Environmental Research 215 (2022) 114385

Contents lists available at ScienceDirect

Environmental Research

journal homepage: www.elsevier.com/locate/envres

Long term exposure to air pollution and kidney parenchyma cancer – Effects of low-level air pollution: a Study in Europe (ELAPSE)

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ARTICLE INFO

Keywords:
air Pollution
Kidney cancer incidence

ABSTRACT

Background: Particulate matter (PM) is classified as a group 1 human carcinogen. Previous experimental studies suggest that particles in diesel exhaust induce oxidative stress, inflammation and DNA damage in kidney cells, but the evidence from population studies linking air pollution to kidney cancer is limited.

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https://doi.org/10.1016/j.envres.2022.114385
Received 11 May 2022; Received in revised form 5 September 2022; Accepted 17 September 2022
Available online 22 September 2022

Nitrogen dioxide
Particulate matter
PM elemental Components
Ozone

Methods: We pooled six European cohorts (N = 302,493) to assess the association of residential exposure to fine particles ($PM_{2.5}$), nitrogen dioxide (NO_2), black carbon (BC), warm season ozone (O_3) and eight elemental components of $PM_{2.5}$ (copper, iron, potassium, nickel, sulfur, silicon, vanadium, and zinc) with cancer of the kidney parenchyma. The main exposure model was developed for year 2010. We defined kidney parenchyma cancer according to the International Classification of Diseases 9th and 10th Revision codes 189.0 and C64. We applied Cox proportional hazards models adjusting for potential confounders at the individual and area-level.

Results: The participants were followed from baseline (1985–2005) to 2011–2015. A total of 847 cases occurred during 5,497,514 person-years of follow-up (average 18.2 years). Median (5–95%) exposure levels of NO_2, $PM_{2.5}$, BC and O_3 were 24.1 μg/m^3 (12.8–39.2), 15.3 μg/m^3 (8.6–19.2), 1.6 10^{-5} m^{-1} (0.7–2.1), and 87.0 μg/m^3 (70.3–97.4), respectively. The results of the fully adjusted linear analyses showed a hazard ratio (HR) of 1.03 (95% confidence interval [CI]: 0.92, 1.15) per 10 μg/m^3 NO_2, 1.04 (95% CI: 0.88, 1.21) per 5 μg/m^3 $PM_{2.5}$, 0.99 (95% CI: 0.89, 1.11) per 0.5 10^{-5} m^{-1} BCE, and 0.88 (95% CI: 0.76, 1.02) per 10 μg/m^3 O_3. We did not find associations between any of the elemental components of $PM_{2.5}$ and cancer of the kidney parenchyma.

Conclusion: We did not observe an association between long-term ambient air pollution exposure and incidence of kidney parenchyma cancer.

1. Introduction

Cancers of the kidney are a large societal burden considering both the incidence and relatively high risk of metastatic advance (Gupta et al., 2008; Safiri et al., 2020). The incidence has increased over the past decades and globally more than 400,000 new cases of kidney cancers are now registered each year and close to 180,000 annual deaths (Sung et al., 2021). The majority of kidney cancer cases (>90%) develop in the kidney parenchyma and are mainly adenocarcinomas (renal cell carcinomas).

The etiology of kidney cancer is largely unknown (Scelo and Larose, 2018). The incidence is higher in males (Sung et al., 2021) and especially obesity is considered an important risk factor for the development of kidney cancer (Wang and Xu, 2014). Other established risk factors include tobacco smoking (Hunt et al., 2005), high blood pressure (Weikert et al., 2008), chronic kidney disease, and diabetes (Gelfond et al., 2018; Larsson and Wolk, 2011). Alcohol consumption has been found to be related to a decrease in risk of kidney cancer, likely through a pathway of increased insulin sensitivity (Scelo and Larose, 2018). Certain environmental and occupational exposures have also been linked with the development of kidney cancers. The most convincing evidence is found for exposure to trichloroethylene, which is used in industry as a metal cleaner (Karami et al., 2012), but arsenic in drinking water and pesticides are also possible environmental risk factors (Karami et al., 2008; Saint-Jacques et al., 2018).

Particulate matter (PM) air pollution is classified as a group 1 human carcinogen by the International Agency for Research on Cancer (IARC) mainly based on the pool of evidence in relation to lung cancer (IARC, 2016). The mechanisms by which air pollution may induce cancer include inflammation and oxidative stress, which are both considered key elements in the development and progression of cancer (Straif et al., 2013). When inhaled, PM exerts DNA damage, promotion of cell turnover, and lung tissue proliferation and beyond the respiratory tract by entering the blood circulation through absorption, metabolism, and distribution of inhaled carcinogens (Chen et al., 2013; Xie et al., 2021). Also, epigenetic modifications and telomere shortenings are suggested mechanisms linking air pollution to cancer (Saini et al., 2019). Evidence from experimental studies of human tissue and animal models propose that particles in diesel exhaust induce oxidative stress, inflammation, and DNA damage in kidney cells (Nemmar et al., 2016; Waly et al., 2013).

