Received: 23 January 2021 | Revised: 25 May 2021 | Accepted: 16 June 2021

DOI: 10.1002/ijc.33743

CANCER EPIDEMIOLOGY

IJC International Journal of Cancer

Long-term exposure to air pollution and liver cancer incidence in six European cohorts

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ABBREVIATIONS: BC, black carbon; CEANS, Cardiovascular Effects of Air Pollution and Noise in Stockholm (cohort); CI, confidence interval; CPS-II, Cancer Prevention Study II; DCH, Diet, Cancer and Health (cohort); DNC, Danish Nurse Cohort; DEHM, Danish Eulerian Hemispheric Model; E3N, Etude Epidémiologique auprès de femmes de la Mutuelle Générale de l'Education Nationale (cohort); EEA, European Environment Agency; ELAPSE, Effects of Low-Level Air Pollution (project); EPIC-MORGEN, EPIC-Monitoring Project on Risk Factor (cohort); EPIC-NL, Dutch European Investigation into Cancer and Nutrition (cohort); EPIC-PROSPECT, EPIC-Chronic Diseases in the Netherlands; ESCAPE, European Study of Cohorts for Air Pollution Effects (project); HR, hazard ratio; ICD-10, International Classification of diseases 10th version; ICD-9, International Classification of diseases ninth version; MAPLE, Mortality-Air Pollution Associations in Low-Exposure Environments (project); NO_2, nitrogen dioxide; NO_x, nitrogen oxides; NUTS-1, Nomenclature of territorial units for statistics; O_3, ozone; PM, particulate matter; $PM_{2.5}$, particulate matter with diameter <2.5 μm; SALT, Stockholm Screening Across the Lifespan Twin study (cohort); SDPP, Stockholm Diabetes Prevention Program (cohort); SES, socioeconomic status; Sixty, Stockholm cohort of 60-year-olds (cohort); SNAC-K, Swedish National Study on Aging and Care in Kungsholmen (cohort); VHM&PP, Vorarlberg Health Monitoring and Prevention Program (cohort).

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Funding information
Health Effects Institute Research Agreement, Grant/Award Number: 4954-RFA14-3/16-5-3; Novo Nordisk Foundation Challenge Programme, Grant/Award Number: NNF17OC0027812

Abstract

Particulate matter air pollution and diesel engine exhaust have been classified as carcinogenic for lung cancer, yet few studies have explored associations with liver cancer. We used six European adult cohorts which were recruited between 1985 and 2005, pooled within the "Effects of low-level air pollution: A study in Europe" (ELAPSE) project, and followed for the incidence of liver cancer until 2011 to 2015. The annual average exposure to nitrogen dioxide (NO_2), particulate matter with diameter <2.5 μm ($PM_{2.5}$), black carbon (BC), warm-season ozone (O_3), and eight elemental components of $PM_{2.5}$ (copper, iron, zinc, sulfur, nickel, vanadium, silicon, and potassium) were estimated by European-wide hybrid land-use regression models at participants' residential addresses. We analyzed the association between air pollution and liver cancer incidence by Cox proportional hazards models adjusting for potential confounders. Of 330 064 cancer-free adults at baseline, 512 developed liver cancer during a mean follow-up of 18.1 years. We observed positive linear associations between NO_2 (hazard ratio, 95% confidence interval: 1.17, 1.02-1.35 per 10 $\mu g/m^3$), $PM_{2.5}$ (1.12, 0.92-1.36 per 5 $\mu g/m^3$), and BC (1.15, 1.00-1.33 per 0.5 $10^{-5}/m$) and liver cancer incidence. Associations with NO_2 and BC persisted in two-pollutant models with $PM_{2.5}$. Most components of $PM_{2.5}$ were associated with the risk of liver

cancer, with the strongest associations for sulfur and vanadium, which were robust to adjustment for $PM_{2.5}$ or NO_2. Our study suggests that ambient air pollution may increase the risk of liver cancer, even at concentrations below current EU standards.

KEYWORDS

air pollution, cohort study, liver cancer incidence, particulate matter

What's new?

Air pollution contains a number of known carcinogens. While air pollution is classified as carcinogenic and is a known risk factor for lung cancer, the evidence for cancers in other organs is limited. In this large European study, the authors detected associations between air pollution and liver cancer incidence, even at levels that are below current EU standards. These results corroborate findings from several earlier, substantially smaller studies, and suggest that ambient air pollution may increase the risk of liver cancer.

1 | INTRODUCTION

Ambient air pollution is a major environmental stressor, posing a huge health burden related to increased risk of cardiometabolic, respiratory disease, and lung cancer.[1] A number of components presented in air pollution are carcinogenic, including polycyclic aromatic hydrocarbons, volatile organic compounds, and other heavy metals.[2] Particulate matter (PM)[2] and diesel engine exhaust[3] are classified as carcinogenic to humans, largely based on literature related to lung cancer.[2,4] However, the epidemiological evidence on air pollution and cancers other than lung cancer remains limited and inconclusive.[5]

Primary liver or hepatic cancer is the second leading cause of cancer death for men and the sixth for women, accounting for nearly 782 000 deaths (8.2% of all cancer deaths) globally in 2018.[6] Alcohol use, cigarette smoking, and Hepatitis B and C virus infections are the main risk factors.[7] Several plausible biological mechanisms support a link between ambient air pollution and liver cancer. Exposure to PM with diameter <2.5 μm ($PM_{2.5}$) in mice led to liver fibrosis as well as nonalcoholic steatohepatitis-like phenotype,[8,9] an increasingly important etiology of liver cancer.[10] Exposure to diesel exhaust in rats caused oxidative stress with DNA damage, apoptosis, and upregulation of DNA repair in the liver.[11,12] Inhalation of particles can result in gastrointestinal exposure through the mucociliary clearance from the airways[13] or cross the alveolar-capillary barrier and reach the liver via the circulatory system.[14,15] In several human studies,[16-19] air pollution has been associated with increased serum levels of hepatic enzymes such as γ-glutamyltranspeptidase, aspartate aminotransferase, and alanine transaminase, markers of liver damage usually caused by inflammation, the main mechanism by which air pollution induces adverse health effects.[20]

