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# 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; E3N, Etude Epidémiologique auprès de femmes de la Mutuelle Générale de l'Education Nationale (cohort); 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-9, International Classification of diseases 9th version; ICD-10, International Classification of diseases 10th version; MAPLE, Mortality–Air Pollution Associations in Low-Exposure

Environments (project); $NO_2$, nitrogen dioxide; $NO_x$, nitrogen oxides; $O_3$, 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 Programme (cohort).

The article category: Cancer Epidemiology

Novelty and Impact: While air pollution is classified as carcinogenic and risk factor for lung cancer, the evidence for cancers in other organs is limited. In the pooled analysis of six European cohorts with 330,064 subjects, the authors detected associations between air pollution and liver cancer incidence, even at low levels, below current EU standards. Corroborating results from several earlier substantially smaller studies, this work brings solid evidence that air pollution is a risk factor for liver cancer.

**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, 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 µg/m$^3$), $PM_{2.5}$ (1.12, 0.92-1.36 per 5 µg/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.

## 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 non-alcoholic 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 (i.e., mean air pollution exposures of one 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 200m 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 Eff ects' (ESCAPE) project, found a positive but statistically non-significant 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 1,003 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.

## Materials and methods

### 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: 1) 'Cardiovascular Effects of Air Pollution and Noise in Stockholm' (CEANS) from Stockholm county of Sweden, which included four sub-cohorts: '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]; 2) DCH[30] from Copenhagen and Aarhus of Denmark; 3) 'Danish Nurse Cohort' (DNC)[31] from entire Denmark, which included two sub-cohorts from recruitment rounds in 1993 and 1999; 4) '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); 5) 'Etude Epidémiologique auprès de femmes de la Mutuelle Générale de l'Education Nationale' (E3N)[33] from entire France; and 6) '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 the Supplementary material page 1-7.

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 9$^{th}$ version (ICD-9) or 10$^{th}$ version (ICD-10) code (155 for ICD-9 and C22 for ICD-10)[23], and excluded persons with any cancer diagnosis before cohort baseline.

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 $NO_2$, $PM_{2.5}$, black carbon [BC], and $O_3$ [warm-season])[35] were developed by supervised linear regression (SLR), 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 NO2, $PM_{2.5}$, 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 European Environment Agency (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 x 26 km spatial resolution across Europe at least back to 1990 and covered all of the study area (downscaled from the original 50 x 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].

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 sub-cohort 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), sub-cohort (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 μg/m³ for $NO_2$, 5 μg/m³ for $PM_{2.5}$, 0.5 $10^{-5}$/m for BC, 10 μg/m³ 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 μg/$m^3$ for $NO_2$, 25 (the EU standard), 20, 15, 12 (the US-EPA NAAQS), and 10 (the WHO guideline) μg/$m^3$ for $PM_{2.5}$, 3, 2.5, 2, 1.5, and 1.0 $10^{-5}$/m for BC, and 120, 100, and 80 μg/$m^3$ 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: <4g/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: 1) 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). 2) 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. 3)

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 pooed cohort with the available information on potential confounders, including educational level (low: primary school or less, medium: up to secondary school or equivalent, or high: university degree or more) and alcohol intake (Low: <4g/day, Medium:4-15 g/day, or High: ≥15 g/day). 4) 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 < 0.05 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.

**Results**

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- 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 the Supplementary material page 1-7.

Over a mean follow-up time of 18.1 years (5,971,185 person-years), 512 participants developed liver cancer. Compare 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 μg/m$^3$ for $PM_{2.5}$ (detailed descriptive statistics on air pollution levels for each cohort are provided in the supplementary material page 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 in Supplementary material). 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 NO2. For the correlation per each cohort, see Table S1 in Supplementary material). $O_3$ was negatively correlated with $PM_{2.5}$ and 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).

Association between liver cancer incidence and air pollution exposure

We found positive associations of all four main pollutants with the risk of liver cancer in Model1, which attenuated after adjustment for smoking status and employment status in Model2 (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-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 to 1.43] and 1.22 [95% CI] 0.87 to 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 to 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 in Supplementary material).