The influence of outdoor air pollution on kidney cancer has been investigated in previous studies. In the large European Study of Cohorts for Air Pollution Effects (ESCAPE) meta-analysis, based on 14 European cohorts and 697 incident kidney parenchyma cases, a hazard ratio (HR) of 1.57 (95% confidence interval [CI]: 0.81, 3.01) per increment of 5 μg/m^3 PM with an aerodynamic diameter of <2.5 μm ($PM_{2.5}$) and a HR of 1.36 (95% CI: 0.84, 2.19) per 10^{-5} m^{-1} $PM_{2.5}$ absorbance (a measure of soot) was reported (Raaschou-Nielsen et al., 2017). An ecological study based on the U.S. cancer registry, including more than 250,000 incident kidney cancer cases in the period 1992–2016, showed a higher incidence rate ratio with higher exposure to $PM_{2.5}$ (Coleman et al., 2020). The results, however, were sensitive to the choice of exposure model, with weaker associations observed when applying a time-dependent exposure model. The most recently published systematic review, including twenty articles (four case-control, nine cohort, and seven ecologic studies) concluded that the evidence for a causal link between ambient air pollution exposure and kidney cancer so far is limited due to large heterogeneity between studies in terms of study design, exposure metrics and confounder models (Zare Sakhvidi et al., 2020).

In this large-scale pooled analysis study of six European cohorts in the framework of the Effects of Low-Level Air Pollution: a Study in Europe (ELAPSE) - a large consortium building on the ESCAPE collaboration - we aim to assess the relationship between long-term air pollution exposure and kidney parenchyma cancer incidence. In addition to $PM_{2.5}$, nitrogen dioxide (NO_2), black carbon (BC), and ozone (O_3), we include eight specific elemental $PM_{2.5}$ components. We add to the findings of the previous ESCAPE publication through a longer follow-up and a newly developed Europe-wide spatial land-use regression model.

2. Methods

2.1. Study population

The study included the following six cohorts from the ELAPSE collaboration, which had information on kidney parenchyma cancer incidence: Cardiovascular Effects of Air Pollution and Noise in Stockholm (CEANS) - which is the collective name of four sub-cohorts (Stockholm Screening Across the Lifespan Twin study [SALT] (Magnusson et al., 2013); Swedish National Study on Aging and Care in Kungsholmen [SNAC-K] (Lagergren et al., 2004); The Stockholm Diabetes Prevention Programme [SDPP] (Eriksson et al., 2008); and The Stockholm Cohort of 60-year-olds [Sixty]) (Wändell et al., 2007); The Danish Nurse Cohort (DNC) (Hundrup et al., 2012); The Danish Diet, Cancer and Health cohort (DCH) (Tjønneland et al., 2007); the Dutch European Investigation into Cancer and Nutrition (EPIC-NL) - comprising the two sub-cohorts EPIC-Monitoring Project on Risk Factors and Chronic Diseases in the Netherlands (EPIC-MORGEN) and (EPIC-Prospect) (Beulens et al., 2010); the Etude Epidémiologique auprès de femmes de la Mutuelle Générale de l'Education Nationale (E3N/EPIC--France) (Clavel-Chapelon, 2015); and the Austrian Vorarlberg Health Monitoring and Prevention Programme (VHM&PP) (Ulmer et al., 2007). All cohorts except the DNC were part of the ESCAPE collaboration. The baseline varied between 1985 and 2005 across the cohorts with follow up until 2011–2015. Data from all cohorts were pooled and stored on a secure server in Utrecht University. All six cohorts had baseline information on age, sex, marital status, employment status, smoking status,

amount and duration of smoking in current smokers (E3N and VHM&PP only in classes), body mass index (BMI), and area-level socio-economic status (SES). These variables were harmonized across the individual cohorts. We have reported details on each included cohort previously (Hvidtfeldt et al., 2021).

We included all participants without any previous cancer at baseline (with the exception of non-melanoma skin cancer).

2.2. Exposure assessment

The exposure model and validation of NO_2, $PM_{2.5}$, BC, O_3, and $PM_{2.5}$ components has been described in detail elsewhere (Chen et al., 2020; de Hoogh et al., 2018). In brief, we applied Europe-wide hybrid land use regression (LUR) models which incorporated the following air pollution predictors: monitoring data, satellite observations, model estimates, land use, road variables, and industrial point sources (Eeftens et al., 2012). The development of BC and $PM_{2.5}$ composition applied ESCAPE monitoring data from 2009 to 2010, and therefore we selected year 2010 as the primary exposure modelling year. In exposure model validation by five-fold Hold Out Validation (HOV) in random subsets (20%) of the monitoring datasets, stratified by site type (background, traffic) and region of Europe, a large fraction of measured spatial variation in the annual average concentration in HOV was explained (e.g. 59% for NO_2, 72% for $PM_{2.5}$, 54% for BC, and 69% for O_3 average concentration in the warm season) (de Hoogh et al., 2018). We used supervised linear regression (SLR) and random forest (RF) algorithms for the PM composition models and included eight components, which represented major air pollution sources: copper (Cu), iron (Fe) and zink (Zn) (non-tailpipe traffic emissions, e.g. brake and tyre wear), silicon (Si) (crustal material), sulfur (S) (secondary inorganic aerosols from long-range transported sulfur containing fuel combustion), nickel (Ni) and vanadium (V) (mixed oil burning/industry emissions), and potassium (K) (biomass burning) (Chen et al., 2020). For all exposures, we applied models for 2010 to create surfaces (100 m $\times$ 100 m grid resolution) and linked these to the cohort members' baseline residential address. The SLR and RF models explained within-area variability similarly (Chen et al., 2020), and we therefore interpret associations with exposures from the two models equally. We truncated negative (SLR) PM component predictions to zero and a small number of unrealistically high predictions at close distance to industrial sources to a maximum modelled concentration for each element (Waly et al., 2013). No truncation was needed for the RF-modelled exposures.