There are only five epidemiological studies on long-term exposure (ie, mean air pollution exposures of 1 year or more) to air pollution and liver cancer with somewhat mixed results.[19,21-24] A cohort study from Taiwan, with 22 062 subjects and 464 liver cancer cases, detected an association with $PM_{2.5}$ and found that elevated serum alanine transaminase levels mediated this association.[19] A study in the Danish Diet, Cancer, and Health (DCH) cohort (54 160 adults, 57 cases) reported an association with traffic density within 200 m of the residence, but not with nitrogen oxides (NO_x).[22] A study in four European cohorts (174 770 adults, 279 cases) which took part in "The European Study of Cohorts for Air Pollution Effects" (ESCAPE) project, found a positive but statistically nonsignificant association with $PM_{2.5}$ and nitrogen dioxide (NO_2).[23] The American Cancer Prevention Study II (CPS-II) cohort, with 623 048 subjects and 1003 liver cancer deaths, found no association with $PM_{2.5}$, NO_2, or ozone (O_3).[24] A US study (ecological study at a county level) with 56 245 cases of hepatocellular carcinoma, the most common histological type of liver cancer, detected a strong positive association with $PM_{2.5}$.[21] Only ESCAPE study had data on PM elemental components and reported associations with sulfur, silicon, nickel, and iron components of $PM_{2.5}$.[23]

Within the "Effects of Low-level Air Pollution: a Study in Europe" (ELAPSE) collaboration, which built on ESCAPE cohorts, we aimed to examine the association between long-term exposure to air pollution and liver cancer incidence and identify relevant sources by analyzing eight specific elements of $PM_{2.5}$. In contrast to the ESCAPE project, which analyzed the individual cohort separately in a standardized way and applied meta-analysis, we performed a pooled data analysis, applied a European-wide harmonized air pollution exposure assessment, and had additional years of follow-up, providing enhanced statistical power to examine the association between air pollution and liver cancer.

2 | MATERIALS AND METHODS

2.1 | Study population

We used the framework of the ELAPSE project, under which nine European cohorts were pooled to study health effects related to low-level air pollution,[25] stored on a secure server in Utrecht, and made available for remote analyses.

Of the nine pooled cohorts from the ELAPSE project, we used six from five European countries, which had information on follow-up for

liver cancer incidence available: (a) "Cardiovascular Effects of Air Pollution and Noise in Stockholm" (CEANS) from Stockholm county of Sweden, which included four subcohorts: "Swedish National Study on Aging and Care in Kungsholmen" (SNAC-K),[26] "Stockholm Screening Across the Lifespan Twin study" (SALT),[27] "Stockholm cohort of 60-year-olds" (Sixty),[28] and "Stockholm Diabetes Prevention Program" (SDPP)[29]; (b) DCH[30] from Copenhagen and Aarhus of Denmark; (c) "Danish Nurse Cohort" (DNC)[31] from entire Denmark, which included two subcohorts from recruitment rounds in 1993 and 1999; (d) "Dutch European Investigation into Cancer and Nutrition" (EPIC-NL)[32] from four cities in the Netherland, consisting of "EPIC-Monitoring Project on Risk Factors" (EPIC-MORGEN) and "EPIC-Chronic Diseases in the Netherlands" (EPIC-PROSPECT); (e) "Etude Epidémiologique auprès de femmes de la Mutuelle Générale de l'Education Nationale" (E3N)[33] from entire France; and (f) "Vorarlberg Health Monitoring and Prevention Programme" (VHM&PP)[34] from Vorarlberg, Austria. Cohorts were recruited between 1985 and 2005 and were followed until 2011 to 2015. Individual-level information on smoking, employment status, alcohol use, education level, and area-level socioeconomic status (SES) have been harmonized across the cohorts. A more detailed description of the cohorts included in this analysis can be found in Appendix S1 (pp. 1-7).

2.2 | Liver cancer definition

We obtained the cancer diagnosis data from national and state cancer registries, except for E3N, where cancer was defined from biannual questionnaires self-reports confirmed by oncologist review of pathological reports or from death certificates. We defined liver cancer incidence as the first diagnosis of primary cancer in liver during the follow-up, according to the International Classification of diseases ninth version (ICD-9) or 10th version (ICD-10) code (155 for ICD-9 and C22 for ICD-10),[23] and excluded persons with any cancer diagnosis before cohort baseline.

2.3 | Air pollution exposure assessment

As our main exposure assessment, we used Europe-wide hybrid land-use regression (LUR) models at a fine spatial scale (100 m × 100 m grids) to estimate annual mean exposure to air pollutants (NO_2, $PM_{2.5}$, black carbon [BC], and O_3 [warm-season]) and eight elemental components of $PM_{2.5}$ for the year 2010 at the participants' residential addresses of the baseline, described in detail elsewhere.[35,36]

The models for NO_2, $PM_{2.5}$, BC, and O_3 (warm-season)[35] were developed by supervised linear regression , based on the European Environment Agency (EEA) AirBase daily concentration data for 2010 for $PM_{2.5}$, NO_2, and O_3, and ESCAPE monitoring data for BC, which was not available from EEA. For annual estimates of BC, $PM_{2.5}$ absorbance data based on reflectance measurement of the filters during 2009 and 2010 were used and treated as 2010 annual mean concentrations. The annual warm-season average concentrations of O_3 were calculated based on the maximum running 8-hour means for each day. The input data for the LUR models included land use and traffic data, satellite observations, and dispersion model estimates. Ordinary kriging was used to additionally explain the residuals of spatial variation from the LUR model. The models explained spatial variation in the measured concentration well; the R^2 for NO_2, $PM_{2.5}$, BC, and O_3 was 0.59, 0.72, 0.54, and 0.69, respectively.

