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Long-term exposure to ambient air pollution and risk of leukemia and lymphoma in a pooled European cohort☆

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Abbreviations: ELAPSE, Effects of Low-level Air Pollution: a Study in Europe; HR, hazard ratio; CI, confidence interval; $PM_{2.5}$, fine particulate matter; NO_2, nitrogen dioxide; BC, black carbon; O_3, ozone; EBV, Epstein-Barr virus; SLE, systemic lupus erythematosus; AML, acute myeloid leukemia; MGUS, Monoclonal Gammopathy of Undetermined Significance; CEANS, the *Cardiovascular Effects of Air Pollution and Noise in Stockholm*; *SDPP*, *Stockholm Diabetes Prevention Program*; SIXTY, *Stockholm Cohort of 60-year-olds*; *SALT*, *Stockholm Screening Across the Lifespan Twin Study*; SNAC-K, *the Swedish National Study on Aging and Care in Kungsholmen*; DCH, the *Diet, Cancer and Health cohort*; *DNC*, *the Danish Nurse Cohort*; *VHM&PP*, *Vorarlberg Health Monitoring and Prevention Programme*; *LUR*, land-use regression; DEHM, Danish Eulerian Hemispheric Model; PPM, Predictive Mean Matching; OR, odds ratio.

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ABSTRACT

Leukemia and lymphoma are the two most common forms of hematologic malignancy, and their etiology is largely unknown. Pathophysiological mechanisms suggest a possible association with air pollution, but little empirical evidence is available. We aimed to investigate the association between long-term residential exposure to outdoor air pollution and risk of leukemia and lymphoma. We pooled data from four cohorts from three European countries as part of the "Effects of Low-level Air Pollution: a Study in Europe" (ELAPSE) collaboration. We used Europe-wide land use regression models to assess annual mean concentrations of fine particulate matter ($PM_{2.5}$), nitrogen dioxide (NO_2), black carbon (BC) and ozone (O_3) at residences. We also estimated concentrations of $PM_{2.5}$ elemental components: copper (Cu), iron (Fe), zinc (Zn); sulfur (S); nickel (Ni), vanadium (V), silicon (Si) and potassium (K). We applied Cox proportional hazards models to investigate the associations. Among the study population of 247,436 individuals, 760 leukemia and 1122 lymphoma cases were diagnosed during 4,656,140 person-years of follow-up. The results showed a leukemia hazard ratio (HR) of 1.13 (95% confidence intervals [CI]: 1.01–1.26) per 10 $\mu g/m^3$ NO_2, which was robust in two-pollutant models and consistent across the four cohorts and according to smoking status. Sex-specific analyses suggested that this association was confined to the male population. Further, the results showed increased lymphoma HRs for $PM_{2.5}$ (HR = 1.16; 95% CI: 1.02–1.34) and potassium content of $PM_{2.5}$, which were consistent in two-pollutant models and according to sex. Our results suggest that air pollution at the residence may be associated with adult leukemia and lymphoma.

1. Introduction

Leukemia and lymphoma are the two most common forms of hematologic malignancies and their etiologies are largely unknown (Ferlay et al., 2021). Established risk factors account for only a small proportion of the overall incidence (Rodriguez-Abreu et al., 2007). Lymphoma, with an incidence rate of 2–3 cases per 100,000 persons per year and a slight male predominance, is one of the most common malignancies in the western world (Ferlay et al., 2021). Lymphoma presents with painless enlargement of lymph nodes, low-grade fever, night sweats, and unexpected weight loss. Lymphoma can occur at any age but has a distinct bimodal age group distribution with the first peak at age 15–25 years and a second peak at age 40–60 years. Known risk factors for lymphoma include past infection with Epstein-Barr virus (EBV) (Hsu and Glaser, 2000), immune suppression (Marshall et al., 2004), HIV-infection (Biggar et al., 2006a), and autoimmune conditions such as systemic lupus erythematosus (SLE) (Bernatsky et al., 2007a), rheumatoid arthritis (Klein et al., 2018), and sarcoidosis (Papanikolaou and Sharma, 2010). Leukemia is the 15th most common cancer worldwide with an age-standardized incidence rate of 6.3 for men and 4.5 for women per 100,000 (Sung et al., 2021). The main risk factors for leukemia include ionizing radiation (Zablotska et al., 2012), occupational exposure to benzene (Khalade et al., 2010), certain types of chemo- (Tarella et al., 2010) and radiation therapy (Wright et al., 2010), and genetic abnormalities such as Down syndrome (Saida, 2017). Other factors with inadequate evidence for final conclusions include obesity (Lichtman, 2010), smoking (specifically for acute myeloid leukemia [AML]) (Musselman et al., 2013; Wang et al., 2015), and exposure to pesticides (Hardell et al., 2002).

The epidemiological literature is generally in support of a positive association between air pollution exposure and leukemias and lymphomas in children (Filippini et al., 2019; Hvidtfeldt et al., 2020; Kreis et al., 2022). However, epidemiological evidence of a link in the adult population is inconsistent. A study from Denmark reported a higher risk of leukemia to be associated with 10 years mean residential exposure to $PM_{2.5}$ (Puett et al., 2020). Also, the National Health Interview Survey (NHIS) study reported positive associations between $PM_{2.5}$ exposure and leukemia mortality (Coleman et al., 2020). The $PM_{2.5}$ components black carbon (BC), ammonium (NH_4), and nitrate (NO_3) at the residential address have been associated with higher risk for AML (Taj et al., 2021c). Another Danish study reported increased risk of AML in association with nitrogen oxides (NO_x) and nitrogen dioxide NO_2 (Raaschou-Nielsen et al., 2016b), and a study from Taiwan reported an increased risk of leukemia among individuals living close to petrochemical industries (Yu et al., 2006). In contrast, other studies reported no increased risk of leukemia in association with residential and traffic related exposure (Raaschou-Nielsen et al., 2011; Winters et al., 2015). Prior epidemiological studies of air pollution and lymphoma have reported inconsistent results. An occupational study from Italy among bus drivers and maintenance workers exposed to high air pollution levels at work, reported an increased incidence of lymphoma (Merlo et al., 2010). The NHIS study reported positive associations between $PM_{2.5}$ exposure and lymphoma mortality in the general US population (Coleman et al., 2020). A population-based study in Germany showed that long-term exposure to air pollution was associated with the incidence of Monoclonal Gammopathy of Undetermined Significance (MGUS), a plasma cell disorder which has been associated with non-Hodgkin lymphomas (Orban et al., 2017). Various other studies of general populations have found no or a decrease in risk among individuals after exposure to air pollution at the residential address in Denmark (Taj et al., 2021a; Taj et al., 2020b) or to industrial waste gas emissions in China (Cong, 2018).