2.3. Outcome

We followed the cohort participants in national cancer registries, death certificates, or medical records - except for the E3N cohort where self-reports from biannual questionnaires or death certificates were applied. This information was confirmed in pathological reports and reviewed by an oncologist. We defined kidney parenchyma cancer according to the International Classification of Diseases and Related Health Problems, 9th and 10th Revision (ICD-9/ICD-10) codes 189.0 and C64, respectively.

2.4. Statistical analysis

We used Cox proportional hazards models with age as the underlying time scale and censored each participant at time of first occurrence of any cancer other than kidney parenchyma cancer, date of death, emigration, loss to follow-up, or at the end of follow-up. We modelled NO_2, $PM_{2.5}$, BC, and O_3 in the warm season (O_3) as a linear function with increments of 10 $\mu g/m^3$, 5 $\mu g/m^3$, 0.5 10^{-5} m^{-1} and 10 $\mu g/m^3$, respectively, and the PM components with increments of 5 ng/m^3 Cu, 100 ng/m^3 Fe, 50 ng/m^3 K, 1 ng/m^3 Ni, 200 ng/m^3 S, 100 ng/m^3 Si, 2 ng/m^3 V, and 10 ng/m^3 Zn. We included strata per individual (sub) cohort in order to account for baseline hazard heterogeneity between the (sub) cohorts and to relax the assumption of proportional hazards.

We modelled the association between the air pollutants and kidney parenchyma cancer incidence in three models: 1) accounting for age (underlying time-scale), sex and (sub) cohort ID (strata), and adjustment for baseline year; 2) further adjusted for individual-level covariates employment status (yes vs. no), marital status (married/cohabiting, divorced, widowed, single), BMI (<18.5, 18.5–24, 25–29, and 30+ kg/m^2), smoking status (never, former, current), smoking duration (years of smoking), and smoking intensity (cigarettes/day); 3) further adjusted for area-level socio-economic status (SES) defined as mean income in 2001. The spatial scale of the area varied from smaller neighborhoods and city districts (CEANS, EPIC-NL, E3N) to municipalities (DNS, DCH, and VHM&PP). We excluded participants with incomplete information on model 3 variables from all analyses. We assessed the shape of the concentration-response function by natural cubic splines (3 degrees of freedom) and performed subset analyses for $PM_{2.5}$, NO_2, BC and O_3 exposures by restricting the main Model 3 analyses to participants with exposure levels below specific cut-off values.

We performed the following sensitivity analyses: 1) Addressing potential effect measure modification between the main exposures and sex (replacing the strata term with an interaction term with air pollutants), smoking status, and BMI (three categories of <25, 25–29, and 30+ kg/m^2), by including an interaction term in the model tested by the Wald test. 2) Investigating the impact of alcohol consumption (linear term, excluding CEANS Sixty and SNAC-K and the VHM&PP), educational level (three categories, excluding the VHM&PP cohort), and occupational status (white collar/blue collar, excluding the DCH, E3N, and EPIC-NL cohorts) by comparing estimates in identical data subsets with and without adjustment. 3) Exploring other exposure definitions of NO_2, $PM_{2.5}$, BC, and O_3 by (a) back-extrapolating to the baseline address, (b) time-varying exposure extrapolated across the address history from baseline to end of follow-up in cohorts with this information (excluding DNC and E3N), and (c) applying the local LUR exposure models developed for ESCAPE (excluding DNC, E3N and parts of DCH which were not included in ESCAPE). We specified a 1-year calendar time-period strata to handle time-trends in air pollution and kidney parenchyma cancers. The extrapolation used air pollution concentrations estimated from the Danish Eulerian Hemispheric Model (DEHM) regional air pollution model, including hourly values of chemical species, which are averaged into monthly concentrations across Europe at a 26 km $\times$ 26 km spatial resolution (Brandt et al., 2012). We applied these trends to calculate annual average concentrations for all years from baseline to end of follow-up, allowing different spatial trends within Europe. We performed back-extrapolation by using the absolute difference and the ratio between the baseline period and 2010.4) Two-pollutant models were conducted by adjustment for the second pollutant to test the sensitivity of the estimates of one pollutant to inclusion of another. 5) We excluded one cohort at a time to assess the impact of individual cohorts on the effect estimates.