The models for $PM_{2.5}$ components were developed based on measurement data from the ESCAPE monitoring campaigns from 2008 to 2011 by two methods: supervised linear regression and random forest.[36] While model performance for explaining within-area variability in measured concentration was similar in two, the random forest method was better performed in explaining the overall variability of pollutant concentration levels across Europe than the supervised linear regression method. Eight elements were a priori selected based on their toxicity and representation of major pollution sources: copper, iron, and zinc mainly from non-tailpipe traffic emissions (i.e., brake and tire wear), sulfur from long-range transport of secondary inorganic aerosols from sulfur-containing fossil fuels combustion, nickel and vanadium from coal or mixed oil burning in buildings/ships, silicon from crustal dust, and potassium from biomass burning.[36]

As a sensitivity analysis, we also assessed the annual mean levels of NO_2, $PM_{2.5}$, BC, and O_3 for each year from recruitment to end of follow-up by a back-extrapolation method incorporating residential history (available only for DCH, VHM&PP, CEANS, and EPIC-NL), as described elsewhere in detail.[25] Briefly, we back-extrapolated the exposure estimates for the year 2010 from the LUR model, using both a difference and a ratio method with the Danish Eulerian Hemispheric Model (DEHM)[37] because the EEA AirBase data did not provide continuous measurement of monitoring data during the study period. DEHM data was complete with giving annual averages for all four pollutants at 26 × 26 km spatial resolution across Europe at least back to 1990 and covered all of the study area (downscaled from the original 50 × 50 km resolution using bilinear interpolation). The differences or the ratios of exposure levels between each year and 2010, estimated from DEHM models, were calculated larger spatial scale of NUTS-1 (Nomenclature of territorial units for statistics), allowing different spatial trends within Europe (for DCH, VHM&PP, CEANS, each cohort considered as one region, and EPIC-NL has four regions), and were added or multiplied the exposure estimates for the year 2010 from the LUR model at each residential. When residential history was incorporated, if someone moved within the same NUTS-1 region, then the ratio or difference values for each year after moving are the same as before.

Additionally, as sensitivity analyses, we used the NO_2, $PM_{2.5}$, and BC estimates from models developed within the ESCAPE, which were developed for each study area,[38,39] and the $PM_{2.5}$ from the Canadian "Mortality-Air Pollution Associations in Low-Exposure Environments" (MAPLE) project.[40]

2.4 | Statistical analysis

We used stratified Cox proportional hazards models with age as the underlying time scale to examine the association between air pollution

and liver cancer incidence. The start of follow-up was the participants' age at cohort entry, and the end of follow-up was the age at the time of the diagnosis of liver cancer (event), the first occurrence of any other cancer, date of death, date of emigration, loss to follow-up, or the end of follow-up, whichever came first. We included the subcohort indicator as strata to account for baseline hazard heterogeneity across the cohorts.

We included one air pollutant at a time as a continuous variable and evaluated the association with liver cancer incidence with increasing adjustment for variables chosen a priori: Model 1 included age (time axis), sex (strata), subcohort (strata), and the cohort baseline year; Model 2 additionally included smoking (never, former, current) and employment status (employed, other); and Model 3 (main model) additionally included neighborhood SES (mean income in 2001). Estimates for main pollutants were expressed as hazard ratio (HR) with 95% confidence interval (95% CI) for increments of 10 $\mu g/m^3$ for NO_2, 5 $\mu g/m^3$ for $PM_{2.5}$, 0.5×10^{-5}/m for BC, 10 $\mu g/m^3$ for O_3, and interquartile range increase for $PM_{2.5}$ components.

To evaluate the shape of the exposure-response function between air pollutants and liver cancer incidence, we applied natural cubic splines with two degrees of freedom, which was selected based on the lowest Akaike Information Criteria (AIC) among various degrees of freedom (between 2 and 4) (AIC results not shown). To investigate the associations below the current air quality standards, we additionally applied the main model (Model 3) to subsets where we only included participants with concentrations below a certain value. We evaluated cut-points of 40 (the WHO guideline and the EU standard), 30, and 20 $\mu g/m^3$ for NO_2, 25 (the EU standard), 20, 15, 12 (the US-EPA NAAQS), and 10 (the WHO guideline) $\mu g/m^3$ for $PM_{2.5}$, 3×10^{-5}, 2.5×10^{-5}, 2×10^{-5}, 1.5×10^{-5}, and 1.0×10^{-5}/m for BC, and 120, 100, and 80 $\mu g/m^3$ for O_3.

We fitted two-pollutant models for NO_2, $PM_{2.5}$, BC, and O_3 to examine the effects of pollutants independently from each other. For $PM_{2.5}$ components, we fitted two-pollutant models with $PM_{2.5}$ and NO_2 as the second pollutant to assess whether associations with the component remained after adjusting for generic $PM_{2.5}$ and NO_2, which is a marker for traffic tailpipe emissions and other fossil fuel combustion sources. The latter is especially important for the non-tailpipe components of copper, iron, and zinc.

We investigated effect modification of the associations between air pollutants and liver cancer by age (<65 years, ≥65 years), alcohol intake (low: <4 g/day, medium: 4-15 g/day, high: >15 g/day), and smoking status (never, former, current), by including an interaction term in the model and testing with the likelihood ratio test.

We performed several sensitivity analyses: (a) In order to account for temporal variation and spatial trend in air pollution and residential mobility, we applied the time-varying analysis with back-extrapolated time-varying exposure for NO_2, $PM_{2.5}$, BC, and O_3 (excluding DNC and E3N) with controlling of time trend (strata per a year or 5-year of follow-up time). (b) To examine the robustness of results to using different exposure metrics, we incorporated the main model (Model 3) for the NO_2, $PM_{2.5}$, and BC from the ESCAPE model (excluding DNC and E3N) and for the $PM_{2.5}$ from MAPLE. (c) To investigate the impact of further adjustment of potential confounders, which were not available in VHM&PP, Sixty, and SNAC-K, we applied the main model with and without the further adjustment to the subsets of the pooled cohort with the available information on potential confounders. Those further adjusted variables are educational level (low: primary school or less, medium: up to secondary school or equivalent, or high: university degree or more) and alcohol intake (Low: <4 g/day, Medium: 4-15 g/day, or High: ≥15 g/day). (d) To evaluate the impact of an individual cohort on the association, we applied the main model to the subsets of data, excluding one cohort at a time.

