, Care Sciences, And Society, Karolinska Institutet and Stockholm University, Stockholm, Sweden
[u] Stockholm Gerontology Research Center, Stockholm, Sweden
[v] Department of Epidemiology and Public Health, University College London, London, United Kingdom
[w] Institute of Epidemiology, Helmholtz Zentrum München, Neuherberg, Germany
[x] Agency for Preventive and Social Medicine (aks), Bregenz, Austria
[y] Department of Internal Medicine 3, LKH Feldkirch, Feldkirch, Austria

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ABSTRACT

Background: Air pollution is a growing concern worldwide, with significant impacts on human health. Multiple myeloma is a type of blood cancer with increasing incidence. Studies have linked air pollution exposure to various types of cancer, including leukemia and lymphoma, however, the relationship with multiple myeloma incidence has not been extensively investigated.

Methods: We pooled four European cohorts (N = 234,803) and assessed the association between residential exposure to nitrogen dioxide (NO_2), fine particles ($PM_{2.5}$), black carbon (BC), and ozone (O_3) and multiple myeloma. We applied Cox proportional hazards models adjusting for potential confounders at the individual and area-level.

* Corresponding author.
E-mail address: ullah@cancer.dk (U.A. Hvidtfeldt).

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Results: During 4,415,817 person-years of follow-up (average 18.8 years), we observed 404 cases of multiple myeloma. The results of the fully adjusted linear analyses showed hazard ratios (95% confidence interval) of 0.99 (0.84, 1.16) per 10 μg/m^3 NO_2, 1.04 (0.82, 1.33) per 5 μg/m^3 $PM_{2.5}$, 0.99 (0.84, 1.18) per 0.5 10^{-5} m^{-1} BCE, and 1.11 (0.87, 1.41) per 10 μg/m^3 O_3.
Conclusions: We did not observe an association between long-term ambient air pollution exposure and incidence of multiple myeloma.

1. Introduction

Air pollution is a modifiable risk factor with extensive public health impact (Global Burden of Disease (GBD) 2019 Risk Factors Collaborators, 2020). Strong evidence exists for a detrimental impact of air pollution exposure on ischemic heart disease, type 2 diabetes, stroke, chronic obstructive pulmonary disease, and lung cancer (Boogaard et al., 2019), and a growing body of evidence suggests that air pollution exposure is also etiologically relevant for other cancers (Turner et al., 2020; IARC, 2016). However, for most cancer endpoints - other than lung cancer - the existing studies are based on a small number of cases, recent as opposed to historical exposure data, and findings are mixed.

The current evidence for a link between air pollution exposure and lymphohematopoietic cancers is also mixed and the majority of the previous studies did not have statistical power to consider their specific subtypes. The National Health Interview Survey (NHIS) study reported positive associations between fine particle ($PM_{2.5}$) exposure and Hodgkin lymphoma, non-Hodgkin lymphoma, and leukemia mortality (Coleman et al., 2020). Results from the large American Cancer Society Cancer Prevention Study II (ACS CPS-II) Nutrition Cohort participants, showed adverse associations between outdoor benzene exposure and T-cell lymphoma and myelodysplastic syndromes and with follicular lymphoma among men (Turner et al., 2017). Recent case-control studies based on the entire adult Danish population, also showed increased risks of acute myeloid and chronic lymphoblastic leukemias in relation to $PM_{2.5}$ exposure (Puett et al., 2020; Taj et al., 2021a). These studies, however, did not show an association between any of the investigated air pollutants and Hodgkin or non-Hodgkin lymphoma (Taj et al., 2020, 2021b).