We investigated any violation of the proportional hazards assumption of the Cox Models for all covariates by test of a non-zero slope in a generalized linear regression of the scaled Schoenfeld residuals on time. All analyses were conducted in R version 3.4.0.

3. Results

After initial exclusions - primarily due to cancer before baseline, missing exposure, and missing covariates (17.7%), the pooled study population included 302,493 individuals and 847 cases of kidney parenchyma cancer during 5,497,514 person-years of follow-up (Table 1). The participants' baseline ranged from 1985 to 2005 with a mean age from 41.7 to 72.5 years across the individual cohorts and a pooled mean of 48.2 (standard deviation, SD: 13.4) years. Four of the cohorts included women only and the pooled cohort included 66% women. The percentage of overweight or obese participants varied from 21% in the French E3N cohort to 65% in the Swedish SIXTY cohort. The baseline

Table 1
Description of the included cohort studies.

	N	Baseline	End of follow-up	Baseline age (mean/SD) years	Kidney[a] tumors	% women	% BMI ≥25 kg/m^2	% Current smokers	% Married/ cohabiting	% Not employed	Mean income area-level[b]
CEANS Stockholm, Sweden											
SDPP	7,305	1992–1998	31-12-2011	47.0 (4.9)	14	59	51	26	84	9	24.3 (4.2)
SALT	5,625	1998–2003	31-12-2011	57.3 (10.4)	18	53	41	21	68	33	25.4 (6.6)
SIXTY	3,660	1997–1999	31-12-2011	60.0 (0.0)	11	50	65	21	74	32	24.7 (6.8)
SNAC-K	2,359	2001–2004	31-12-2011	72.5 (10.4)	4	62	53	15	46	76	28.7 (2.2)
DCH, Copenhagen/ Aarhus, Denmark	52,779	1993–1997	31-12-2015	56.7 (4.4)	221	53	56	36	71	22	20.1 (3.4)
DNC, Denmark											
DNC-1993	15,556	1993	31-12-2012	56.0 (8.3)	36	100	28	37	68	29	19.2 (2.5)
DNC-1999	7,430	1999	31-12-2012	47.9 (4.1)	9	100	30	28	76	5	19.0 (2.4)
EPIC-NL, Netherlands											
Prospect	13,640	1993–1997	31-12-2012	57.6 (6.0)	47	100	55	23	77	49	13.1 (1.4)
MORGEN	17,792	1993–1997	31-12-2012	42.7 (11.2)	30	54	49	35	65	31	12.2 (1.6)
E3N, France	36,258	1989–1991	08-12-2014	52.8 (6.7)	81	100	21	13	84	31	11.2 (3.0)
VHM&PP, Vorarlberg, Austria	140,089	1985–2005	31-12-2014	41.7 (14.9)	376	56	42	20	69	29	22.9 (1.7)
Pooled cohort	**302,493**	**1985–2005**	**2011–2015**	**48.2 (13.4)**	**847**	**66**	**42**	**24**	**72**	**29**	**19.8 (5.3)**

CEANS: Cardiovascular Effects of Air Pollution and Noise in Stockholm; SDPP: The Stockholm Diabetes Preventive Programme; SALT: the Screening Across the Lifespan Twin Study; SIXTY: The Stockholm cohort of 60-year-olds; SNAC-K: The Swedish National Study of Aging and Care in Kungsholmen; DCH: Diet, Cancer and Health; DNC: Danish Nurses Cohort; EPIC-NL: European Prospective Investigation into Cancer and Nutrition, the Netherlands; MORGEN: Monitoring Project on Risk Factors and chronic diseases in the Netherlands; E3N (EPIC-France): Etude Epidémiologique auprès de femmes de la Mutuelle Générale de l'Education Nationale; VHM&PP: Vorarlberg Health Monitoring and Prevention Programme.

[b] Kidney parenchyma cases.

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

Table 2
Pooled analyses of air pollution exposure and risk of kidney parenchyma (N = 847).

	Increment	Model 1[a] N = 302,493			Model 2[b] N = 302,493			Model 3[c] N = 302,493		
		HR	95% CI		HR	95% CI		HR	95% CI	
NO_2	10 μg/m^3	1.04	0.94	1.16	1.03	0.93	1.14	1.03	0.92	1.15
$PM_{2.5}$	5 μg/m^3	1.05	0.90	1.23	1.04	0.89	1.21	1.04	0.88	1.21
BC	0.5 10^{-5}m^{-1}	1.00	0.90	1.12	0.99	0.89	1.11	0.99	0.89	1.11
O_3	10 μg/m^3	0.86	0.75	1.00	0.88	0.76	1.02	0.88	0.76	1.02

HR, hazard ratio; CI, confidence interval; O_3, Ozone in the warm season.

[a] Adjusted for study (strata), age, sex (strata), year of baseline visit.

[b] Further adjusted for BMI, smoking status, duration, intensity, marital status, and employment status.