All statistical tests were two-sided, and *P*-values of <.05 were considered statistically significant. We performed all analyses and graphical presentations in R, version 3.4.0, with common R scripts developed within the ELAPSE project.

3 | RESULTS

3.1 | Description of the study population and exposure

Of the total of 367 404 participants from six pooled cohorts, we excluded 3 348 with missing information on the date of start or end of follow-up, 10 446 with cancer before enrollment, 136 with missing information on the prevalent cancer status, 1 830 with missing air pollution exposure data, and 21 580 with missing data on the individual-level and area-level risk factors, leaving 330 064 participants for the final analysis. The number of excluded subjects in each (sub) cohort is presented in Appendix S1 (pp. 1-7).

Over a mean follow-up time of 18.1 years (5 971 185 person-years), 512 participants developed liver cancer. Compared to those free of liver cancer at the end of follow-up, those who developed liver cancer were older and more likely to be men, current or former smokers, unemployed, moderate or high alcohol drinkers, highly educated, and live in the higher-income neighborhood at baseline (Table 1). The mean concentrations of NO_2 and $PM_{2.5}$ for the year 2010 at the residential address of baseline ranged from 19.8 (in CEANS) to 35.1 $\mu g/m^3$ (in EPIC-NL) for NO_2, and 8.1 (in CEANS) to 17.5 $\mu g/m^3$ (in EPIC-NL) for $PM_{2.5}$, respectively, which were well below the current EU standards of 40 $\mu g/m^3$ for NO_2 and 25 $\mu g/m^3$ for $PM_{2.5}$ (detailed descriptive statistics on air pollution levels for each cohort are provided in Appendix S1, pp. 1-7). Varying levels of exposure were observed between the individual cohorts with generally lower $PM_{2.5}$ and BC in northern countries (Figure S1). For $PM_{2.5}$, exposure contrast within cohorts was smaller than for BC and NO_2. BC and NO_2 were highly correlated in all cohorts (The mean of cohort-specific Pearson correlations is 0.83), whereas $PM_{2.5}$ was moderately to highly correlated with BC and NO_2 (The mean of cohort-specific Pearson correlations is 0.57 with BC, 0.62 with NO_2. For the correlation per each cohort, see Table S1). O_3 was negatively correlated with $PM_{2.5}$, especially with NO_2 and BC (the mean of correlations is -0.38, -0.64, and -0.58 for $PM_{2.5}$, NO_2, and BC, respectively).

TABLE 1 Descriptive statistics for 330 064 participants at baseline by liver cancer incidence status at the end of follow-up

Characteristic	Total (N = 330 064)	No liver cancer (N = 329 552)	Liver cancer (N = 512)	*P*-value[a]
Age, years (Mean ± SD)	48.2 ± 13.4	48.2 ± 13.4	55.8 ± 8.9	<.001
Age category, N (%)				.003
<65 years old	305 744 (92.6)	305 288 (92.6)	456 (89.1)	
≥65 years old	24 320 (7.4)	24 264 (7.4)	56 (10.9)	
Women, N (%)	220 292 (66.7)	220 104 (66.8)	188 (36.7)	<.001
Smoking status, N (%)				<.001
Never	180 703 (54.7)	180 461 (54.8)	242 (47.3)	
Former smoker	65 465 (19.8)	65 361 (19.8)	104 (20.3)	
Current smoker	83 896 (25.4)	83 730 (25.4)	166 (32.4)	
Unemployed, N (%)	94 225 (28.5)	93 973 (28.5)	252 (49.2)	<.001
Intake of alcohol[b], N (%)				<.001
Low (<4 g/day)	35 413 (23.1)	35 380 (23.1)	33 (17.9)	
Medium (4–15 g/day)	58 047 (37.9)	57 996 (37.9)	51 (27.7)	
High (15> g/day)	59 593 (38.9)	59 493 (38.9)	100 (54.3)	
Education level[c], N (%)				<.001
Low	21 148 (11.8)	21 105 (11.8)	43 (19.6)	
Medium	70 980 (39.7)	70 886 (39.7)	94 (42.9)	
High	86 504 (48.4)	86 422 (48.4)	82 (37.4)	
Mean income at neighborhood level in 2001, € (Mean ± SD)	19 496.2 ± 5426.5	19 494.2 ± 5428.0	20 791.4 ± 4161.3	<.001
Air pollutants for the year 2010 (Mean ± SD)				
NO_2, μg/m^3	24.9 ± 8.0	24.9 ± 8.0	24.8 ± 7.4	.71
$PM_{2.5}$, μg/m^3	15.0 ± 3.2	15.0 ± 3.2	14.9 ± 2.9	.45
BC, 10^{-5}/m	1.5 ± 0.4	1.5 ± 0.4	1.5 ± 0.4	.35
O_3, μg/m^3	85.6 ± 9.0	85.6 ± 9.0	85.9 ± 9.2	.38
$PM_{2.5}$ components (Mean ± SD)[d]				
Copper, ng/m^3	3.5 ± 2.6	3.5 ± 2.4	3.5 ± 2.6	.82
Iron, ng/m^3	87.6 ± 46.8	87.9 ± 40.9	87.6 ± 46.8	.85
Zinc, ng/m^3	16.9 ± 11.3	16.1 ± 10.9	17.0 ± 11.3	.10
Sulfur, ng/m^3	659.1 ± 142.1	638.8 ± 126.2	659.2 ± 142.1	.001
Nickel, ng/m^3	0.8 ± 0.7	0.7 ± 0.7	0.8 ± 0.7	.10
Vanadium, ng/m^3	1.4 ± 1.4	1.3 ± 1.7	1.4 ± 1.4	.58
Silicon, ng/m^3	96.2 ± 21.1	97.4 ± 19.1	96.2 ± 21.1	.20
Potassium, ng/m^3	167.2 ± 52.4	168.7 ± 53.8	167.2 ± 52.4	.52

Abbreviations: BC, black carbon; N, number; NO_2, nitrogen dioxide; O_3, ozone; $PM_{2.5}$, particulate matter with aerodynamic diameters of less than 2.5 μm; SD, standard deviation.