Multiple myeloma is characterized by the neoplastic proliferation of plasma cells producing monoclonal immunoglobulins and it is the second most common hematological cancer accounting for 10–15% of all hematological cancers (Turesson et al., 2018; Alexander et al., 2007). The incidence has increased during the past decades and the highest incidence rates are observed in Europe, North America, Australia, and New Zealand (Zhou et al., 2021). The etiology of multiple myeloma is poorly understood, but risk factors include a family history of the disease, male gender, black race, and advanced age (Zhou et al., 2021; Psaltopoulou et al., 2013; Kamath et al., 2020). Generally, previous studies do not support a role of tobacco smoking, while an inverse relationship with alcohol intake and an increased risk with higher BMI has been suggested (Psaltopoulou et al., 2013; Andreotti et al., 2015; Cheah et al., 2022; Lauby-Secretan et al., 2016; Ugai et al., 2019). Potential environmental risk factors include exposures to pesticides, petroleum products, and benzene (Kachuri et al., 2013; Sergentanis et al., 2015; Stenehjem et al., 2015; Onyije et al., 2021). The possible mechanisms linking air pollution to cancer include oxidative stress, inflammation, and endocrine disruption (Straif et al., 2013; Traboulsi et al., 2017; Darbre, 2018). Immune alteration is considered an important biologic mechanism in the etiology of multiple myeloma, which is supported by increases in multiple myeloma incidence among patients with AIDS and certain autoimmune diseases (Alexander et al., 2007). However, whereas several previous studies have been conducted on air pollution and risk of other hematopoietic cancers, the literature concerning a potential link with incidence of multiple myeloma is basically non-existing. A few mortality studies on air pollution and cancer reported specifically on multiple myeloma. Their results showed no association between exposure to $PM_{2.5}$, nitrogen dioxide (NO_2), and ozone (O_3) and multiple myeloma mortality (Coleman et al., 2020; Turner et al., 2017). It is important to note, that with recent advancement in treatment regimes, the relative survival rates have improved dramatically (Turesson et al., 2018), and thus, incidence of multiple myeloma does not compare to mortality rates. On the other hand, a German cohort study observed an association of long-term air pollution exposure with Monoclonal Gammopathy of Undetermined Significance (MGUS), a precursor of multiple myeloma (Orban et al., 2017).

The aim of the present study was to investigate the association between long-term exposure to NO_2, $PM_{2.5}$, black carbon (BC), and O_3 and incidence of multiple myeloma in a pooled cohort of four studies within the Effects of Low-level Air Pollution: a Study in Europe (ELAPSE). By application of a comprehensive air pollution exposure model to a large, pooled cohort of the general population with detailed confounder information, our study adds to the understudied research field concerning environmental risk factors for multiple myeloma incidence.

2. Methods

2.1. Study population

Nine European cohorts were pooled for the ELAPSE study, for which key covariates were identified and harmonized (Hvidtfeldt et al., 2021; Strak et al., 2021), and the data were securely stored at Utrecht University. Among the nine cohorts, data on incident multiple myeloma cases were available for four cohorts. These cohorts included: Cardiovascular Effects of Air Pollution and Noise in Stockholm (CEANS) – consisting of four sub-cohorts (Swedish National Study on Aging and Care in Kungsholmen [SNAC-K] (Lagergren et al., 2004); Stockholm Screening Across the Lifespan Twin study [SALT] (Magnusson et al., 2013); The Stockholm Cohort of 60-year-olds [Sixty] (Wändell et al., 2007); and Stockholm Diabetes Prevention Program [SDPP] (Eriksson et al., 2008); the Danish Diet, Cancer and Health cohort (DCH) (Tjønneland et al., 2007); the Danish Nurse Cohort (DNC) (Hundrup et al., 2012); and the Austrian Vorarlberg Health Monitoring and Prevention Programme (VHM&PP) (Ulmer et al., 2007). All four cohorts had information on age, sex, smoking status, amount and duration of smoking in current smokers (VHM&PP only in classes), body mass index (BMI), employment status, and area-level socio-economic status (SES) at baseline. Participants were cancer-free at baseline (not counting non-melanoma skin cancer). A detailed description has been provided previously (Hvidtfeldt et al., 2021).

2.2. Exposure assessment

The methodology for assessment of air pollution exposures has been extensively described (de Hoogh et al., 2018; Chen et al., 2020). In summary, we developed Europe-wide hybrid land-use regression (LUR) models, combining numerous predictors such as satellite NO_2 and $PM_{2.5}$ observations, chemical transport model (CTM) air pollution estimates, land use, and road variables. To model $PM_{2.5}$, NO_2 and O_3 (warm season), routine monitoring data from EEA (the European Environmental Agency) in 2010 (AirBase) were used. For BC, monitoring data (2009–2010) from a Europe-wide research study were applied (Eeftens et al., 2012). The air pollution raster surfaces at a 100 m × 100 m spatial resolution were ascribed to the geocoded residential addresses at