[c] Further adjusted for 2001 mean income at the area level.

percentage of married or cohabiting participants was 72 in the pooled cohort, ranging from 46% to 84%, and unemployment ranged from 76% to 5% with a pooled percentage of 29. The percentage of baseline current smokers varied from 13% to 37% with a pooled percentage of 24.

We generally observed lower mean levels of $PM_{2.5}$, NO_2 and BC in northern compared to more southern cohorts (Figure A.1), and mean O_3 levels were highest in the French and Austrian cohorts. The exposure distribution of each $PM_{2.5}$ component according to individual cohort is provided in Figure A.2. In general, the concentrations were lower in Northern compared to Southern cohorts - with the exception of $PM_{2.5}$ Ni, Si, and V. For NO_2, BC, Cu, Fe, and Si the within-cohort exposure contrast was large and less so for $PM_{2.5}$, O_3, K, Ni, S, V, and Zn. The exposures derived by SLR and RF were mostly similar, however, with large differences in individual cohorts and a smaller within-cohort exposure contrast for RF-modelled exposures compared to SLR.

In most of the cohorts, exposure to $PM_{2.5}$ was moderately to highly correlated with exposure to NO_2 and BC (Table A.1). The correlation between $PM_{2.5}$ and O_3 was generally moderately negative but varied substantially between the cohorts. Also, the correlations of $PM_{2.5}$ components with $PM_{2.5}$ mass and NO_2 varied greatly from low to moderate across the cohorts (Tables S2 and S3). The correlations between specific $PM_{2.5}$ components varied markedly across individual cohorts (Table A.4).

The results of the fully adjusted linear analyses (Model 3) showed a HR of 1.03 (95% CI: 0.92, 1.15) per 10 μg/m^3 NO_2, a HR of 1.04 (95% CI: 0.88, 1.21) per 5 μg/m^3 $PM_{2.5}$, a HR of 0.99 (95% CI: 0.89, 1.11) per 0.5 10^{-5} m^{-1} BCE, and a HR of 0.88 (95% CI: 0.76, 1.02) per 10 μg/m^3 O_3 (Table 2). The estimates of the three models of increasing adjustment were similar. The natural cubic splines with 3 degrees of freedom indicated a linear increase in the exposure-response function at the low end of the exposure range for NO_2, $PM_{2.5}$, and BC (Fig. 1). However, we observed an indication of a decreasing trend at the end of the exposure range with very wide CI's. The results for $PM_{2.5}$ components are provided in Fig. 2 and supplement Figure A.3, and these showed elevated risks in association with $PM_{2.5}$ Ni, S and especially Si estimated with SLR models. For PM components estimated by the RF-model, slightly elevated HRs were observed for Cu, Ni, and V. Especially the HRs based on exposures derived by the RF algorithm had very wide confidence bounds due to a smaller variability of the elemental components.

Analyses of subsets of the data showed a higher risk for kidney cancer when restricting to NO_2 concentrations below 20 μg/m^3 (HR 1.20; 95% CI: 0.75, 1.91), $PM_{2.5}$ concentrations below 15 μg/m^3 (HR 1.31; 95% CI: 0.89, 1.94), and BC concentrations below 1.5 10^{-5} m^{-1} (HR 1.45; 95% CI: 1.12, 1.89) (Table A.5). We found no clear indications of effect