[a]The *t*-test for a continuous variable and chi-square test for a discrete variable to test the difference of a participant characteristic variable between cases and non-cases.

[b]n = 153 043.

[c]n = 178 632, low: primary school or less, medium: up to secondary school or equivalent, or high: university degree or more.

[d]Based on the supervised linear regression exposure model.

3.2 | Association between liver cancer incidence and air pollution exposure

We found positive associations of all three main pollutants, except for O_3, with the risk of liver cancer in Model 1, which attenuated after adjustment for smoking status and employment status in Model 2 (Table 2). In a fully adjusted model, we detected an association between NO_2 and liver cancer incidence with a HR of 1.17 (95% CI 1.02-1.35) per 10 μg/m^3, while associations with $PM_{2.5}$ (HR: 1.12 [95% CI 0.92-1.36] per 5 μg/m^3) and BC (HR: 1.15 [95% CI 1.00-1.33] per 0.5 × 10^{-5}/m) were statistically non-

TABLE 2 Associations between long-term exposure to air pollution and the risk for liver cancer incidence

Air pollutant	Model 1[a]	Model 2[b]	Model 3[c]	Two-pollutant model			
				Model 3 + NO_2	Model 3 + $PM_{2.5}$	Model 3 + BC	Model 3 + O_3
NO_2	1.14 (1.00-1.31)	1.12 (0.98-1.29)	1.17 (1.02-1.35)	–	1.19 (1.00-1.43)	1.22 (0.87-1.70)[d]	0.95 (0.78-1.16)
$PM_{2.5}$	1.10 (0.91-1.33)	1.09 (0.90-1.32)	1.12 (0.92-1.36)	0.96 (0.75-1.23)	–	0.98 (0.76-1.27)	0.88 (0.70-1.11)
BC	1.13 (0.98-1.30)	1.11 (0.97-1.28)	1.15 (1.00-1.33)	0.96 (0.68-1.36)[d]	1.16 (0.96-1.41)	–	0.94 (0.77-1.14)
O_3	0.69 (0.58-0.84)	0.71 (0.59-0.86)	0.70 (0.58-0.85)	0.67 (0.51-0.88)	0.66 (0.52-0.82)	0.66 (0.51-0.86)	–

Note: Results are presented as hazard ratio and 95% confidence interval [HR (95% CI)] for the following increments: 5 μg/m^3 for $PM_{2.5}$, 10 μg/m^3 for NO_2, 0.5 10^{-5} /m for BC and 10 μg/m^3 for O_3.

Abbreviations: BC, black carbon; CI, confidence interval; HR, hazard ratio; NO_2, nitrogen dioxide; O_3, ozone; $PM_{2.5}$, particulate matters with aerodynamic diameters of less than 2.5 μm.

[a]Model 1 was adjusted for age (time scale), sex (strata), subcohort (strata), and calendar year of baseline.

[b]Model 2 was adjusted for age (time scale), sex (strata), subcohort (strata), and calendar year of baseline, smoking status, and employment status.

[c]Model 3 was adjusted for age (time scale), sex (strata), subcohort (strata), calendar year of baseline, smoking status, employment status, and mean income at the neighborhood level in 2001.

[d]The results from the model with NO_2 and BC are difficult to interpret because of their high correlation, which reached 0.83.

