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Long-term exposure to air pollution and incidence of gastric and the upper aerodigestive tract cancers in a pooled European cohort: The ELAPSE project

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Abstract

Air pollution has been shown to significantly impact human health including cancer. Gastric and upper aerodigestive tract (UADT) cancers are common and increased risk has been associated with smoking and occupational exposures. However, the association with air pollution remains unclear. We pooled European subcohorts (N = 287,576 participants for gastric and N = 297,406 for UADT analyses) and investigated the association between residential exposure to fine particles ($PM_{2.5}$), nitrogen dioxide (NO_2), black carbon (BC) and ozone in the warm season (O_{3w}) with gastric and UADT cancer. We applied Cox proportional hazards models adjusting for potential confounders at the individual and area-level. During 5,305,133 and 5,434,843 person-years, 872 gastric and 1139 UADT incident cancer cases were observed, respectively. For gastric cancer, we found no association with $PM_{2.5}$, NO_2 and BC while for UADT the hazard ratios (95% confidence interval) were 1.15 (95% CI: 1.00–1.33) per 5 μg/m^3 increase in $PM_{2.5}$, 1.19 (1.08–1.30) per 10 μg/m^3 increase in NO_2, 1.14 (1.04–1.26) per 0.5×10^{-5} m^{-1} increase in BC and 0.81 (0.72–0.92) per 10 μg/m^3 increase in O_{3w}. We found no association between long-term ambient air pollution exposure and incidence of gastric cancer,

For affiliations refer to page 1908

while for long-term exposure to $PM_{2.5}$, NO_2 and BC increased incidence of UADT cancer was observed.

KEYWORDS

air pollution, gastric cancer, nitrogen dioxide, ozone, particular matter, UADT

What's new?

Exposure to long-term ambient air pollution increases mortality and cancer incidence. However, most evidence exists for high exposure levels and lung cancer. In this large European study focusing on air pollution levels even below current EU standards, long-term exposure to fine particles, nitrogen dioxide and black carbon increased the incidence of upper aerodigestive tract cancers, while no association was found with gastric cancer. These results indicate that ambient air pollution may increase the risk of upper aerodigestive tract cancers, and support the need for aligning current EU air pollution levels with the new WHO Air Quality Guidelines.

1 | INTRODUCTION

Exposure to long-term ambient air pollution has been shown to increase the risk of mortality, cardiometabolic diseases and cancer.[1] The public health recommendations regarding cancer are dominated by the existing evidence on lung cancer.[2] Gastric cancer is an important cause of cancer mortality contributing to 8% of all cancer-related deaths in 2020.[3] Upper aerodigestive tract (UADT) cancers are located in the tongue, mouth, pharynx, larynx and esophagus, which share smoking as a main risk factors.[4] To date, there is limited evidence regarding the association between air pollution and the incidence of gastric and UADT cancers, though for lung cancer there is strong evidence for an association. Common risk factors for gastric and UADT cancers are smoking and alcohol consumption. Other risk factors for gastric cancers are helicobacter pylori infection, excess weight and diet high in salt and meat and low in fruit and vegetables.[4] Indirect indication for an association of airborne pollutants with gastric and UADT cancer comes from occupational and industrial settings.[5,6] Further indication for an association of $PM_{2.5}$ with gastric and UADT cancer comes from wildfire exposure in Brazil.[7] Pritchett et al[8] summarized the results for an association between outdoor particulate matter (PM) air pollution and the risk of gastrointestinal cancers. They found, that most previous studies were on stomach cancer mortality[2,9–12] and two studies from the ESCAPE project on gastric cancer incidence.[13,14] Overall, Pritchett et al saw no evidence for an association between PM and stomach cancer as well as esophageal risk.[8] However, there are only a few epidemiological studies to date.

Furthermore, most previous studies on long-term air pollution were performed in settings (industrial, urban) with high exposure levels. The aim of the Effects of Low-Level Air Pollution: A Study in Europe (ELAPSE) project[15] was to investigate low exposure levels as defined as less than the current European Union (EU) Limit Values and/or World Health Organization (WHO) 2005 year Air Quality Guideline values for $PM_{2.5}$, NO_2 and O_3.[15] To investigate the associations of ambient air pollution with gastric and UADT cancer incidence in the general population, we conducted analyses in a large pooled cohort within the ELAPSE project.