In this study, we examine the association between long-term exposure to air pollution and risk of leukemia and lymphoma in a large study combining four European cohorts with an average follow-up of 18.8 years.

[1] Contributed equally.

2. Materials and methods

2.1. Study population

We used data from "The Effects of Low-Level Air Pollution: a Study in Europe" (ELAPSE) collaboration (Hvidtfeldt et al., 2021b; Strak et al., 2021). Four cohorts from three countries had available data on leukemia and lymphoma incidence and relevant confounders. These included: 'the *Cardiovascular Effects of Air Pollution and Noise in Stockholm'* (CEANS) from Sweden, comprising four sub cohorts: the *Stockholm Diabetes Prevention Program* (SDPP) (Eriksson et al., 2008), the *Stockholm Cohort of 60-year-olds* (SIXTY) (Wändell et al., 2007), the *Stockholm Screening Across the Lifespan Twin Study* (SALT) (Magnusson et al., 2013) and *the Swedish National Study on Aging and Care in Kungsholmen* (SNAC-K) (Lagergren et al., 2004); 'the *Diet, Cancer and Health cohort'* (DCH) (Tjønneland et al., 2007), and the *Danish Nurse Cohort* (DNC) (Hundrup et al., 2012) from Denmark, entailing two sub cohorts from surveys conducted in 1993 and 1999. Finally, we used data from the Austrian '*Vorarlberg Health Monitoring and Prevention Programme'* (VHM&PP) cohort. Data from all cohorts were pooled and stored on a secure server in Utrecht University, the Netherlands. Covariates from each cohort have been harmonized using a common codebook. Participants were free of cancer at baseline (not counting non-melanoma skin cancer). See Table A1 for a detailed description of the cohorts and sub cohorts.

2.2. Outcome

Leukemia and lymphoma cases were identified in cancer registries. We identified lymphoma cases using the International Classification of Diseases 10 (ICD-10) codes C81–C88 and the ICD-9 codes 200–202. Lymphomas were specified into Hodgkin (ICD-10: C81; ICD-9: 201) and non-Hodgkin (ICD-10: C82–C88; ICD-9: 200, 202), and follicular (ICD-10: C82) and non-follicular lymphoma (ICD-10: C83). Leukemia cases were identified using ICD-10 codes C91–C95 and ICD-9 codes 204–208. Leukemia subtypes were categorized as lymphoid (ICD-10: C91 and ICD-9: 204) and myeloid leukemia (ICD-10: C92 and ICD-9: 205).

2.3. Air pollution exposure assessment

We estimated the annual average concentrations of air pollutants NO_2, $PM_{2.5}$, BC, and O_3 (warm season: June, July and August) using Europe-wide hybrid land-use regression (LUR) models for the year 2010. The model was described in detail previously (De Hoogh et al., 2018). In brief, the hybrid model combined satellite observations, dispersion model estimates, traffic and land use variables, and air pollution monitoring data for 2010. Potential predictor variables included road density, population, elevation, and land use variables covering residential, industry, ports, urban green space, total built up land, and natural land (Chen et al., 2020). The rationale for choosing 2010 as the primary exposure was that this was the earliest year with sufficient European monitoring data of $PM_{2.5}$ to develop empirical air pollution models. We previously documented that predictions from a model developed based on monitoring data in the year 2000 correlated well with the 2010 model (De Hoogh et al., 2018). Europe-wide BC and elemental composition were included from the research project ESCAPE with study-specific particle collection in 2009 and 2010 (Beelen et al., 2015). We also assessed eight $PM_{2.5}$ elemental components representing major exposure sources: for non-tailpipe traffic emissions, copper (Cu), iron (Fe), and zinc (Zn); for long-range transport of secondary inorganic aerosols, sulfur (S); for mixed oil burning/industry, nickel (Ni) and vanadium (V), for crustal material, silicon (Si) and for biomass burning, potassium (K) (Chen et al., 2020). Air pollution estimates at a 100m × 100m resolution were linked to the study participant's baseline residential address. Exposure distributions are presented as box-plots in Figure A1. Annual mean concentrations, assessed at the residential addresses of participants by the Danish Eulerian Hemispheric Model (DEHM) (Brandt et al., 2012), were used to extrapolate the 2010 concentrations to each year from enrollment until end of follow-up, with resolutions ranging from 150 km × 150 km to 5.56 km × 5.56 km.

2.4. Statistical analysis

We used Cox proportional hazards models with age as underlying time scale to examine the associations between air pollution and risk of leukemia and lymphoma. Follow-up started at enrollment and ended at the time of any cancer (except for melanoma skin cancer), or date of death, date of emigration, loss to follow-up, or the end of follow-up (between 2011 and 2015 for different cohorts), whichever occurred first.

We determined potential confounders a priori based on the literature on suspected risk factors of leukemia or lymphoma and data availability. We adjusted for potential confounders in three steps: model 1 included age (as the time axis), sub-cohort (as strata), sex (as strata), and year of enrollment. Sub-cohort strata were used to account for heterogeneity in baseline rates between cohorts; model 2 further adjusted for individual-level covariates, including smoking status (never, former, current), BMI in categories (<18.5, 18.5–24.9, 25.0–29.9, and >30.0 kg/m^2), and employment status (employed vs. unemployed); model 3 (main model) further adjusted for area-level mean income in 2001. We used complete case analyses meaning that participants with missing exposure or incomplete information on any covariate were excluded from all analyses. Each air pollutant was included as a linear term and hazard ratios

Table 1
Descriptive statistics for participants at baseline and at the end of follow-up.