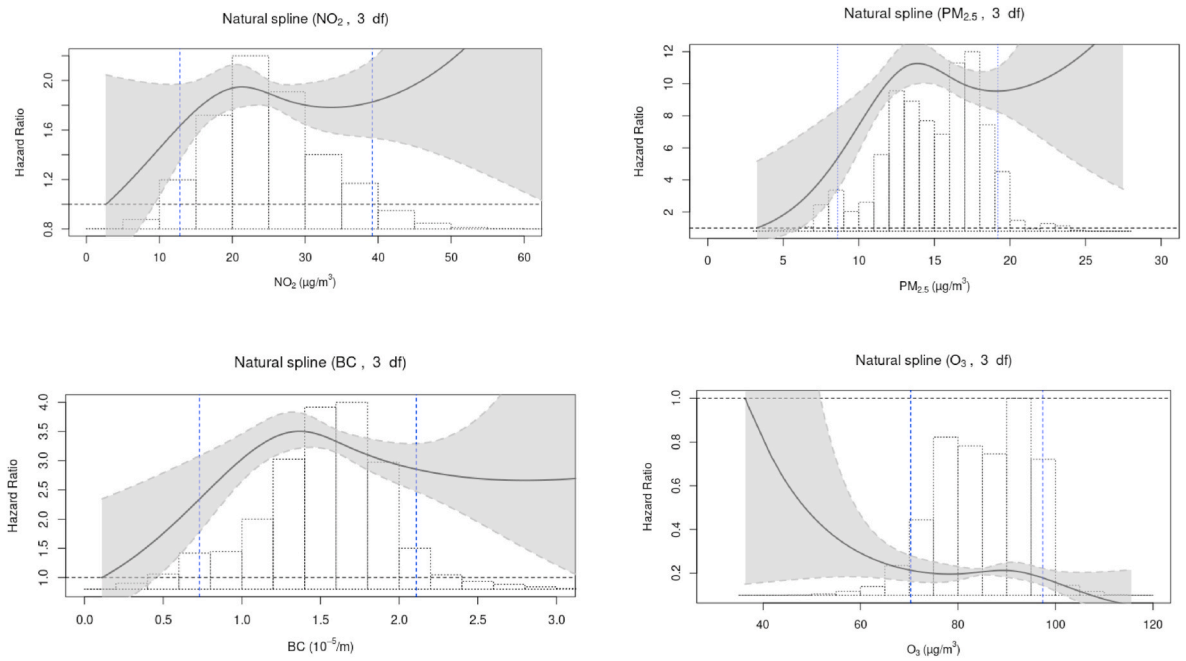

Fig. 1. Natural spline functions (3 df) of air pollutants and kidney parenchyma cancer incidence.

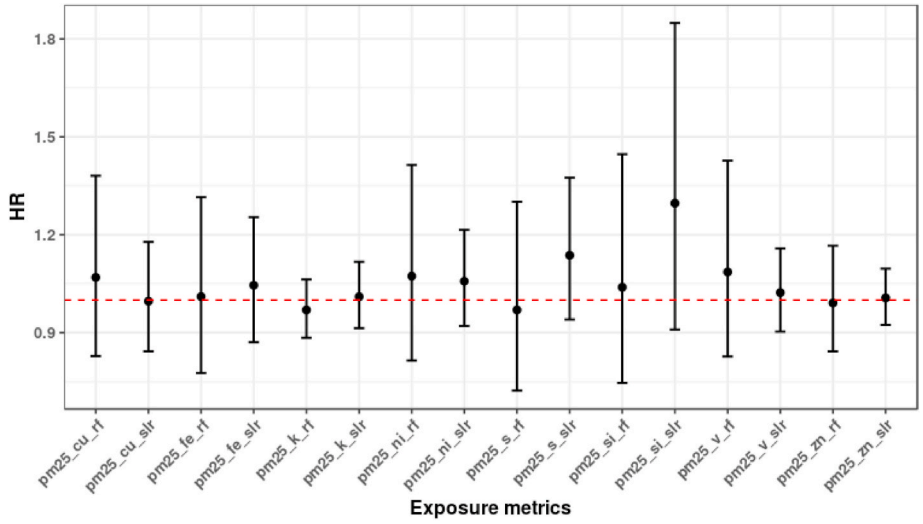

Fig. 2. Associations between $PM_{2.5}$ components and kidney parenchyma cancer based on SLR and random forest exposure algorithms (N = 302,493).

measure modification (Table A.6). The effect for NO_2 and BC was higher for smokers compared to ex- and never-smokers, whereas the opposite was true for $PM_{2.5}$. The results were also stable in the additional analysis adjusting for alcohol consumption, educational level, and occupational class in a pooled cohort including the cohorts with the available information (Table A.7). Back-extrapolation of the exposures to the baseline address of cohort members did not affect the estimates notably (Table A.8). The results of the time-varying analysis, taking into account the residential history of participants, resulted in effect estimates for NO_2, $PM_{2.5}$, and BC below 1, and a HR just above unity for O_3 compared to the main model 2010 exposure. We observed a moderate to high correlation between the ELAPSE air pollution exposure concentrations and the local study area specific LUR models from ESCAPE in all cohorts except CEANS (Figure A.4). The contrast in NO_2 exposure did not vary markedly for ELAPSE compared to ESCAPE, whereas for BC exposure the contrast was generally larger for the ELAPSE compared to the ESCAPE exposure. For $PM_{2.5}$, the contrast varied across the cohorts. For DCH, EPIC_NL, and VHM&PP the contrast was larger for the ELAPSE exposure compared to ESCAPE, while ESCAPE exposure had a larger exposure contrast in the CEANS cohort. The HR for BC in relation to kidney cancer was similar in analyses based on the ESCAPE LUR model compared to the ELAPSE exposure model in the cohorts and individuals for which both exposure models were available (Table A.9). For $PM_{2.5}$ and NO_2 the effect estimates were higher when based on the ELAPSE compared to the ESCAPE exposure model (1.04 [95% CI: 0.87; 1.24] vs. 0.96 [95% CI: 0.83; 1.10] for NO_2 and 1.01 [95% CI: 0.80; 1.29] vs. 0.91 [95% CI: 0.62; 1.33] for $PM_{2.5}$). However with both exposure methods, no indication of an association was found.

The results of the two-pollutant models are provided in Figures A.5 and A.6. Generally, the estimates remained stable after adjustment for co-pollutants, but estimates for NO_2 and BC were sensitive to mutual adjustment. The results were generally unaffected by exclusion of individual cohorts (Figure A.7). We detected deviation from the proportional hazards assumption for employment status. A sensitivity analysis

incorporating this variable in strata did not show results deviating from the main analysis with HRs of 1.03 (95% CI: 0.93, 1.15) per 10 μg/m^3 NO_2, 1.04 (95% CI: 0.88, 1.21) per 5 μg/m^3 $PM_{2.5}$, 0.99 (95% CI: 0.89, 1.11) per 0.5 10^{-5} m^{-1}, and 0.88 (95% CI: 0.76, 1.02) per 10 μg/m^3 O_3.