2 | MATERIALS AND METHODS

2.1 | Study population

The study is based on data from 10 European subcohorts from five countries pooled within the Effects of Low-Level Air Pollution: A Study in Europe' (ELAPSE) project, which has been described in detail elsewhere.[15] For the current analyses, we selected subcohorts with at least 10 gastric or UADT cancer cases, respectively. We therefore included the following European subcohorts in the analyses of UADT cancer: Sweden (Cardiovascular Effects of Air Pollution and Noise in Stockholm [CEANS], comprising the following four subcohorts: Swedish National Study on Aging and Care in Kungsholmen [SNAC-K],[16] Stockholm Screening Across the Lifespan Twin study [SALT],[17] Stockholm 60 years old study [Sixty],[18] and Stockholm Diabetes Prevention Program [SDPP])[19]; Denmark (Diet, Cancer and Health cohort [DCH][20] and 1993 subcohort of the Danish Nurse Cohort [DNC][21]); the Netherlands (Dutch European Investigation into Cancer and Nutrition [EPIC-NL] consisting of EPIC-Monitoring Project on Risk Factors and Chronic Diseases in the Netherlands [EPIC-MORGEN] and [EPIC-Prospect])[22]; France (Etude Epidémiologique auprès de femmes de la Mutuelle Générale de l'Education Nationale [E3N])[23] and Austria (Vorarlberg Health Monitoring and Prevention Programme [VHM&PP]).[24] The subcohorts and the covariates have been described in detail previously.[25] For gastric cancer we excluded CEANS-SDPP (3 cases of gastric cancer) and CEANS-SNACK (6 cases) resulting in 8 subcohorts for the analysis in the analyses of cancer gastric cancer and 10 subcohorts for the analyses of UADT.

2.2 | Air pollution exposure assessment

The methods to estimate the exposure to air pollution within ELAPSE has been described comprehensively elsewhere.[26] In brief, annual mean concentrations of $PM_{2.5}$, NO_2, BC and warm season ozone (O_{3w}) for 2010 were estimated at the baseline residential addresses of

all individuals in the subcohorts using hybrid land-use regression (LUR) models based on monitoring data for $PM_{2.5}$, NO_2 and O_3,[26] offering a wide range of potential predictors including satellite-derived estimates, chemical transport model estimates, land-use, road and population density data. The modelling of $PM_{2.5}$, NO_2 and O_{3w} exposures was based on the European Environmental Agency AirBase routine monitoring data[26] whereas the modelling of BC used ESCAPE monitoring data[27] to develop and evaluate models.[26] The LUR models performed well in fivefold hold-out validation, explaining 66%, 58%, 51% and 60% of the measured spatial variation for $PM_{2.5}$, NO_2, BC and O_{3w}, respectively.[26]

The exposure models were applied to create 100 × 100 m grids of the predicted air pollution concentrations covering the entire study area. Exposure to air pollution was assigned to participants' baseline residential addresses.

A back-extrapolation of the air pollution concentrations was applied for the subset of subcohorts with available residential address history. We used two different back-extrapolation methods: (a) ratio and (b) difference. The detailed methods can be found in previous publications.[15,28] Briefly, we used the air pollution estimated by the Danish Eulerian Hemispheric Model (DEHM) to extrapolate each individual's annual air pollution level by applying the ratio or difference between the annual averages of each year of follow-up and the year 2010. DEHM provides monthly mean concentration estimates at 26 km × 26 km spatial resolution across Europe back to at least 1990. Time-varying annual levels were calculated using the two different back-extrapolation methods incorporating residential history.

2.3 | Outcome definition

Gastric and UADT cancers were mainly identified in high-quality national or local cancer registries, one exception was E3N, in which self-reports from biannual questionnaires or death certificates were used and verified through pathological reports. All were following consistently the international approach of cancer registration and using the International Statistical Classification of Diseases and Related Health Problems, 9th and 10th revision [ICD9 and ICD10]: for gastric cancer C16 [ICD10] and 151 [ICD9], and for UADT cancers: C01-06 and 141-145 (oral cavity), C09, C10 (oropharynx), C12, C13 (hypo-pharynx) and 146 (pharynx), C14, C32 and 161 (larynx), C15 and 150 (esophagus). The analyses focused on primary cancer and also only first cancer. Any prevalent cancers at baseline were excluded (except non-melanoma skin cancers).

2.4 | Statistical analysis

We applied Cox proportional hazard models with age as the timescale to analyze the associations between air pollution and cancer outcomes with increasing control for individual-covariates and one area-level covariate (mean income at neighborhood or municipality level). Censoring occurred at time of first occurrence of any cancer other than the cancer of interest, date of death, emigration, loss to follow-up or at the end of follow-up, whichever came first. A priori we specified three confounder models: Model 1 included only age (time axis), sex (as strata), cohort (as strata) and calendar year(s) of enrollment. Model 2 added individual-level variables that were consistently available in the subcohorts contributing to the pooled cohort: smoking status (never/former/current), smoking intensity (linear and squared) and smoking duration (continuously in years); marital status (single/married or living with partner/divorced or separated/widowed) and employment status (yes/no). Model 3 added to the model 2 mean income at neighborhood or municipality level. A priori model 3 was selected as the main model. Only subjects with complete information for model 3 variables were included in the analyses.