Sub cohort	Population size	N Main model 3 (%)	Leukemia cases	Lymphoma cases	Female (%)	Mean age at baseline (SD)	Employed (%)	BMI (%) 18.5–24.9	Current smokers (%)	Area level income[a] (Mean ± SD)
Pooled cohort	276,978	247,436 (89)	760	1122	59	47.2 ± 14.3	73	51	27	22095 ± 3173.9
CEANS-SDPP	7,835	7,349 (94)	17	22	59	47.0 ± 4.9	91	48	26	24338 ± 4223.8
CEANS-SIXTY	4,180	3,705 (89)	26	11	50	60.0 ± 0.0	68	35	21	24659 ± 6839.7
CEANS-SALT	6,724	5,860 (87)	24	14	53	57.8 ± 10.6	65	59	20	25305 ± 6600.2
CEANS-SNACK	3,248	2,431 (75)	10	12	62	72.6 ± 10.4	24	44	15	28660 ± 2223.1
DCH	56,308	54,978 (98)	290	362	52	56.7 ± 4.4	78	43	36	20184 ± 3389.9
DNC-1993	19,664	16,443 (84)	83	64	100	56.3 ± 8.5	69	69	38	19222 ± 2566.1
DNC-1999	8,769	7,684 (88)	15	11	100	47.9 ± 4.3	95	68	28	19004 ± 2438.9
VHM_PP	170,250	148,986 (88)	295	626	55	41.5 ± 14.9	71	55	23	22870 ± 1657.8

[a] The spatial scale varied from smaller neighborhoods and city districts (CEANS) to municipalities (DCH, DNC, VHM_PP).

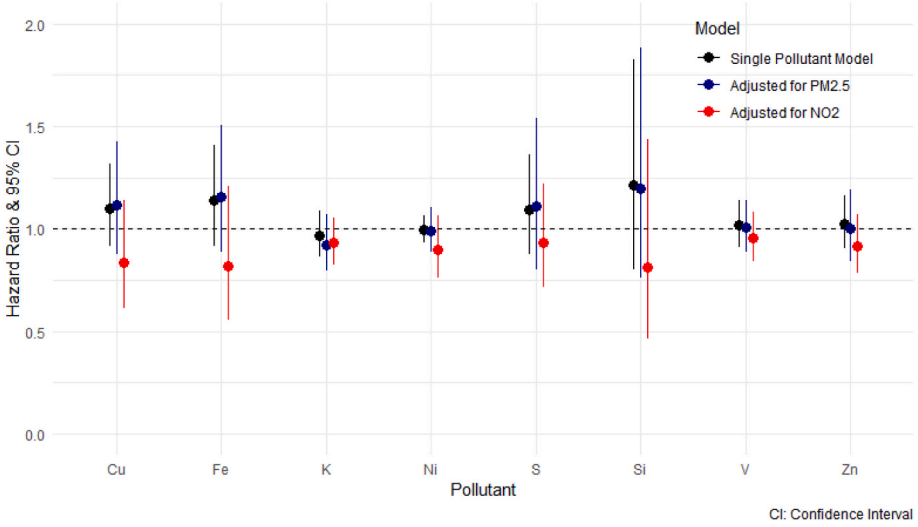

Fig. 1. Association between $PM_{2.5}$ elements and risk for leukemia
Abbreviation: Cu, cupper; Fe, iron; Zn, zinc; S, sulfur; Ni, nickel; V, vanadium; Si, Silicon; K, potassium.
Associations adjusted for age (time scale), sex (strata), sub-cohort (strata), and calendar year of baseline, smoking status, employment status, and mean income at area level in 2001. (For interpretation of the references to colour in this figure legend, the reader is referred to the Web version of this article.)

(HRs) along with 95% confidence intervals (CIs) were calculated per fixed increments of $PM_{2.5}$–5 $\mu g/m^3$, NO_2 – 10 $\mu g/m^3$, BC – 0.5*10^{-5}/m, O_3 – 10 $\mu g/m^3$, $PM_{2.5}$ Cu – 5 ng/m^3, $PM_{2.5}$ Fe – 100 ng/m^3, $PM_{2.5}$ K–50 ng/m^3, $PM_{2.5}$ Ni – 1 ng/m^3, $PM_{2.5}$ S–200 ng/m^3, $PM_{2.5}$ Si – 100 ng/m^3, $PM_{2.5}$ V–2 ng/m^3, $PM_{2.5}$ Zn – 10 ng/m^3. Increments selected for pollutants were in accordance with previous ESCAPE and ELAPSE studies (Beelen et al., 2015; Hvidtfeldt et al., 2021a). The increments were obtained in ESCAPE as the rounded average difference between the 90th and 10th percentile in the included study areas. We also analyzed associations between air pollution and subcategories of leukemia and lymphoma.

In addition to the single pollutant models, we ran two-pollutant models for $PM_{2.5}$, NO_2, BC, and O_3. We adjusted the $PM_{2.5}$ element concentration for total $PM_{2.5}$ concentration to help understand the independent effect of each individual elemental component. We also adjusted the $PM_{2.5}$ element concentration for NO_2 to try to isolate the individual component effect from the effects of traffic exhaust emission. To evaluate the shape of the exposure-response function for air pollution exposure and leukemia or lymphoma incidence, we used natural cubic splines with two degrees of freedom with knots at the 10th, 50th, and 90th percentiles (Figures A.2–A.3). We also ran subset analyses for subpopulations with exposure below predefined cut-off concentrations for $PM_{2.5}$:<25 $\mu g/m^3$, <20 $\mu g/m^3$, <15 $\mu g/m^3$, <12 $\mu g/m^3$, <10 $\mu g/m^3$; for NO_2: <40 $\mu g/m^3$, <30 $\mu g/m^3$, <20 $\mu g/m^3$; for BC: <3.0 $\mu g/m^3$, <2.5 $\mu g/m^3$, <2.0 $\mu g/m^3$, <1.5 $\mu g/m^3$, <1 $\mu g/m^3$; and for O_3: <120 $\mu g/m^3$ < 100 $\mu g/m^3$ < 80 $\mu g/m^3$.