baseline of all cohort members. The exposure model was validated by five-fold Hold Out Validation (HOV) in random subsets (20%) of the monitoring datasets, stratified by European region and site type (background, traffic). The validation results showed that the modelled exposure explained a large part of the measured spatial variability in annual average concentration (e.g. 59% for NO_2, 72% for $PM_{2.5}$, 54% for BC, and 69% for O_3) (de Hoogh et al., 2018). In sensitivity analyses, we explored extrapolation of the air pollution exposure applying estimated concentrations from the DEHM (Danish Eulerian Hemispheric Model), which contains hourly values of air pollutants, averaged into monthly concentrations across Europe at a spatial resolution of 26 km × 26 km (Brandt et al., 2012). We applied predicted trends from the DEHM for NO_2, $PM_{2.5}$, BC, and O_3 to calculate annual average concentrations for all years from baseline to the end of follow-up. The method allowed different spatial trends within Europe and applied the absolute difference and the ratio between the baseline and 2010 periods.

2.3. Outcome

We followed up participants for multiple myelomas with information from national cancer registries, death certificates, or medical records. We defined multiple myelomas according to the International Classification of Diseases and Related Health Problems, 10th Revision (ICD-10) codes C90.0 and correspondingly the International Classification of Diseases and Related Health Problems, 9th Revision (ICD-9) code 203.0.

2.4. Statistical analysis

We modelled the association between the air pollutants and multiple myeloma in Cox proportional hazards (PH) models. We applied age as the underlying time scale and modelled the risk of multiple myeloma from the (cohort specific) baseline censoring participants at time of first occurrence of any cancer other than multiple myeloma, date of death, emigration, loss to follow-up, or at the end of follow-up. We modelled each pollutant as a linear function and derived hazard ratios (HRs) for increments of 10 μg/m^3 NO_2, 5 μg/m^3 $PM_{2.5}$, 0.5 10^{-5} m^{-1} BC, and 10 μg/m^3 O_3, respectively. We included strata per individual (sub) cohort and sex to relax the proportional hazards assumption accounting for baseline hazard heterogeneity across the cohorts.

We defined three confounder models á priori based on existing knowledge: 1) age (underlying time-scale), (sub) cohort ID (strata), sex (strata), and adjustment for year of enrolment to handle time-trends in exposure and outcome; 2) variables in (1) plus BMI (<18.5, 18.5–24, 25–29, and 30+ kg/m^2), smoking status (never, former, current), duration (years of smoking) and intensity (cigarettes/day) for current smokers, marital status (married/cohabiting, divorced, single, widowed), and employment status (yes vs. no); 3) (main model) additionally adjusted for SES at the area-level (mean income in 2001, which was the most consistently available variable and year across cohorts). The spatial scale of the areas ranged from smaller neighborhoods and city districts (CEANS) to municipalities (DNS, DCH, and VHM&PP). Participants with inadequate information on variables for Model 3 were excluded from all analyses. We evaluated the shape of the concentration-response function by natural cubic splines with 3 degrees of freedom.

We performed a range of sensitivity analyses including 1) exploration of alternative exposure definitions, i.e., back-extrapolating exposures to the baseline address for all cohort members and time-varying air pollution exposure extrapolated based on address history from enrolment to end of follow-up (excluding DNC due to lack of address history information). For the time-varying analyses, we specified a 1-year calendar time-period strata in order to account for time trends in air pollution and multiple myeloma. 2) we explored potential effect measure modifications by the inclusion of an interaction term in the model for sex, age, BMI (<25, 25–29, 30+ kg/m^2), and smoking status. These interaction terms were tested using the Wald test. 3) We performed two-pollutant models to examine the sensitivity of the estimates of one

Table 1
Description of the included (sub)cohort studies.