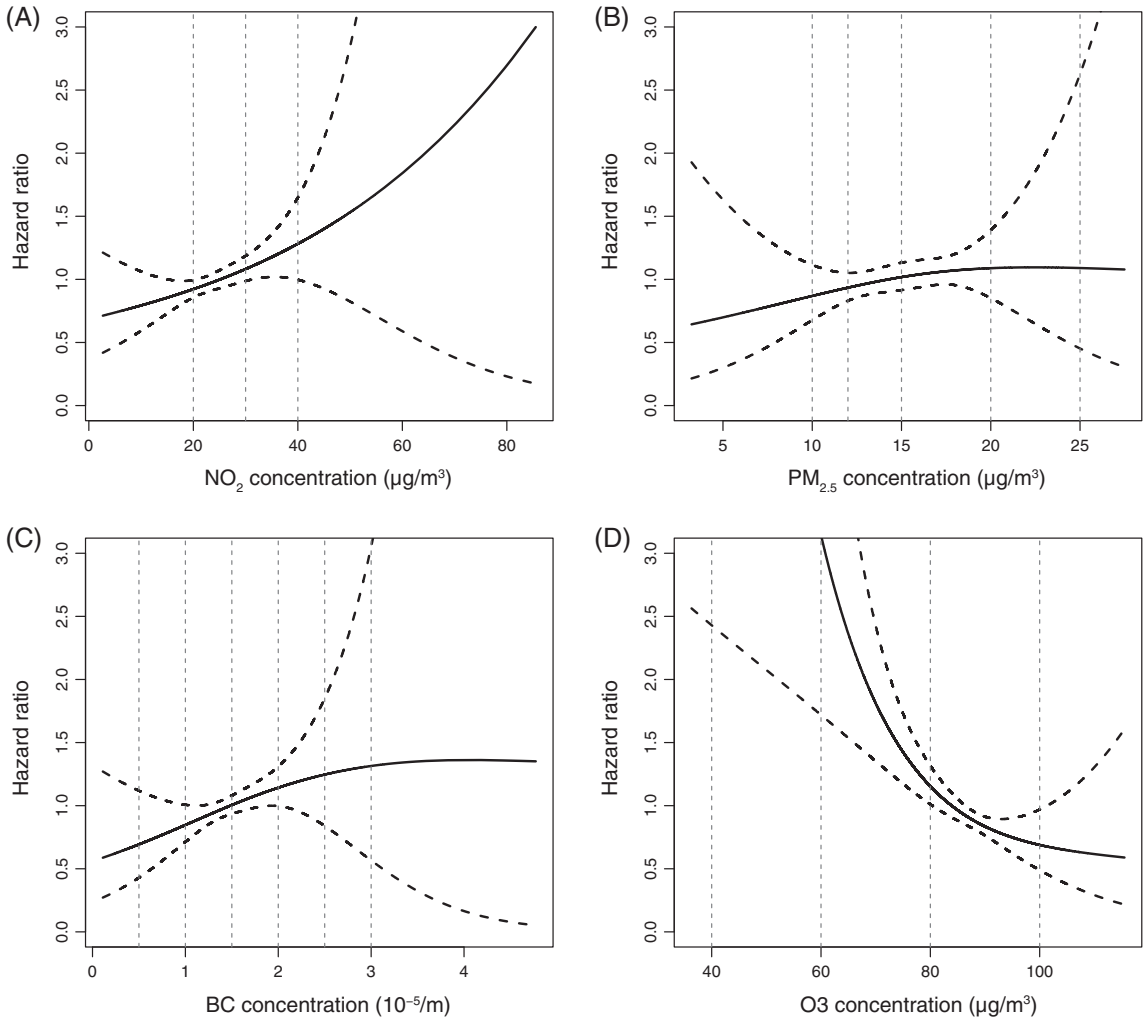

FIGURE 1 Estimated exposure-response curves for associations between (A) NO_2, (B) $PM_{2.5}$, (C) BC, and (D) O_3 concentration at the residential addresses of baseline and liver cancer incidence. NO_2, nitrogen dioxide; $PM_{2.5}$, particulate matter with aerodynamic diameters of less than 2.5 μm; BC, black carbon; O_3, ozone. Natural splines with 2 degrees of freedom. Black solid lines indicate hazard ratio values, and dashed lines indicate their 95% confidence intervals. Gray vertical dotted lines mean the values used for the subset analyses. Models were adjusted for age (time scale), sex (strata), sub-cohort (strata), calendar year of baseline, smoking status, employment status, and mean income at the neighborhood level in 2001

significant. The modest attenuation in HRs for NO_2, $PM_{2.5}$, and BC from Model 1 to Model 2 was mainly due to adjustment for smoking, while the inclusion of neighborhood SES in the model modestly increased HRs. However, differences in HRs between Models 1, 2, and 3 were small, suggesting limited confounding. A statistically significant negative association was observed with O_3.

In the two pollutant models, the associations for NO_2 remained positive after adjusting for $PM_{2.5}$ or BC (HR: 1.19 [95% CI 1.00-1.43]

TABLE 3 Associations between long-term exposure to air pollution and incident liver cancer, below various cut-points

Air pollutants	Subset[a]	Participants, N	Cases, N	Hazard ratio (95% CI)[b]
NO_2	Full dataset	330 064	512	1.17 (1.02-1.35)
	<40 μg/m^3 (EU standard)	315 023	498	1.20 (1.03-1.40)
	<30 μg/m^3	252 154	392	1.03 (0.83-1.28)
	<20 μg/m^3	90 300	135	1.01 (0.57-1.77)
$PM_{2.5}$	Full dataset	330 064	512	1.12 (0.92-1.36)
	<25 μg/m^3 (EU standard)	330 024	512	1.12 (0.92-1.36)
	<20 μg/m^3	320 759	505	1.12 (0.92-1.36)
	<15 μg/m^3	153 720	264	1.56 (0.96-2.55)
	<12 μg/m^3	52 349	72	1.02 (0.32-3.26)
	<10 μg/m^3	24 495	24	0.39 (0.06-2.73)
BC	Full dataset	330 064	512	1.15 (1.00-1.33)
	$<3.0 \times 10^{-5}$/m	329 305	512	1.17 (1.01-1.35)
	$<2.5 \times 10^{-5}$/m	324 258	506	1.16 (0.99-1.35)
	$<2.0 \times 10^{-5}$/m	299 519	471	1.16 (0.97-1.38)
	$<1.5 \times 10^{-5}$/m	142 778	206	1.29 (0.91-1.84)
	$<1.0 \times 10^{-5}$/m	34 477	37	0.57 (0.20-1.61)
O_3	Full dataset	330 064	512	0.70 (0.58-0.85)
	<120 μg/m^3	330 064	512	0.70 (0.58-0.85)
	<100 μg/m^3	324 120	507	0.67 (0.55-0.81)
	<80 μg/m^3	97 767	142	0.65 (0.45-0.95)

Abbreviations: BC, black carbon; CI, confidence interval; N, number; NO_2, nitrogen dioxide; O_3, ozone $PM_{2.5}$, particulate matters with aerodynamic diameters of less than 2.5 μm.

[a]Participants with concentrations above a cut-point were excluded.

[b]From models adjusting for age (time scale), sex (strata), subcohort (strata), calendar year of baseline, smoking status, employment status, and mean income at the neighborhood level in 2001.