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 in Supplementary material). Analyses using alternative air pollution exposure estimates from ESCAPE and MAPLE project showed stronger associations with liver cancer, but presented the overlapped confidence intervals (Table S4 and Table S5 in Supplementary material) compared to those with ELAPSE exposure model.

Associations were also robust to additional adjustments for education level or alcohol intake (Table S6 in Supplementary material) 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 in Supplementary material).

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 in Supplementary material). 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

in Supplementary material). Associations were mostly robust (slightly attenuated or enhanced) to adjustment for $PM_{2.5}$ and $NO_2$ (Figure 2).

**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 most not statistically significant[19,21–24]. In our study, HR per 10 μg/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 μg/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 [~12 μg/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 μg/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 studies[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 in Supplementary material) 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 modeling approaches used in ESCAPE and ELAPSE projects may explain the difference in risk estimates in the sensitivity analysis (Table S4). Briefly, unlike our main 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 effect of air pollution on cancers other than lung cancer

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**Conflict of Interest**

Marie-Christine Boutron-Ruault has a potential personal conflict of interest regarding two conferences sponsored by pharmaceutical companies as follows: 1) 03/07/2020 - 30/07/2020 MAYOLI-SPINDLER: Symposium: Pancreatology in practice in 2020 e-JFHOD 2020 Conference « Why do I see more and more pancreatic cancers? »; 2) 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.

**Disclaimers**

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views and policies of the EPA or motor vehicle and engine manufacturers.

**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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**Figure legends**

**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.**

Abbreviation: $NO_2$, 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. Grey 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.

**Figure 2. Associations between $PM_{2.5}$ components and liver cancer incidence.**

Abbreviation: $PM_{2.5}$, particulate matter with aerodynamic diameters of less than 2.5 μm; $NO_2$, nitrogen dioxide; Cu, copper; Fe, iron; Zn, zinc; S, sulfur; Ni, nickel; V, vanadium; Si, Silicon; K, potassium.

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 Cu, 55.8 $ng/m^3$ for Fe, 10.7 $ng/m^3$ for Zn, 212.2 $ng/m^3$ for S, 0.8 $ng/m^3$ for Ni, 1.7 $ng/m^3$ for V, 24.1 $ng/m^3$ for Si, 82.3 $ng/m^3$ for K.

$PM_{2.5}$ components were estimated by the supervised linear regression method

**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[c] |
|---|---|---|---|---|
| **Age, years (Mean ± SD)** | 48.2 ± 13.4 | 48.2 ± 13.4 | 55.8 ± 8.9 | <.001 |
| **Age category, N (%)** | | | | 0.003 |
| **< 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[a], 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[b], 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 ± 5,428.0 | 20,791.4 ± 4,161.3 | <.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 | 0.71 |
| **$PM_{2.5}$, µg/$m^3$** | 15.0 ± 3.2 | 15.0 ± 3.2 | 14.9 ± 2.9 | 0.45 |
| **BC, $10^{-5}$/m** | 1.5 ± 0.4 | 1.5 ± 0.4 | 1.5 ± 0.4 | 0.35 |
| **$O_3$, µg/$m^3$** | 85.6 ± 9.0 | 85.6 ± 9.0 | 85.9 ± 9.2 | 0.38 |
| **$PM_{2.5}$ components (Mean ± SD)[d]** | | | | |
| **Copper, ng/$m^3$** | 3.5 ± 2.6 | 3.5 ± 2.4 | 3.5 ± 2.6 | 0.82 |
| **Iron, ng/$m^3$** | 87.6 ± 46.8 | 87.9 ± 40.9 | 87.6 ± 46.8 | 0.85 |
| **Zinc, ng/$m^3$** | 16.9 ± 11.3 | 16.1 ± 10.9 | 17.0 ± 11.3 | 0.10 |
| **Sulfur, ng/$m^3$** | 659.1 ± 142.1 | 638.8 ± 126.2 | 659.2 ± 142.1 | 0.001 |
| **Nickel, ng/$m^3$** | 0.8 ± 0.7 | 0.7 ± 0.7 | 0.8 ± 0.7 | 0.10 |

| | | | | |
|---|---|---|---|---|
| **Vanadium, ng/m$^3$** | 1.4 ± 1.4 | 1.3 ± 1.7 | 1.4 ± 1.4 | 0.58 |
| **Silicon, ng/m$^3$** | 96.2 ± 21.1 | 97.4 ± 19.1 | 96.2 ± 21.1 | 0.20 |
| **Potassium, ng/m$^3$** | 167.2 ± 52.4 | 168.7 ± 53.8 | 167.2 ± 52.4 | 0.52 |

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

[a] n=153,043

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

[c] 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.