	Total participants	Baseline period	End of follow-up	Follow-up (mean/IQR) years	Baseline age (mean/SD) years	NO_2 (mean/SD)[a] μg/m^3	$PM_{2.5}$ (mean/SD)[a] μg/m^3	BC (mean/SD)[a] (10^{-5}m^{-1})	O_3 (mean/SD)[a] μg/m^3	Multiple myelomas
CEANS, Stockholm, Sweden										
SDPP	7305	1992–1998	31-12-2011	15.3 (3.6)	47.0 (4.9)	15.4 (4.3)	7.6 (0.9)	0.6 (0.2)	77.6 (1.9)	17
SIXTY	3660	1997–1999	31-12-2011	12.0 (1.2)	60 (0)	20.6 (6.1)	8.3 (0.9)	0.8 (0.3)	76.7 (2.5)	11
SALT	5625	1998–2003	31-12-2011	9.9 (2.3)	57.3 (10.4)	21.2 (6.2)	8.4 (0.9)	0.8 (0.3)	76.6 (2.7)	7
SNAC-K	2359	2001–2004	31-12-2011	7.0 (4.3)	72.5 (10.4)	27.4 (5.1)	8.6 (0.8)	1.1 (0.2)	75.1 (2.7)	2
DCH, Copenhagen/ Aarhus, Denmark	52,779	1993–1997	31-12-2015	16.9 (4.5)	56.7 (4.4)	28.1 (6.9)	13.2 (1.4)	1.4 (0.4)	77.4 (5.1)	142
DNC, Denmark										
DNC-1993	15,556	1993	31-12-2012	16.9 (3.7)	56.0 (8.3)	21.8 (8.0)	12.7 (1.5)	1.1 (0.4)	80.4 (4.0)	27
DNC-1999	7430	1999	31-12-2012	13.0 (0.0)	47.9 (4.1)	25.8 (8.5)	13.8 (1.5)	1.3 (0.4)	80.6 (3.8)	7
VHM&PP, Vorarlberg, Austria	140,089	1985–2005	31-12-2014	21.0 (11.0)	41.7 (14.9)	22.0 (5.3)	15.7 (2.6)	1.6 (0.3)	92.6 (3.6)	191
Pooled cohort	**234,803**	**1985–2005**	**2011–2015**	**18.2 (7.1)**	**47.3 (14.2)**	**23.3 (6.7)**	**14.3 (3.1)**	**1.5 (0.4)**	**86.7 (8.2)**	**404**

CEANS: Cardiovascular Effects of Air Pollution and Noise in Stockholm; SDPP: The Stockholm Diabetes Preventive Program; SIXTY: The Stockholm cohort of 60-year-olds; SALT: Screening Across the Lifespan Twin Study; SNAC-K: The Swedish National Study of Aging and Care in Kungsholmen; DCH: Diet, Cancer and Health; DNC: Danish Nurses Cohort; VHM&PP: Vorarlberg Health Monitoring and Prevention Programme.
[a] 2010 exposure model.

Table 2
Baseline characteristics of the included (sub)cohort studies.

	% women	% BMI ≥25 kg/m^2	% Not employed	% Married/cohabiting	% Current smokers	Mean (SD) Cigarettes/day[a]	Mean (SD) years of smoking[a]	Mean (SD) income at area-level[b]
CEANS, Stockholm, Sweden								
SDPP	59	51	9	84	26	13.5 (7.4)	27.8 (8.6)	24.3 (4.2)
SIXTY	50	65	32	74	21	13.3 (7.7)	36.2 (10.1)	24.7 (6.8)
SALT	53	41	33	68	21	12.7 (8.0)	37.6 (9.1)	25.4 (6.6)
SNAC-K	62	53	76	46	15	11.7 (8.3)	43.2 (13.5)	28.7 (2.2)
DCH, Copenhagen/Aarhus, Denmark	53	56	22	71	36	16.5 (9.0)	36.3 (7.7)	20.1 (3.4)
DNC, Denmark								
DNC-1993	100	28	29	68	37	13.8 (8.1)	31.4 (9.9)	19.2 (2.5)
DNC-1999	100	30	5	76	28	13.2 (7.4)	27.1 (7.1)	19.0 (2.4)
VHM&PP, Vorarlberg, Austria	56	42	29	69	20	15.6 (8.9)	13.4 (8.2)	22.9 (1.7)
Pooled cohort	**60**	**46**	**26**	**70**	**25**	**15.4 (8.8)**	**24.4 (13.6)**	**22.1 (3.2)**

CEANS: Cardiovascular Effects of Air Pollution and Noise in Stockholm; SDPP: The Stockholm Diabetes Preventive Program; SIXTY: The Stockholm cohort of 60-year-olds; SALT: Screening Across the Lifespan Twin Study; SNAC-K: The Swedish National Study of Aging and Care in Kungsholmen; DCH: Diet, Cancer and Health; DNC: Danish Nurses Cohort; VHM&PP: Vorarlberg Health Monitoring and Prevention Programme.