Sensitivity analyses included: 1) Assessment of associations between NO_2, $PM_{2.5}$, BC, and O_3 and leukemia and lymphoma incidence when excluding one cohort at a time and for each of the cohorts separately; 2) examination of associations with back extrapolated estimates of NO_2, $PM_{2.5}$ BC, and O_3; 3) examination of the influence of further adjustment for blue-collar work, which was available in all cohorts except for DCH, and further adjustment for educational level (low, medium, or high) and alcohol intake, which were available in all cohorts except VHM&PP; 4) Investigating effect measure modification by sex and smoking status by including an interaction term in the model tested by the Wald test; and 5) examination of the influence of further adjustment for smoking pack-years, which was available in all cohorts except for VHM&PP. 6) We investigated if the main results based on complete case analyses differed when using multiple imputation for missing values of co-variates. We used 50 iterations to create imputed datasets, which were then pooled together to obtain a single dataset with imputed values. We used the mice package in R and the Predictive Mean Matching (PMM) for continuous variable and Polynomial Regression (Polyreg) for categorical variables. All analyses were performed in R version 3.4.0.

3. Results

A total of 276,978 participants were recruited in the period 1985–2005 from four cohorts. We excluded 9,318 (3.4%) participants with cancer before enrollment or missing air pollution data and 20,224 (7.3%) participants with missing information on potential confounders (Table A1). In total, the pooled study population comprised 247,436 individuals, among whom 760 were diagnosed with leukemia and 1,122 with lymphoma during 4,656,140 person-years of follow-up (Table 1).

The mean age at baseline was 47.2 years with variation across (sub-) cohorts (Table 1 and Table A1), while 59% of the pooled cohort were women, 27% were current smokers, 73% were employed, and 51% had a normal BMI (Table 1). The mean concentrations of pollutants estimated for 2010 varied between the cohorts with mean levels of $PM_{2.5}$, NO_2, BC, and O_3 of 14.3 $\mu g/m^3$, 23.1 $\mu g/m^3$, 1.5 $10^{-5}m^{-1}$ and 86.8 $\mu g/m^3$, respectively (Table A2 and Figure A1). $PM_{2.5}$ was moderately to highly correlated with BC and NO_2, and concentrations of $PM_{2.5}$ and O_3 were negatively correlated (Table A3). The correlations between $PM_{2.5}$ and its elements were moderate to low, whereas the correlation between NO_2 and the elements $PM_{2.5}$ Cu, $PM_{2.5}$ Fe, $PM_{2.5}$ Si and $PM_{2.5}$ Zn was moderate to high (Tables A.4–A.5).

For leukemia, we observed HRs of 1.13 (95% CI: 1.01–1.26) per 10 $\mu g/m^3$ NO_2, 1.05 (95% CI: 0.87–1.26) per 5 $\mu g/m^3$ $PM_{2.5}$, 1.09 (95% CI: 0.97–1.22) per 0.5 $10^{-5}m^{-1}$ BC, and 0.95 (95% CI: 0.80–1.13) per 10 $\mu g/m^3$ O_3, respectively, in the fully adjusted model (Table 2). Adjustment for potential confounders had only a minor influence on the HRs. The HR for NO_2 remained elevated in two-pollutant models with adjustment for $PM_{2.5}$, BC, or O_3, for example, with an HR of 1.17 (95% CI: 1.02–1.35) in a model with $PM_{2.5}$ (Table 3). An elevated HR was observed for the two subtypes of leukemia in relation to NO_2 exposure, with HRs of 1.15 (95% CI: 0.99–1.33) for lymphoid leukemia and 1.12 (95% CI: 0.92–1.35) for myeloid leukemia, and for myeloid leukemia in relation to BC exposure (HR: 1.11 [95% CI: 0.91–1.35]). The remaining HRs for subtypes of leukemia showed HRs close to one (Table 4).

The HRs for lymphoma were 1.00 (95% CI: 0.90–1.10) per 10 $\mu g/m^3$ NO_2, 1.16 (95% CI: 1.01–1.33) per 5 $\mu g/m^3$ $PM_{2.5}$, 1.00 (95% CI:

Table 2
Associations between long-term exposure to air pollution and risk for leukemia and lymphoma.

Exposure	Increment	Model 1	Model 2	Model 3
		HR (95% CI)	HR (95% CI)	HR (95% CI)
Leukemia				
NO_2	10 μg/m^3	1.14 (1.02–1.28)	1.14 (1.02–1.27)	1.13 (1.01–1.26)
$PM_{2.5}$	5 μg/m^3	1.06 (0.88–1.27)	1.05 (0.88–1.26)	1.05 (0.87–1.26)
BC	0.5 $10^{-5}m^{-1}$	1.10 (0.98–1.23)	1.10 (0.98–1.23)	1.09 (0.97–1.22)
O_3	10 μg/m^3	0.95 (0.80–1.12)	0.96 (0.81–1.13)	0.95 (0.80–1.13)
Lymphoma				
NO_2	10 μg/m^3	1.03 (0.94–1.14)	1.03 (0.93–1.13)	1.00 (0.90–1.10)
$PM_{2.5}$	5 μg/m^3	1.17 (1.02–1.34)	1.16 (1.02–1.34)	1.16 (1.01–1.33)
BC	0.5 $10^{-5}m^{-1}$	1.03 (0.93–1.14)	1.02 (0.93–1.13)	1.00 (0.91–1.11)
O_3	10 μg/m^3	1.06 (0.92–1.23)	1.07 (0.93–1.24)	1.07 (0.93–1.23)

Abbreviation: HR, hazard ratio; CI, confidence interval; NO_2, nitrogen dioxide; $PM_{2.5}$, particulate matter with aerodynamic diameter of less than 2.5 μm; BC, black carbon; O_3, ozone.
Model 1 adjusting for age (time scale), sex (strata), sub-cohort (strata), and calendar year at baseline.
Model 2 adjusting for age (time scale), sex (strata), sub-cohort (strata), and calendar year at baseline, smoking status, employment status, and BMI.
Model 3 adjusting for age (time scale), sex (strata), sub-cohort (strata), and calendar year at baseline, smoking status, employment status, BMI, and mean income at area level in 2001.