4. Discussion

In this pooled study of more than 300,000 individuals across Europe, we did not observe an increased risk of kidney parenchyma cancer in association with long-term air pollution exposures of NO_2, $PM_{2.5}$, BC, O_3, or elemental components of $PM_{2.5}$.

Our effect estimates differ from those reported in the ESCAPE analysis in which higher risks were reported with higher exposure to $PM_{2.5}$ and $PM_{2.5}$ absorbance, with HRs of 1.57 (95% CI: 0.81, 3.01) per increment of 5 μg/m^3 $PM_{2.5}$ and 1.36 (95% CI: 0.84, 2.19) per 10^{-5} m^{-1} $PM_{2.5}$ absorbance (BC proxy) (Raaschou-Nielsen et al., 2017). The CI's in both studies do, however, widely overlap. The current study builds on the ESCAPE collaboration, with some differences, which may explain the differential results. First, we performed a pooled analysis as opposed to a meta-analysis of individual study effect estimates. However, since we used a stratum term in the current analysis, we also primarily exploited exposure contrasts within cohorts. Second, in the current study we used a longer follow-up resulting in a larger number of cases of kidney parenchyma cancer. Consistently, confidence intervals were much narrower in the current analysis. In addition, we applied an improved exposure model incorporating outputs from chemical transport models and satellite data. Also, the observed difference may in part be due to differential inclusion of cohorts, although our analysis excluding single cohorts, did not suggest the results to be particularly sensitive to such heterogeneity. The cohorts from ESCAPE were selected based on the air pollution levels and willingness to pool data and a relatively recent recruitment date. The ELAPSE project specifically aims to investigate health effects of low-level air pollution. Of the ESCAPE cohorts included in the original Kidney cancer study, the Turin cohort was dropped for not contributing to analysis of low level air pollution, EPIC Varese was excluded because of missing information on individual SES data, and EPIC Umeå and San Sebastian because they did not include assessment of particles. The Oslo-based HUBRO study and the English EPIC-Oxford study were initially included, but both studies were unable to transfer data because internal procedures took much longer owing to unforeseen changes in privacy regulations. However, the two cohorts providing the largest number of cases (VHM and DCH) were included in both analyses. Of the 697 cases in the ESCAPE study, 538 are included in the present study. The spline and subset analyses suggest an association with kidney cancer for NO_2, $PM_{2.5}$, and BC for the lowest exposure levels – these mainly include the Scandinavian study areas. The steeper slope at lower exposure levels was also found for other endpoints in ELAPSE, including mortality (Strak et al., 2021). We cannot disentangle whether the steeper slope was related to the exposure level per se or other characteristics of the cohorts experiencing those exposure levels.

The few other published studies on air pollution and kidney cancers generally report elevated risk estimates with higher exposure to $PM_{2.5}$ (Zare Sakhvidi et al., 2020). An Italian study based on 196 incident cases of kidney cancer reported a HR of 1.24 (95% CI: 1.11, 1.29) and 1.20 (95% CI: 1.07, 1.33) per increments of 10 μg/m^3 $PM_{2.5}$ and NO_2, respectively (Gandini et al., 2018). The results were stronger for rural areas (2005 mean $PM_{2.5}$ of 20.9 μg/m^3) compared to urban (24.5 μg/m^3) and metropolitan (32.5 μg/m^3). The study was based on a crude exposure assignment (municipality-level) of each participant. In the American Cancer Society Cancer Prevention Study-II cohort, $PM_{2.5}$ exposure was found to be associated with kidney cancer mortality with a HR of 1.14 per 4.4 μg/m^3 (95% CI: 1.03, 1.27) (Turner et al., 2017). The study was based on hybrid LUR exposure assigned to the residential address of 623,048 participants and a total of 927 kidney cancer deaths (mean $PM_{2.5}$ 12.6 μg/m^3). Given the relatively high 5-year survival rate of kidney cancers, the mortality end point does not reflect disease incidence very well. We have not been able to identify previous studies concerning exposure to PM constituents and kidney cancer risk.