[a] Among current smokers.

[b] Euros x 1,000, year 2001.

pollutant to inclusion of others. Lastly, we investigated whether the pooled effect estimates were sensitive to the exclusion of single cohorts.

To evaluate violation of the PH assumption of the Cox model for all covariates, we performed a test of a non-zero slope in a generalized linear regression of the scaled Schoenfeld residuals on time. We performed all analyses in R version 3.4.0.

3. Results

The included cohorts were recruited in the period 1985–2005 with a follow up until 2011–2015 (Table 1). In total, we included 234,803 participants of whom 404 developed multiple myeloma during 4,415,817 person-years of follow-up. The mean age at baseline for the pooled cohort was 47.3 years ranging from 41.7 to 72.5 years in the individual (sub)cohorts. The air pollution exposures differed among the (sub)cohorts. BC and NO_2 exhibited substantial variations within cohorts as illustrated in Figure S1. Moreover, BC and NO_2 displayed strong positive correlations across all cohorts, while $PM_{2.5}$ exhibited moderate to high correlations with BC and NO_2. Conversely, O_3 showed negative correlations with $PM_{2.5}$ and particularly with NO_2 and BC (Table S1).

Table 2 displays the baseline characteristics of each (sub)cohort and the pooled cohort. The pooled cohort consisted of 60% women, 46% were overweight or obese, 26% were not employed, and 70% were married or cohabiting at baseline. The fraction of current smokers was 25%. The mean number of cigarettes smoked per day among current smokers was 15.4, and the mean duration of smoking was 24.4 years.

The results of the linear analyses of air pollutants and multiple myelomas with increasing levels of confounder-adjustment are shown in Table 3. The HR's for NO_2 and BC varied between 0.99 and 1.01 across the three models per increments of 10 μg/m^3 and 0.5 10^{-5} m^{-1}, respectively. In the fully adjusted model 3, we observed a HR of 1.04 (95% confidence interval [CI]: 0.82, 1.33) per increment of 5 μg/m^3 $PM_{2.5}$. Correspondingly, we observed a HR of 1.11 (95% CI: 0.87, 1.41) per increment of 10 μg/m^3 O_3. Stricter covariate adjustment did not affect the HRs of any of the exposures. The natural cubic splines showed a tendency towards a linear increase in the exposure-response function for NO_2 and $PM_{2.5}$ levelling off around 20 μg/m^3 for NO_2 and 12 μg/m^3 for $PM_{2.5}$ (Figure S2). An indication of a decreasing trend at the end of the exposure range for O_3 was observed.

Fig. 1 shows the results concerning potential effect modification by smoking, BMI, age, and sex. The HR for $PM_{2.5}$, BC, and O_3 varied somewhat according to smoking status, with the largest HR observed among previous smokers, although these differences of HRs across smoking categories were not statistically significant. For BMI, we observed higher HRs in the category of obese persons (30+ kg/m^2) compared to normal- and overweight for both NO_2 and $PM_{2.5}$, whereas the HR for O_3 was highest in the group of persons with a BMI below 25 kg/m^2. The HRs were below 1 in the elderly (65+ years) for all pollutants. The effect estimates for $PM_{2.5}$, BC, and O_3 also varied according to sex with HRs above 1 for women and below for men. This pattern was opposite with NO_2 exposure.

Supplement Table S2 shows the means, standard deviations (SD) and effect estimates of exposures extrapolated to the baseline year of the cohort participants and for the time-varying exposure analysis. The back-extrapolated baseline exposures were somewhat higher and more variable than the 2010-concentration, especially for $PM_{2.5}$. The effect estimates did not vary considerably between the back-extrapolated baseline exposure model and the 2010-exposure model. In the time-varying analysis applying exposure extrapolated across the address history, we observed higher effect estimates for NO_2, $PM_{2.5}$, and BC compared to the 2010-exposure model. The estimates for the time-varying exposure of O_3 were lower than those of the main 2010-exposure. The effect estimates were not sensitive to the inclusion of co-pollutants (Figure S3). Also, the estimates were generally not sensitive to exclusion of single cohorts (Figure S4). The highest estimates for NO_2, $PM_{2.5}$, and BC were observed in a pooled cohort excluding the DCH

Table 3
Pooled analyses of air pollution exposure and risk of multiple myelomas[d] (N = 404).