0.91–1.11) per 0.5 $10^{-5}m^{-1}$ BC, and 1.07 (95% CI: 0.93–1.23) per 10 μg/m^3 O_3. Adjustment for potential confounders had only a minor influence on the HRs (Table 2). The HRs for $PM_{2.5}$ and O_3 increased in two pollutant models with estimates for $PM_{2.5}$ of 1.26 (95% CI: 1.06–1.49), 1.28 (95% CI: 1.07–1.53), and 1.31 (95% CI: 1.11–1.56) after adjustment for NO_2, BC, and O_3, respectively (Table 5). Analyses of four subcategories of lymphoma showed several positive associations, for example between $PM_{2.5}$ and Non-Hodgkin lymphoma (HR: 1.15 [95% CI: 0.99–1.32] per 5 μg/m^3) and some negative, for example in relation to follicular lymphoma with HRs of 0.80 (95% CI: 0.61–1.05) per 10 μg/m^3 NO_2 and 0.79 (95% CI: 0.60–1.04) per 0.5 BC $10^{-5}m^{-1}$ BC (Table 4).

We observed an elevated HR for leukemia in relation to $PM_{2.5}$-Cu, Fe, S, and Si, which was attenuated following adjustment for NO_2 (Fig. 1). For lymphoid leukemias, $PM_{2.5}$ content analyses showed HRs of 1.10 (95% CI: 0.87–1.41) per 5 ng/m^3 Cu, 1.15 (95% CI: 0.87–1.53) per 100 ng/m^3 Fe, and 1.13 (95% CI: 0.65–1.96) per 100 ng/m^3 Si (Table A.6). For myeloid leukemias, we observed HRs of 1.09 (95% CI: 0.81–1.47) per 5 ng/m^3 Cu, 1.13 (95% CI: 0.79–1.61) per 100 ng/m^3 Fe, 1.19 (95% CI: 0.83–1.71) per 200 ng/m^3 S, 1.54 (95% CI: 0.79–3.02) per 100 ng/m^3 Si, 1.10 (95% CI: 0.92–1.31) per 2 ng/m^3 V, and 1.10 (95% CI: 0.89–1.34) per 10 ng/m^3 Zn, respectively. $PM_{2.5}$-K showed an HR of 1.10 (95% CI: 1.01–1.20) per 50 ng/m^3 in association with lymphoma and similar results in two-pollutant models (Fig. 2). $PM_{2.5}$-K also showed associations with Hodgkin lymphoma (HR: 1.20 [95% CI: 0.89–1.63] per 50 ng/m^3), Non-Hodgkin lymphoma (HR: 1.09 [95% CI: 0.99–1.19] per 50 ng/m^3), and follicular lymphoma (HR: 1.28 [95% CI: 1.01–1.63] per 50 ng/m^3) (Table A.7). $PM_{2.5}$ content of Cu, Fe, S, and Zn showed positive relationships with Hodgkin lymphoma, however with wide confidence intervals. $PM_{2.5}$ content of Si showed an inverse relationship with lymphoma, which was enhanced in two-pollutant models (Fig. 2). The negative association seemed driven by Non-Hodgkin and follicular lymphomas with HRs of 0.74 (95% CI: 0.50–1.08) and 0.38 (95% CI: 0.13–1.09), respectively. Subset analyses indicated the lowest HRs for the participants with the lowest exposure (except O_3 and lymphoma), but the confidence intervals were wide (Tables A.8–A.9).

Supplement Tables A.10 and A.11 show that the association between NO_2 and leukemia in the pooled cohort also existed in each of the four cohorts and the result for the pooled cohort was robust to the exclusion of any of the cohorts. In contrast, the association between $PM_{2.5}$ and lymphoma showed different results in the different cohorts and was sensitive to the exclusion of the VHM&PP cohort, which contributed more than half the cases (appsec1Table A.11). In individual analyses of each cohort, an HR of 1.23 (95% CI: 1.05–1.44) was observed for VHM&PP and negative associations for the remaining cohorts (Table A.10). The uncertainty of the HRs in these individual cohorts was, however, large because of the small number of cases.

Sensitivity analyses showed that the HR for leukemia observed when

Table 3
Associations between long-term exposure to air pollution and risk for leukemia based on single and two pollutant models.

Exposure	Single pollutant HR [a]	HR adjusted for NO_2	HR adjusted for $PM_{2.5}$	HR adjusted for BC	HR adjusted for O_3
NO_2	1.13 (1.01–1.26)	–	1.17 (1.02–1.35)	1.29 (0.99–1.68)	1.19 (1.02–1.39)
$PM_{2.5}$	1.05 (0.87–1.26)	0.90 (0.71–1.13)	–	0.95 (0.75–1.20)	1.03 (0.83–1.28)
BC	1.09 (0.97–1.22)	0.86 (0.65–1.13)	1.11 (0.96–1.29)	–	1.11 (0.95–1.29)
O_{3w}	0.95 (0.80–1.13)	1.13 (0.90–1.42)	0.97 (0.79–1.18)	1.05 (0.84–1.31)	–

[a] Model adjusting for age (time scale), sex (strata), sub-cohort (strata), and calendar year of baseline, smoking status, employment status, BMI, and mean income at area level in 2001.