Strengths of the present study include the large sample size gained through pooling data from six European cohorts and the detailed information on important covariates, which were harmonized specifically for the ELAPSE project. The cohorts covered a large part of Europe and the large sample size enabled two-pollutant models to disentangle potential inter-dependencies between pollutants as well as analyses of interaction. The findings, however, were sensitive to mutual adjustment of NO_2 and BC - probably as a consequence of high correlations between these two pollutants in some cohorts (Table A.1). Comparable exposure estimates for the entire study population were ensured by applying hybrid air pollution models developed centrally for the ELAPSE collaboration. The exposure model was, however, developed based on year 2010 measurements, which represent exposure towards the end of the follow-up period. The back-extrapolated analysis performed to investigate the potential exposure misclassification as a consequence of this approach yielded stable results. Previous European studies have reported the spatial distribution of NO_2, black smoke, and traffic intensities to be historically stable (Beelen et al., 2007; Cesaroni et al., 2012; Gulliver et al., 2011), and the applied 2010-model has shown high correlations with models developed for 2000 and 2005 (2013 for $PM_{2.5}$) (de Hoogh et al., 2018). We did not have available data on time-trends of $PM_{2.5}$ components to perform back-extrapolated analyses, and therefore we are not able to exclude the possibility that the spatial contrast has been less stable over time for the elemental components. In addition, applying a model for exposure assignment unavoidably imposes misclassification because of uncertainties in input data and due to the fact that exposure modelled at the residential address does not cover the true personal exposure. Our results were generally stable across the three models of increasing confounder adjustment and the adjustment for occupational class and educational level in sensitivity analyses. However, residual confounding from e.g. occupational exposures or cumulative smoking dose cannot be excluded. Also, we cannot rule out the possibility of residual spatial confounding, however, adjustment for area-level income did not affect the effect estimates. The individual cohorts might differ according to underlying risk of kidney parenchyma cancer as a consequence of such unmeasured factors, but the analyses were stratified by cohort in order to account for differences in baseline hazards. Lastly, censoring at the time of any other cancer event than renal cancer might bias the results toward the null by ignoring potential renal cancer outcome data that comes to clinical attention after a separate cancer. However, the risk for the cancer under investigation very likely changes (in an unpredictable way) when diagnosed with another cancer. Hence, the potential bias cannot be evaluated.

The findings of this study were based on a pool of cohorts collected from across Europe, which were selected to represent areas in the lower exposure range. Thus, the results might not be generalized to populations exposed to higher levels of air pollution.

In conclusion, our study does not provide further evidence of a role of air pollution in the development of kidney parenchyma cancers.

Credit author statement

Ulla Arthur Hvidtfeldt: Formal analysis, Methodology, Software, Visualization, Writing – original draft; **Tahir Taj:** Data curation, Methodology, Writing - review & editing; **Jie Chen:** Data curation, Methodology, Project administration, Software, Writing - review & editing; **Sophia Rodopoulou:** Data curation, Methodology, Software, Writing - review & editing; **Maciej Strak:** Data curation, Methodology, Writing - review & editing; **Kees de Hoogh:** Data curation, Methodology, Writing - review & editing; **Zorana Jovanovic Andersen:** Methodology, Writing - review & editing; **Tom Bellander:** Methodology, Writing - review & editing; **Jørgen Brandt:** Data curation, Methodology, Writing - review & editing; **Daniela Fecht:** Methodology, Writing - review & editing;

Francesco Forastiere: Writing - review & editing; **John Gulliver:** Methodology, Writing - review & editing; **Ole Hertel:** Data curation, Methodology, Writing - review & editing; **Barbara Hoffmann:** Methodology, Writing - review & editing; **Jeanette Therming Jørgensen:** Methodology, Writing - review & editing; **Klea Katsouyanni:** Methodology, Writing - review & editing; **Matthias Ketzel:** Data curation, Methodology, Writing - review & editing; **Anton Lager:** Data curation, Writing - review & editing; **Karin Leander:** Resources, Writing - review & editing; **Petter L.S. Ljungman:** Methodology, Writing - review & editing; **Patrik K.E. Magnusson:** Writing - review & editing; **Gabriele Nagel:** Data curation, Methodology, Writing - review & editing; **Göran Pershagen:** Data curation, Writing - review & editing; **Debora Rizzuto:** Data curation, Methodology, Writing - review & editing; **Evangelia Samoli:** Methodology, Software, Writing - review & editing; **Rina So:** Methodology, Writing - review & editing; **Massimo Stafoggia:** Methodology, Writing - review & editing; **Anne Tjønneland:** Data curation, Resources, Writing - review & editing; **Roel Vermeulen:** Methodology, Writing - review & editing; **Gudrun Weinmayr:** Methodology, Writing - review & editing; **Kathrin Wolf:** Data curation, Software, Methodology, Writing - review & editing; **Jiawei Zhang:** Methodology, Writing - review & editing; **Emanuel Zitt:** Methodology, Writing - review & editing; **Bert Brunekreef:** Conceptualization, Funding acquisition, Methodology, Project administration, Resources, Software, Supervision, Validation, Writing - review & editing; **Gerard Hoek:** Conceptualization, Funding acquisition, Methodology, Project administration, Supervision, Validation, Writing - review & editing; **Ole Raaschou-Nielsen:** Conceptualization, Data curation, Methodology, Supervision, Writing - review & editing.

Funding

The research described in this article was conducted under contract to the Health Effects Institute (HEI), an organisation 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.

Declaration of competing interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

Data availability

The authors do not have permission to share data.

Acknowledgements

We thank Marjan Tewis for the data management tasks in creating the pooled cohort database and the National Institute for Public Health and the Environment (RIVM), Bilthoven, the Netherlands, for their contribution to the ELAPSE Study.

Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.envres.2022.114385.

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