	Increment	Model 1[a] N = 234,803			Model 2[b] N = 234,803			Model 3[c] N = 234,803		
		HR	95% CI		HR	95% CI		HR	95% CI	
NO_2	10 μg/m^3	1.00	0.85	1.17	1.01	0.86	1.18	0.99	0.84	1.16
$PM_{2.5}$	5 μg/m^3	1.04	0.82	1.32	1.05	0.83	1.33	1.04	0.82	1.33
BC	0.5 $10^{-5}m^{-1}$	1.00	0.85	1.18	1.01	0.86	1.19	0.99	0.84	1.18
O_3	10 μg/m^3	1.12	0.88	1.42	1.11	0.87	1.42	1.11	0.87	1.41

HR, hazard ratio; CI, confidence interval; O_3, Ozone in the warm season.
[a] Adjusted for study (strata), age, sex (strata), year of baseline visit.
[b] Further adjusted for smoking status, duration, intensity, BMI, marital status, and employment status.
[c] Further adjusted for 2001 mean income at the area level.
[d] ICD 10: C90.0/ICD9: 203.0.

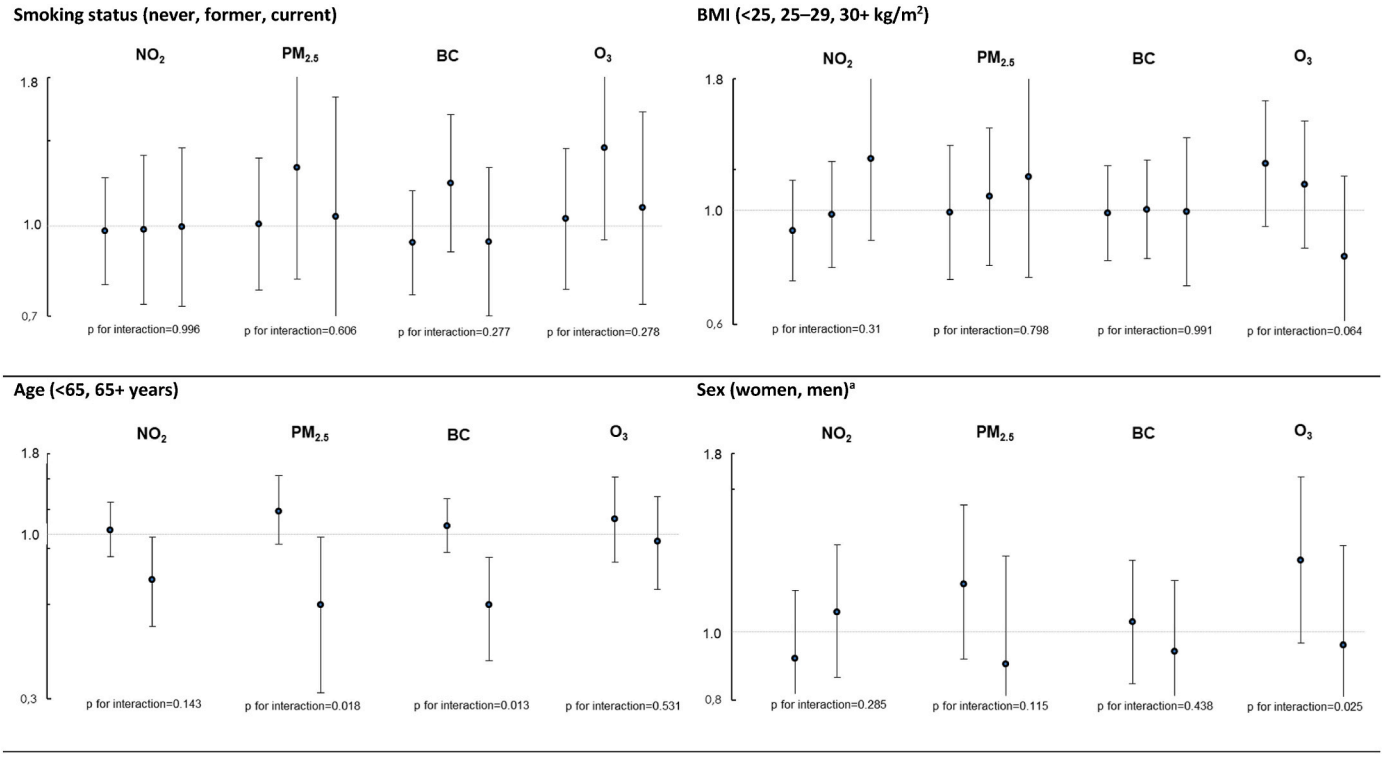

Fig. 1. Effect modification by smoking, BMI, age, and sex on the relation between NO_2, $PM_{2.5}$, BC, and O_3 and multiple myeloma (N = 234,803).
Hazard ratios with confidence intervals adjusted for study (strata), age, sex, year of baseline visit, smoking status, duration, intensity, BMI, marital status, employment status, and 2001 mean income at the neighborhood level. [a]The DNC includes women only.

cohort, whereas we found the highest estimates for O_3 when excluding the VHM&PP cohort.

We detected deviation from the proportional hazards assumption for employment status. A sensitivity analysis incorporating this variable in strata did not show results deviating from the main analysis.

4. Discussion

Long-term exposure to NO_2, $PM_{2.5}$, BC, and O_3 was not consistently associated with multiple myeloma incidence in this large pooled analysis study of European cohorts.