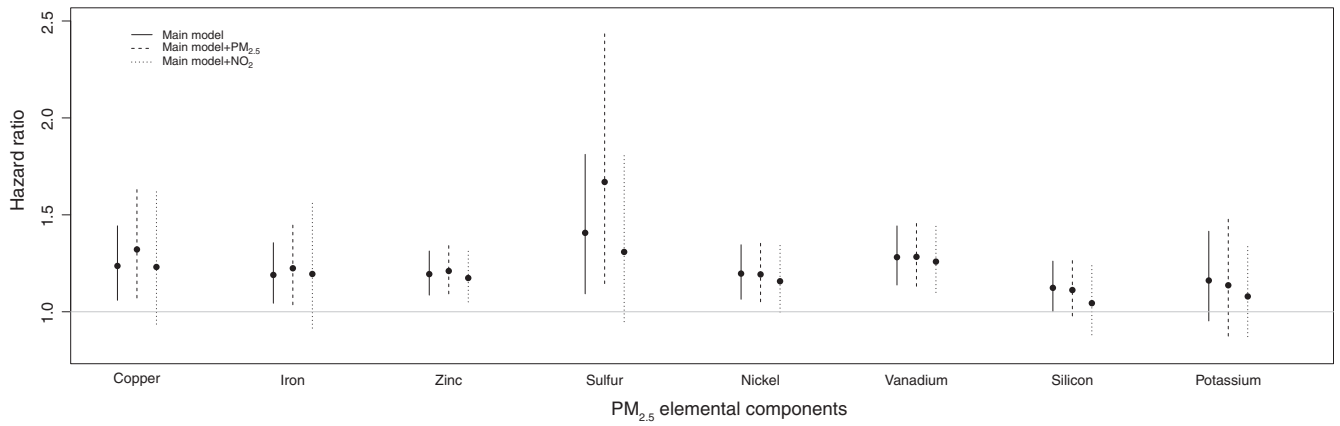

FIGURE 2 Associations between $PM_{2.5}$ components and liver cancer incidence. $PM_{2.5}$, particulate matter with aerodynamic diameters of less than 2.5 μm; NO_2, nitrogen dioxide. Models were adjusted for age (time scale), sex (strata), sub-cohort (strata), calendar year of baseline, smoking status, employment status, and mean income at the neighborhood level in 2001. Associations were expressed as hazard ratios with 95% confidence intervals per interquartile range increase for each of $PM_{2.5}$ components: 3.7 ng/m^3 for copper, 55.8 ng/m^3 for iron, 10.7 ng/m^3 for zinc, 212.2 ng/m^3 for sulfur, 0.8 ng/m^3 for nickel, 1.7 ng/m^3 for vanadium, 24.1 ng/m^3 for silicon, and 82.3 ng/m^3 for potassium. $PM_{2.5}$ components were estimated by the supervised linear regression method

and 1.22 [95% CI] 0.87-1.70, respectively), while those for $PM_{2.5}$ attenuated to unity after adjusting for NO_2 or BC. The HRs for BC attenuated to unity after adjusting for NO_2 and remained unchanged after adjusting for $PM_{2.5}$ (HR: 1.16 [95% CI: 0.96-1.41]). Furthermore, the associations with NO_2, $PM_{2.5}$, and BC attenuated to unity after adjustment O_3 but remained unchanged for O_3, possibly reflecting negative correlations between O_3 and other urban or traffic-related pollutants than NO_2 and BC. Due to the high correlation between BC and NO_2, as well as NO_2 and O_3, these two pollutant models should be interpreted with caution.

We observed no deviations from linearity for the associations with $PM_{2.5}$, NO_2, and BC (Figure 1). Associations with NO_2 and $PM_{2.5}$ persisted below current EU standards of 40 and 25 $\mu g/m^3$ for NO_2 and $PM_{2.5}$, respectively, but leveled off at below 30 $\mu g/m^3$ for NO_2 and 12 $\mu g/m^3$ for $PM_{2.5}$ (Table 3). The associations with BC were persisted in the subset with the concentration below 1.5×10^{-5}/m.

The associations between NO_2 and liver cancer were statistically significantly stronger in older participants, while no interaction was detected with alcohol intake and smoking status (Table S2).

Observed associations with NO_2, $PM_{2.5}$, and BC were robust to including time-varying air pollution concentrations and control for time trends (Table S3). Analyses using alternative air pollution exposure estimates from ESCAPE and MAPLE project showed stronger associations with liver cancer, but presented the overlapped confidence intervals (Tables S4 and S5) compared to those with ELAPSE exposure model.

Associations were also robust to additional adjustments for education level or alcohol intake (Table S6) and to the exclusion of one cohort at a time except for association with $PM_{2.5}$, which attenuated to unity after exclusion of VHM&PP (Table S7).

3.3 | Association between liver cancer incidence and $PM_{2.5}$ components exposure

Single pollutant models for $PM_{2.5}$ components estimated by supervised linear regression showed statistically significant HRs for almost all components, with the strongest associations with sulfur and vanadium (Figure 2; Table S8). For $PM_{2.5}$ components estimated with the random forest method, weaker associations were observed than those with the supervised linear regression method for all components, statistically significant only for sulfur and vanadium (Table S8). Associations were mostly robust (slightly attenuated or enhanced) to adjustment for $PM_{2.5}$ and NO_2 (Figure 2).

4 | DISCUSSION

In this pooled analysis of six cohorts from five European countries, we detected associations between long-term exposure to NO_2, $PM_{2.5}$, and BC and liver cancer incidence. The exposure-response curves were linear for all three pollutants, and the associations persisted below the current EU standards for NO_2 and $PM_{2.5}$. We found associations with sulfur and vanadium components of $PM_{2.5}$.