Table 4
Associations between long-term exposure to air pollution and risk for leukemia and lymphoma subcategories.

Exposure		Leukemia		Lymphoma			
		Lymphoid (433 cases)	Myeloid (276 cases)	Hodgkin (76 cases)	Non-Hodgkin (1046 cases)	Follicular (148 cases)	Non-Follicular (487 cases)
	Increment	Model 3 [a]	Model 3 [a]	Model 3 [a]	Model 3 [a]	Model 3 [a]	Model 3 [a]
		HR (95% CI)	HR (95% CI)	HR (95% CI)	HR (95% CI)	HR (95% CI)	HR (95% CI)
NO_2	10 μg/m^3	1.15 (0.99–1.33)	1.12 (0.92–1.35)	1.03 (0.69–1.53)	1.00 (0.90–1.11)	0.80 (0.61–1.05)	0.96 (0.82–1.13)
$PM_{2.5}$	5 μg/m^3	1.05 (0.83–1.34)	1.02 (0.76–1.37)	1.31 (0.79–2.16)	1.15 (0.99–1.32)	1.13 (0.77–1.65)	1.05 (0.86–1.27)
BC	0.5 $10^{-5}m^{-1}$	1.07 (0.92–1.25)	1.11 (0.91–1.35)	1.08 (0.72–1.62)	1.00 (0.90–1.11)	0.79 (0.60–1.04)	0.96 (0.81–1.12)
O_{3w}	10 μg/m^3	0.96 (0.77–1.19)	0.94 (0.70–1.24)	1.28 (0.71–2.29)	1.05 (0.91–1.22)	1.22 (0.82–1.88)	1.18 (0.94–1.47)

[a] Model 3 adjusting for age (time scale), sex (strata), sub-cohort (strata), and calendar year of baseline, smoking status, BMI, employment status, and mean income on a neighborhood level in 2001.

Table 5
Associations between long-term exposure to air pollution and risk for lymphoma based on single and two pollutant models.

Exposure	Single pollutant HR [a]	HR adjusted for NO_2	HR adjusted for $PM_{2.5}$	HR adjusted for BC	HR adjusted for O_3
NO_2	1.00 (0.90–1.10)	–	0.90 (0.80–1.02)	0.99 (0.78–1.24)	1.07 (0.93–1.23)
$PM_{2.5}$	1.16 (1.01–1.33)	1.26 (1.06–1.49)	–	1.28 (1.07–1.53)	1.31 (1.11–1.56)
BC	1.00 (0.91–1.11)	1.02 (0.80–1.29)	0.89 (0.78–1.02)	–	1.07 (0.93–1.24)
O_{3w}	1.07 (0.93–1.23)	1.14 (0.93–1.40)	1.26 (1.06–1.51)	1.15 (0.94–1.40)	–

[a] Model adjusting for age (time scale), sex (strata), sub-cohort (strata), and calendar year of baseline, smoking status, employment status, BMI, and mean income at area level in 2001.

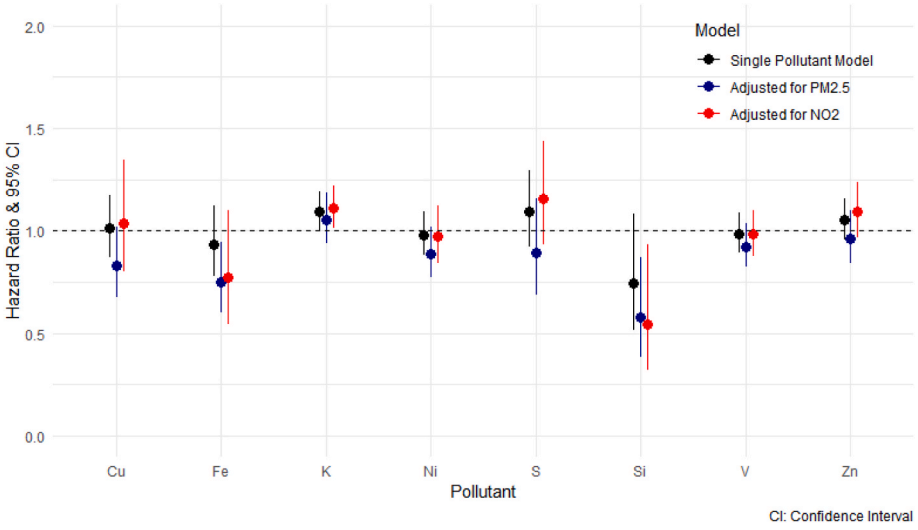

Fig. 2. Association between $PM_{2.5}$ elements and risk for lymphoma
Abbreviation: Cu, cupper; Fe, iron; Zn, zinc; S, sulfur; Ni, nickel; V, vanadium; Si, Silicon; K, potassium.
Associations adjusted for age (time scale), sex (strata), sub-cohort (strata), and calendar year of baseline, smoking status, employment status, and mean income at area level in 2001. (For interpretation of the references to colour in this figure legend, the reader is referred to the Web version of this article.)

using back-extrapolated NO_2 exposure to the year of enrollment was similar to the HR observed for NO_2 exposure estimated for 2010 (Table A.12). This also applied for lymphoma and $PM_{2.5}$. Further adjustment of the main results of Table 2 for blue/white collar status, alcohol intake, pack-years of smoking, and education had virtually no influence on the HRs (Tables A.13–A.14). The results of the analyses of effect modification are presented in Table A.15. We observed an elevated HR for leukemia with higher NO_2 exposure in men, but not in women (P-value for interaction = 0.003). Similar tendencies were observed for $PM_{2.5}$ and BC, but with overlapping confidence bounds. The HRs for lymphoma did not vary by sex. In analyses stratified by smoking, we observed elevated HRs for leukemia in both never- and current smokers in relation to NO_2 and BC exposure. For $PM_{2.5}$, elevated HRs were observed among previous and current smokers, however, with wide confidence bounds (P-value for interaction = 0.86). No differences across smoking status were observed for O_3 exposure. The results for lymphoma showed elevated HRs in both never- and current smokers with higher $PM_{2.5}$ exposure, whereas only elevated HRs were observed in never smokers in relation to higher exposure to NO_2 and BC. For O_3, an elevated HR was observed in current smokers. Finally, applying multiple imputation instead of complete case analyses provided very similar results (Tables A.16–A.18).