[d] Based on the supervised linear regression exposure model

**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 to 1.31) | 1.12 (0.98 to 1.29) | 1.17 (1.02 to 1.35) | - | 1.19 (1.00 to 1.43) | 1.22 (0.87 to 1.70)* | 0.95 (0.78 to 1.16) |
| **$PM_{2.5}$** | 1.10 (0.91 to 1.33) | 1.09 (0.90 to 1.32) | 1.12 (0.92 to 1.36) | 0.96 (0.75 to 1.23) | - | 0.98 (0.76 to 1.27) | 0.88 (0.70 to 1.11) |
| **BC** | 1.13 (0.98 to 1.30) | 1.11 (0.97 to 1.28) | 1.15 (1.00 to 1.33) | 0.96 (0.68 to 1.36)* | 1.16 (0.96 to 1.41) | - | 0.94 (0.77 to 1.14) |
| **$O_3$** | 0.69 (0.58 to 0.84) | 0.71 (0.59 to 0.86) | 0.70 (0.58 to 0.85) | 0.67 (0.51 to 0.88) | 0.66 (0.52 to 0.82) | 0.66 (0.51 to 0.86) | - |

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

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

*: The results from the model with $NO_2$ and BC are difficult to interpret because of their high correlation, which reached 0.83. [a] Model1 was adjusted for age (time scale), sex (strata), sub-cohort (strata), and calendar year of baseline.

[b] Model2 was adjusted for age (time scale), sex (strata), sub-cohort (strata), and calendar year of baseline, smoking status, and employment status.

[c] Model3 was 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.

**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 to 1.35) |
| | <40 µg/m$^3$ (EU standard) | 315,023 | 498 | 1.20 (1.03 to 1.40) |
| | <30 µg/m$^3$ | 252,154 | 392 | 1.03 (0.83 to 1.28) |
| | <20 µg/m$^3$ | 90,300 | 135 | 1.01 (0.57 to 1.77) |
| **$PM_{2.5}$** | Full dataset | 330,064 | 512 | 1.12 (0.92 to 1.36) |
| | <25 µg/m$^3$ (EU standard) | 330,024 | 512 | 1.12 (0.92 to 1.36) |
| | <20 µg/m$^3$ | 320,759 | 505 | 1.12 (0.92 to 1.36) |
| | <15 µg/m$^3$ | 153,720 | 264 | 1.56 (0.96 to 2.55) |
| | <12 µg/m$^3$ | 52,349 | 72 | 1.02 (0.32 to 3.26) |
| | <10 µg/m$^3$ | 24,495 | 24 | 0.39 (0.06 to 2.73) |
| **BC** | Full dataset | 330,064 | 512 | 1.15 (1.00 to 1.33) |
| | < 3.0 10$^{-5}$/m | 329,305 | 512 | 1.17 (1.01 to 1.35) |
| | < 2.5 10$^{-5}$/m | 324,258 | 506 | 1.16 (0.99 to 1.35) |
| | < 2.0 10$^{-5}$/m | 299,519 | 471 | 1.16 (0.97 to 1.38) |

| | | | | |
|---|---|---|---|---|
| | < 1.5 $10^{-5}$/m | 142,778 | 206 | 1.29 (0.91 to 1.84) |
| | < 1.0 $10^{-5}$/m | 34,477 | 37 | 0.57 (0.20 to 1.61) |
| **$O_3$** | Full dataset | 330,064 | 512 | 0.70 (0.58 to 0.85) |
| | < 120 μg/$m^3$ | 330,064 | 512 | 0.70 (0.58 to 0.85) |
| | < 100 μg/$m^3$ | 324,120 | 507 | 0.67 (0.55 to 0.81) |
| | < 80 μg/$m^3$ | 97,767 | 142 | 0.65 (0.45 to 0.95) |

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

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

[b] From models adjusting 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.

**Novelty and Impact:**

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 components 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.