Previous studies on air pollution and liver cancer generally reported associations, though mostly not statistically significant.[19,21-24] In our study, HR per 10 $\mu g/m^3$ increase in NO_2 was 1.17 (95% CI 1.02-1.35), stronger but comparable to that of 1.10 (95% CI 0.93-1.30) from the ESCAPE.[23] The DCH cohort study[22] reported HR of 1.66 (95% CI 0.70-3.94) per 100 $\mu g/m^3$ increase in NO_x, and the American CPS-II study[24] found no association between NO_2 and liver cancer mortality (HR: 1.03 [95% CI 0.93-1.14] per 6.5 ppb [$\sim$12 $\mu g/m^3$] increase in NO_2). In the American CPS-II study,[24] only primary liver cancer death was included, and since liver cancer is a highly fatal cancer type, results from this study are comparable with those from ours on liver cancer incidence. With re-calculated HRs of each study per the same unit as ours (per 5 $\mu g/m^3$ for $PM_{2.5}$) for the comparison, our findings of the association between $PM_{2.5}$ and liver cancer with a HR of 1.12 (95% CI 0.92-1.36) was weaker than one reported in ESCAPE study (HR: 1.34 [95% CI 0.76-2.35]), comparable to those reported in the US study[21] with a HR of 1.12 (95% CI 1.03-1.21), and stronger than Pan et al.[19] study with a HR of 1.08 (95% CI 0.98-1.17) and the American CPS-II study[24] with a mortality rate ratio of 1.06 (95% CI 0.93-1.18). Our finding of an association between BC and liver cancer incidence with a HR of 1.15 (95% CI 1.00-1.33) per 0.5×10^{-5}/m showed a more precise estimate compared to the ESCAPE finding with $PM_{2.5}$ absorbance (BC equivalent) with a HR of 1.21 (95% CI 0.68-2.15) per 10^{-5}/m increase. Two pollutant models showed robust associations with NO_2 and BC after adjustment of $PM_{2.5}$, indicating the relevance of traffic emission-related pollution for liver cancer. However, we cannot determine whether NO_2 per se or the associated gaseous pollutants and particles from local combustion sources are responsible for the observed association. Finally, we found an inverse association between O_3 and liver cancer, whereas the only other study on O_3 and liver cancer, the American CPS-II study, found no association.[24] Despite the varying size and statistical power to detect associations with this rare cancer type, all studies to date on NO_2, $PM_{2.5}$, and BC, report HRs above 1.

We present novel findings on the association between specific elemental components of $PM_{2.5}$ and liver cancer. A single previous study[23] on elemental components in PM and liver cancer incidence detected associations with sulfur, silicon, nickel, and iron components of $PM_{2.5}$. Our association with the sulfur component of $PM_{2.5}$ is consistent with this study[23] and indicates the possible relevance of long-range transported secondary inorganic aerosols from sulfur-containing fossil fuels combustion. Furthermore, the strong association with the vanadium component of $PM_{2.5}$ is in line with the large population-based cohort study in Rome[41] showing a strong association between the vanadium component of PM_{10} and liver cirrhosis, as well as experimental studies[42,43] showing the association of inhaled vanadium with oxidative stress and cell alteration suggestive for liver regeneration. Still, overall evidence on which components and sources of air pollution are most relevant for liver cancer development is premature and demands attention in future research.

Our main strength is the large sample size obtained by pooling six European cohorts with a long follow-up over 18 years and sufficient

statistical power to examine the association between air pollution and this rare cancer type. Furthermore, we benefited from the European-wide air pollution exposure model which provided comparable air pollution data over the six European cohorts, detailed data on relevant confounders, and liver cancer incidence information from cancer registries with high validity. Limitations include lack of information on occupational exposures such as benzene (one of the hepatotoxic chemicals), alcohol intake, and hepatitis B or C infection status. Additional adjustment for alcohol intake (Table S6) did not affect the main results. Furthermore, we adjusted for SES, a strong determinant of hepatitis B or C infection.[44,45] Furthermore, the differences in the two air pollution exposure modeling approach used in ESCAPE and ELAPSE projects may explain the difference in risk estimates in the sensitivity analysis (Table S4). Briefly, unlike our main exposure assessment method of Europe-wide hybrid LUR model, the ESCAPE model was the LUR model developed for each study area, using local predictor data. The discrepancy in distributions of air pollution exposure concentrations between two exposure assessment methods can be checked elsewhere.[25]

In conclusion, our study suggests that long-term exposure to air pollution may increase the risk of liver cancer, even at concentrations below current EU standards, and adds evidence of detrimental health effects of air pollution on cancers other than lung cancer.

ACKNOWLEDGMENTS

This work was supported by funding from Health Effects Institute Research Agreement (#4954-RFA14-3/16-5-3) and by the Novo Nordisk Foundation Challenge Programme (#NNF17OC0027812). The funders had no role in the design of the study; the collection, analysis, and interpretation of the data; the writing of the manuscript; and the decision to submit the manuscript for publication. The research described in this article was conducted under contract to the Health Effects Institute (HEI), an organization jointly funded by the United States Environmental Protection Agency (EPA) (Assistance Award No. R-82811201) and certain motor vehicle and engine manufacturers. The contents of this article do not necessarily reflect the views of HEI, or its sponsors, nor do they necessarily reflect the views and policies of the EPA or motor vehicle and engine manufacturers.

CONFLICT OF INTEREST

Marie-Christine Boutron-Ruault has a potential personal conflict of interest regarding two conferences sponsored by pharmaceutical companies as follows: (a) 03/07/2020-July 30, 2020 MAYOLI-SPINDLER: Symposium: Pancreatology in practice in 2020 e-JFHOD 2020 Conference "Why do I see more and more pancreatic cancers?"; (b) 04/12/2020-04/12/2020- GILEAD e-conference Weight gain and HIV infection in 2020. The other authors have no conflicts of interest to disclose.

DATA AVAILABILITY STATEMENT

The exposure maps are available on request from Dr Kees de Hoogh (c.dehoogh@swisstph.ch). The ELAPSE study protocol is available at http://www.elapseproject.eu/. Further information and a detailed statistical analysis plan is available on reasonable request from the corresponding author (rina.so@sund.ku.dk).

ETHICS STATEMENT

All original cohort studies were approved by the local institutional medical review board and ethics committees in accordance with the national regulations.

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SUPPORTING INFORMATION

Additional supporting information may be found online in the Supporting Information section at the end of this article.

How to cite this article: So R, Chen J, Mehta AJ, et al. Long-term exposure to air pollution and liver cancer incidence in six European cohorts. *Int. J. Cancer*. 2021;1-11. https://doi.org/10.1002/ijc.33743