4. Discussion

In this pooled analysis of 247,436 adults of four European cohorts, we found that NO_2 concentration at the residence was associated with an increased risk of leukemia; the result was robust in two-pollutant models and consistent across cohorts and according to smoking status. Sex-specific analyses suggested that the association was confined to the male population. We also found associations between $PM_{2.5}$, and the potassium content of $PM_{2.5}$, and elevated risk of lymphoma, which did not vary according to sex.

Few studies have analyzed associations between ambient air pollution and adult leukemia and lymphoma. Recently, Puett et al. used data from the Danish Cancer Register and reported an odds ratio (OR) of 1.17 (95% CI: 1.03, 1.32) for adult leukemia in association with 10-year average exposure to $PM_{2.5}$ per 5 $\mu g/m^3$ (Puett et al., 2020). In this study, we found a similar association but lower in magnitude. Another recent study from Denmark reported that the $PM_{2.5}$ constituents BC and secondary inorganic aerosols, and its components NO_3 and NH_4, were associated with adult leukemia (Taj et al., 2021b). Both studies reported no association of leukemia with NO_2 exposure. A prior study from Denmark also reported no elevated risk of myeloid and lymphocytic leukemia in association with NO_2 (Raaschou-Nielsen et al., 2016a). In the NHIS, a positive association was reported between $PM_{2.5}$ exposure and leukemia mortality (Coleman et al., 2020), whereas a study based on the American Cancer Prevention Study II (CPS-II) cohort found no association between leukemia mortality and exposure to $PM_{2.5}$ and NO_2 - and a negative association with O_3 (Turner et al., 2017). A study from Italy by Parodi et al. reported a higher risk of adult leukemia in association with living in highly polluted areas (Parodi et al., 2015). Unlike our findings and some of the studies mentioned above, a study from Canada reported an inverse association between NO_2 and risk of adult leukemia (Winters et al., 2015). The study used case-control design and the authors suggested selection bias as a possible explanation.

Two large population-based studies from Denmark reported no association between outdoor air pollution and the risk of adult Hodgkin and non-Hodgkin lymphoma (Taj et al., 2021a; Taj et al., 2020a). The Danish study investigating non-Hodgkin lymphoma reported a higher

risk of follicular lymphoma (OR 1.15, 95% CI: 0.98, 1.34) in association with $PM_{2.5}$ exposure, which corresponds to the result of the present study (HR 1.13, 95% CI: 0.77, 1.65). In the NHIS, positive associations were observed between exposure to $PM_{2.5}$ and Hodgkin and Non-Hodgkin lymphoma mortality (Coleman et al., 2020) and results from the CPS-II cohort showed elevated HR's of Hodgkin lymphoma mortality in relation to exposure to $PM_{2.5}$, NO_2, and O_3 (Turner et al., 2017). Our results for element content of $PM_{2.5}$ suggested an association between potassium (K) and overall lymphoma and between Cu, Fe, S, and Zn exposure and Hodgkin lymphoma; potassium is a marker of biomass burning, whereas Cu, Fe, and Zn represent non-tailpipe traffic emissions and S is a marker of long-range transport of secondary inorganic aerosols. Although a number of epidemiological studies have investigated adult lymphoma in association with unspecific air pollution assessed by crude methods (Cocco et al., 2010; Fritschi et al., 2005a; Fritschi et al., 2005b; Iavarone et al., 2018; Kane and Newton, 2010; Pronk et al., 2013) none of these studies allows for an interpretation of the results in relation to the elemental content of the particulate matter air pollution. The results of the Danish study on Hodgkin lymphoma, did not show overall associations with air pollutants and lymphoma, but in sub-analyses separating 'classical' Hodgkin Lymphoma, with large biannulate Reed-Sternberg cells, from 'nodular' Hodgkin Lymphoma, with predominant lymphocytes, a positive association was observed for secondary inorganic aerosols – and particularly SO_4 – and the classic Hodgkin lymphomas (Taj et al., 2021a). Our results also indicated a negative association for lymphoma with exposure to $PM_{2.5}$ content of Si. Sensitivity analyses of individual cohorts revealed that the association between $PM_{2.5}$ and lymphoma was mainly driven by the large VHM&PP cohort. This finding could indicate inherent differences between subjects in these cohorts for which we were unable to account, or alternatively, since the VHM&PP contributes with the highest $PM_{2.5}$-values among all cohorts (mean = 15.7, SD = 2.7), these findings could suggest indications of a threshold below which $PM_{2.5}$ does not affect the risk of lymphoma. In the subset analysis, such a threshold was observed at $PM_{2.5}$ concentration values below 10 $\mu g/m^3$. Another potential explanation could be differences in the composition of the $PM_{2.5}$ mass between cohorts, with VHM&PP being above average in the Cu, Fe, Zn, and K elemental content of $PM_{2.5}$ and below for V and Ni. The HR for $PM_{2.5}$ and lymphoma was strengthened following adjustment for each of the other main pollutants. This finding could suggest a strong independent effect of $PM_{2.5}$ on lymphoma risk - or it could be a result of differential measurement error between these pollutants, suggesting that $PM_{2.5}$ was estimated with the highest precision (Evangelopoulos et al., 2020). In analyses of other outcomes within the ELAPSE project, $PM_{2.5}$ estimates have been sensitive to adjustment for NO_2, which speaks against one being measured with more precision than the other. We have not been able to fully analyze the complex measurement error structure in the data (Brunekreef et al., 2021).