We are only aware of few previous studies concerning the association between air pollution exposure and risk of multiple myeloma. The large-scale prospective ACS CPS-II consisted of 623,048 persons from across the US who were followed up for 22 years in relation to cancer mortality linking concentrations of NO_2, $PM_{2.5}$, and O_3 to participant's residential address at baseline (Turner et al., 2017). A total of 1421 participants died of multiple myeloma during follow-up. The resulting HRs (95% CI) of the study were 1.00 (0.92, 1.09) per 6.5 ppb NO_2, 0.97 (0.89, 1.07) per 4.4 μg/m^3 $PM_{2.5}$, and 0.99 (0.90, 1.09) per 6.9 ppb O_3, which is in line with the results of our study based on incidence. Similar results were reported from the NHIS cohort with a HR of 0.99 (0.64, 1.53) per 10 μg/m^3 $PM_{2.5}$ based on 541 multiple myeloma deaths (Coleman et al., 2020). A study from South Korea, reported a HR of 0.63 (0.18–2.18) per 10 μg/m^3 increments of $PM_{2.5}$ (Shin et al., 2022). The results, however, were based on only 22 multiple myeloma deaths, which is reflected in the very wide confidence interval. Findings from a recent Canadian prospective study on long-term exposure to wildfires, including 3900 cases of multiple myeloma, also did not show evidence of an association (Korsiak et al., 2022). Except for the Canadian study, all studies evaluated multiple myeloma mortality. Our study added an analysis of multiple myeloma incidence. Because of the moderate prognosis,(Turesson et al., 2018) associations of air pollution with mortality can be different from incidence, the preferred outcome metric.

Several factors strengthen the conclusions of our study: 1) We had a relatively large sample size, 2) Comparable exposure estimates across the included cohort studies were ensured by the comprehensive, standardized exposure model which was developed within the ELAPSE

collaboration. 3) We had detailed information on individual and area level SES factors and data on individual lifestyle which was thoroughly harmonized across the (sub)cohorts. This allowed us to adjust for several potential confounders.