Various pathophysiological mechanisms could suggest a possible association between air pollution and the risk of leukemia and lymphoma. Hematopoietic stem cells are pluripotent cells, which can differentiate into erythrocytes, leucocytes, and platelets (Jagannathan-Bogdan and Zon, 2013). Numerous growth factors and cytokines regulate this complex process, and both in vitro and in vivo evidence suggest that exposure to air pollution can alter this process. An in vitro study showed that exposure to long-term low concentration of fine particulate matter ($PM_{2.5}$) resulted in the release of various inflammatory cytokines and ROS-mediated STAT3 activation of human myeloid leukemia cells (Jin et al., 2016). It has been shown that air pollution exposure mutates the gene related to circulatory cytokines and other regulatory markers (Lee and Yang, 2012). This mechanism can increase the incidence and progression of leukemia by cytokine expression (Chen et al., 2018). Another in vitro study exposed human cells to benzene and its metabolites, and showed chromosomal changes similar to those observed in leukemia; the study showed an exposure-response association with more changes at higher exposure levels (Zhang et al., 2011). The present study showed a higher risk of lymphoma among individuals with higher concentrations of $PM_{2.5}$ at their residence. A biological explanation for this finding might relate to PM exposures' ability to interfere with apoptosis of the normal cell cycle. Apoptosis is a main control mechanism of hematopoiesis, and any anomaly in this process might result in leukemia and lymphoma (Bertolini et al., 2000). In vitro evidence shows that exposure to PM suppresses apoptosis and results in uncontrolled cell proliferation. The suppression of apoptosis is a direct result of the immunoglobulin heavy chain gene's translocation on chromosome 14 with the bcl-2 gene on chromosome 18 t (14; 18) due to PM exposure (Dagher et al., 2007b), and this can lead to leukemia and lymphoma. Classical Hodgkin-lymphoma is – as mentioned above - characterized by Reed-Sternberg cells. The presence of Reed-Sternberg cells depicts that these cells have not undergone successful immunoglobulin gene rearrangement and are, therefore, destined for apoptosis. NF-kB is a light chain immunoglobulin which is present in the cytoplasm, and it activates apoptosis of Reed-Sternberg cells. An in-vitro study of $PM_{2.5}$ exposure in human epithelial lung cells exhibited that $PM_{2.5}$ exposure caused the inactivation of NF-kB inhibitory kappa B (IκB-α) (Dagher et al., 2007a). Overexpression of IκB-α has been shown in several lymphoma cell lines (Benharroch et al., 2016; Cabannes et al., 1999; Morotti et al., 2017). A population based study from Germany reported unspecific activation of the adaptive immune system (serum free light chains FLC) with residential exposure of air pollution (Ohlwein et al., 2021).

The present study has several strengths. We had access to four European cohorts from three European countries and pooled data including detailed information on individual level characteristics, such as smoking status, BMI, and employment status as well as area level socioeconomic status. For exposure, we used Europe-wide air pollution models incorporating outputs from chemical transport models and satellite data (Chen et al., 2020; De Hoogh et al., 2018). The ELAPSE collaboration ensured comparable exposure estimates for the entire study population. However, utilizing modeled exposure estimates will imply some degree of exposure misclassification, which we expect to be non-differential and thus likely affect the HRs towards null. Our exposure was modeled for the year 2010 and applied to the baseline addresses; the cohorts had their baselines during the 1990's with follow-up until 2011–2015. Our exposure, therefore, represents exposure at the end of follow-up. The rationale of using exposure at the end of the follow-up period is that the spatial contrast is stable for at least a decade, implying that highly exposed locations according to the 2010 model were also highly exposed historically (De Hoogh et al., 2018), consistent with the previous European studies on air pollution exposure, which have reported stable spatial distribution of pollutants over past several years (Beelen et al., 2007; Gulliver et al., 2011). Further, we performed sensitivity analysis utilizing back-extrapolated exposure to the baseline year and the HRs for NO_2 and leukemia, and $PM_{2.5}$ and lymphoma, were robust to this back-extrapolation.

Major limitations include lack of information on some factors previously linked with leukemia and lymphoma. These risk factors include family history (Skibola et al., 2014), history of auto immune condition such as SLE (Bernatsky et al., 2007b), exposure to ionizing radiation, and history of EBV (Hsu and Glaser, 2000), HIV (Biggar et al., 2006b), Hep-C (Hartridge-Lambert et al., 2012) and HHV-8 viral infection (Sanchez et al., 2020). Overall prevalence of SLE, Hep-C and HIV is fairly low in the European population, and we would expect a limited effect on the results. Further, we had no information about air pollution inside the residences. We have undertaken many analyses and cannot rule out that some of our findings are due to chance. Therefore, we consider the results of our eight main analyses (all leukemia and all lymphoma, $PM_{2.5}$, NO_2, BC and O_3, fully adjusted models) most reliable, whereas we consider the results from the analyses of subcategories of leukemia and lymphoma, two-pollutant models and from models with more crude adjustment as more likely to be affected by chance. This seems consistent with three of such sub-analyses showing statistically significant

lower risk in association with air pollution. There are a large number of leukemia and lymphoma subtypes and the categorization has changed over time. Our analyses of subcategories were limited by both the level of specification in the ICD-9 and ICD-10 coding system, and by the need for enough cases in each subcategory for reliable analyses with sufficient statistical power. Therefore, several of the categories analyzed consisted of various disease subtypes, which might be associated differently with air pollution. Grouping together subtypes being differentially associated with air pollution may have masked stronger associations for some of the subtypes.

Our study population included European populations of primarily Caucasians, which may limit generalizability to populations with another genetic constitution.

5. Conclusions

Our results suggest that the risk of adult leukemia and lymphoma may be associated with air pollution at the residential address.

Credit author statement

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Ethics approval and consent to participate

This study involved no contact with the study population. The analyses were undertaken in a secure IT environment where no individual level data can be retrieved. All included cohort studies were approved by the medical ethics committees in their respective countries.

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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

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