However, some limitations also need mention: 1) Despite being founded on a large cohort with a long follow-up period, the number of cases of multiple myeloma was low in this study, which lead to effect estimates with relatively wide confidence intervals. We therefore cannot exclude that small risks may be present, especially for $PM_{2.5}$ and O_3, for which we observe HRs above unity consistently. Multiple myeloma presents with non-specific symptomatology and has the longest time-to-diagnosis among all cancers (Swann et al., 2018), and therefore under-reporting of cases could be an issue in this study. If such underreporting is related to certain areas/hospitals and thereby to the levels of exposure, the reported risk estimates could be biased. However, the completeness and the quality of the cancer registration in each included study is considered high (Gjerstorff, 2011; Barlow et al., 2009; Hackl and Waldhoer, 2013; van der Willik et al., 2020). 2) Also, since risk factors for multiple myeloma are not well described, we cannot exclude residual confounding. African ancestry is a recognized risk factor for multiple myeloma (Alexander et al., 2007), and since ethnicity is likely also related to area of residence – and hence the residential air pollution exposure levels – some residual confounding is plausible. Nevertheless, the adjustment for individual and area-level SES presumably accounted for some of this confounding. The small difference in HRs in the three confounder models suggests that residual confounding may not be substantial. 3) Another point to consider is that model-based air pollution exposure involves some degree of misclassification because of uncertainties in the input data and since exposure modelled at the residential address does not entirely capture personal exposure (Evangelopoulos et al., 2020). Moreover, we lacked information on indoor sources of air pollution and time-activity patterns. We do, nonetheless, expect these uncertainties to cause non-differential exposure misclassification with respect to multiple myeloma incidence, thus leading to bias of the effect estimate towards the null. However, these generic limitations of exposure assessment applied to all outcomes evaluated within the ELAPSE project. We found significant associations with e.g., lung cancer and cause-specific mortality (Hvidtfeldt et al., 2021; Strak et al., 2021), which suggests that limitations in exposure assessment do not fully explain our general null findings for multiple myeloma. Also, the exposure model applied to the baseline address of the study participants was developed for the year 2010. Previous European studies have shown that the spatial distributions of NO_2, black smoke, and traffic intensities remain stable over several years (Beelen et al., 2007; Cesaroni et al., 2012; Gulliver et al., 2011). We validated our exposure model by comparing with different time points in order to evaluate the stability of the spatial structure (de Hoogh et al., 2018; Chen et al., 2019), and the predictions from the 2010-model exhibited high correlations with models developed for 2000 and 2005 (2013 for $PM_{2.5}$) at the European scale. Our sensitivity analysis, where we back-extrapolated exposures to the baseline year of participants, did not show markedly different results compared to the 2010 exposure. 4) Finally, our study population was obtained from Denmark, Sweden, and Austria, thus, restrictive in terms of generalizability across Europe.

In conclusion, the results of the present study did not indicate a role of long-term ambient air pollution in the development of multiple myeloma.

Credit authorship contribution statement

Ulla Arthur Hvidtfeldt: Formal analysis, Methodology, Software, Visualization, Writing – original draft; Jie Chen: Data curation, Methodology, Project administration, Software, Writing – review & editing; Sophia Rodopoulou: Data curation, Methodology, Software, Writing – review & editing; Maciej Strak: Data curation, Methodology, Writing – review & editing; Kees de Hoogh: Data curation, Methodology, Writing – review & editing; Zorana Jovanovic Andersen: Methodology, Writing – review & editing; Tom Bellander: Methodology, Writing – review & editing; Jørgen Brandt: Data curation, Methodology, Writing – review & editing; Francesco Forastiere: Writing – review & editing; Boel Brynedal: Data curation, Methodology, Writing – review & editing; Ole Hertel: Data curation, Methodology, Writing – review & editing; Barbara Hoffmann: Methodology, Writing – review & editing; Klea Katsouyanni: Methodology, Writing – review & editing; Matthias Ketzel: Data curation, Methodology, Writing – review & editing; Karin Leander: Resources, Writing – review & editing; Patrik K.E. Magnusson: Writing – review & editing; Gabriele Nagel: Data curation, Methodology, Writing – review & editing; Göran Pershagen: Data curation, Writing – review & editing; Debora Rizzuto: Data curation, Methodology, Writing – review & editing; Evangelia Samoli: Methodology, Software, Writing – review & editing; Rina So: Methodology, Writing – review & editing; Massimo Stafoggia: Methodology, Writing – review & editing; Anne Tjønneland: Data curation, Resources, Writing – review & editing; Gudrun Weinmayr: Methodology, Writing – review & editing; Kathrin Wolf: Data curation, Software, Methodology, Writing – review & editing; Emanuel Zitt: Methodology, Writing – review & editing; Bert Brunekreef: Conceptualization, Funding acquisition, Methodology, Project administration, Resources, Software, Supervision, Validation, Writing – review & editing; Gerard Hoek: Conceptualization, Funding acquisition, Methodology, Project administration, Supervision, Validation, Writing – review & editing; Ole Raaschou-Nielsen: Conceptualization, Data curation, Methodology, Supervision, Writing – review & editing.

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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

Data will be made available on request.

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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.2023.117230.

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