We investigated exposure-response functions by applying natural splines with three degrees of freedom, as a flexible method allowing multiple shapes in different parts of the exposure distribution.[29]

In addition, several sensitivity analyses were performed. First, we performed two pollutant models, adjusting pollutants mutually for each other. Some of the pollutants were highly correlated (>0.7) and the respective associations were labelled in the results. Second, we explored alternative exposures by back-extrapolation to the baseline year concentrations and time-varying air pollution exposure extrapolated based on the address history from enrolment to the end of follow-up. Third, models adjusting for additional potential confounders including variables for smoking status and intensity, environmental tobacco smoke (ETS) and dietary variables (alcohol, fruit, vegetable and meat consumption) were calculated in subsets of the pooled cohort. Fourth, we investigated the change in association by excluding one cohort at a time from the analysis.

Analyses were performed in R (version 3.4.0; R Development Core Team), using the packages survival (version: 2.42-3), coxme (version: 2.2-10), Matrix (version: 1.2-14), foreach (version: 1.4.4), glmnet (version: 2.0-16), multcomp (version: 1.4-8), survey (version: 3.33-2), splines (version: 3.4.0), Hmisc (version: 4.1-1), mfp (version: 1.5.2), VIM (version: 4.7.0), ggplot2 (version: 2.2.1), MASS (version: 7.3-50) and rms (version: 5.1-2).

3 | RESULTS

Out of 343,625 for the UADT cancer and 333,525 participants for the gastric analyses we excluded 13,374 individuals due to missing exposures (13,364 for gastric cancer), 42,968 individuals with missing values in individual covariates (42,700 for gastric cancer). And 3251 (3249 for gastric cancer) due to missing values for neighborhood mean income, leaving a total of 287,576 participants in the gastric cancer and 297,406 participants in the UADT cancer analysis, with a mean follow-up of 18.5 and of 18.3 years respectively. During 5,305,133 and 5,434,843 person-years, 872 gastric and 1139 UADT incident cancer cases were observed (Table 1). Enrollment year and end of follow-up varied between 6.9 and 21 years by subcohorts, ranging from 1985 to 2005 for the enrollment year, and 2011 to 2015 for end of follow-up. The mean age at baseline was 48.3

TABLE 1 Description of the included subcohort studies.

Subcohort	Population size[a] (N)	Persons in model 3 (N)	% lost[b]	Baseline period	Years of follow up (mean)[c]	Gastric cancer cases (N)	UADT cancer cases (N)	Age at baseline (mean ± SD)	Female (%)	Current smokers (%)	(Self-) employed (%)	Married/ cohabiting (%)	Small-area level income[d] (mean ± SD)
CEANS-SALT	6098	5717	6.2%	1998–2003	9.90	11	25	57.44 ± 10.51	54	21	66	68	25.33 ± 6.6
CEANS-SDPP	7403	7325	1.1%	1992–1998	15.34	–[e]	18	47.02 ± 4.94	59	26	91	84	24.33 ± 4.21
CEANS-SIXTY	3856	3660	5.1%	1997–1999	11.95	14	18	60 ± 0	50	21	68	74	24.66 ± 6.85
CEANS-SNAC-K	2697	2505	7.1%	2001–2004	6.93	–[e]	10	73.48 ± 11.0	64	14	23	44	28.66 ± 2.22
DCH	55,401	52,817	4.7%	1993–1997	16.89	189	452	56.65 ± 4.35	53	36	78	71	20.14 ± 3.39
DNC-1993	17,922	15,664	12.6%	1993	16.85	35	47	56.07 ± 8.36	100	37	70	68	19.22 ± 2.57
E3N	49,740	38,171	23.3%	1989–1991	15.85	32	40	52.87 ± 6.75	100	13	68	83	11.17 ± 3.02
EPIC-NL-Morgen	20,096	17,797	11.4%	1993–1997	16.43	27	48	42.68 ± 11.23	54	35	69	65	12.2 ± 1.59
EPIC-NL-Prospect	15,054	13,651	9.3%	1993–1998	15.66	46	29	57.6 ± 6.02	100	23	51	77	13.08 ± 1.38
VHMPP	165,358	140,099	15.3%	1985–2005	20.97	518	452	41.7 ± 14.92	56	20	71	69	22.87 ± 1.66
Pooled cohort-gastric	333,525	287,576	13.8%	1985–2005	18.45	872	–	48.07 ± 13.53	66	24	71	71	19.56 ± 5.3
Pooled cohort-UADT	343,625	297,406	13.5%	1985–2005	18.27	–	1139	48.26 ± 13.56	65	24	71	72	19.76 ± 5.35

[a]Number of individuals included in the pooled cohort from the cohorts of interest.
[b]Percentage of persons not included in model 3.
[c]For persons in model 3 (as for all the following columns).
[d]In Euros × 1000, year 2001.
[e]For gastric cancer analyses we excluded the following cohorts due to a case number lower than 10: CEANS-SDPP (3 cases of gastric cancer), CEANS-SNACK (6) and DNC-1999 (5). For UADT analyses we only excluded DNC-1999 (9 UADT cases).

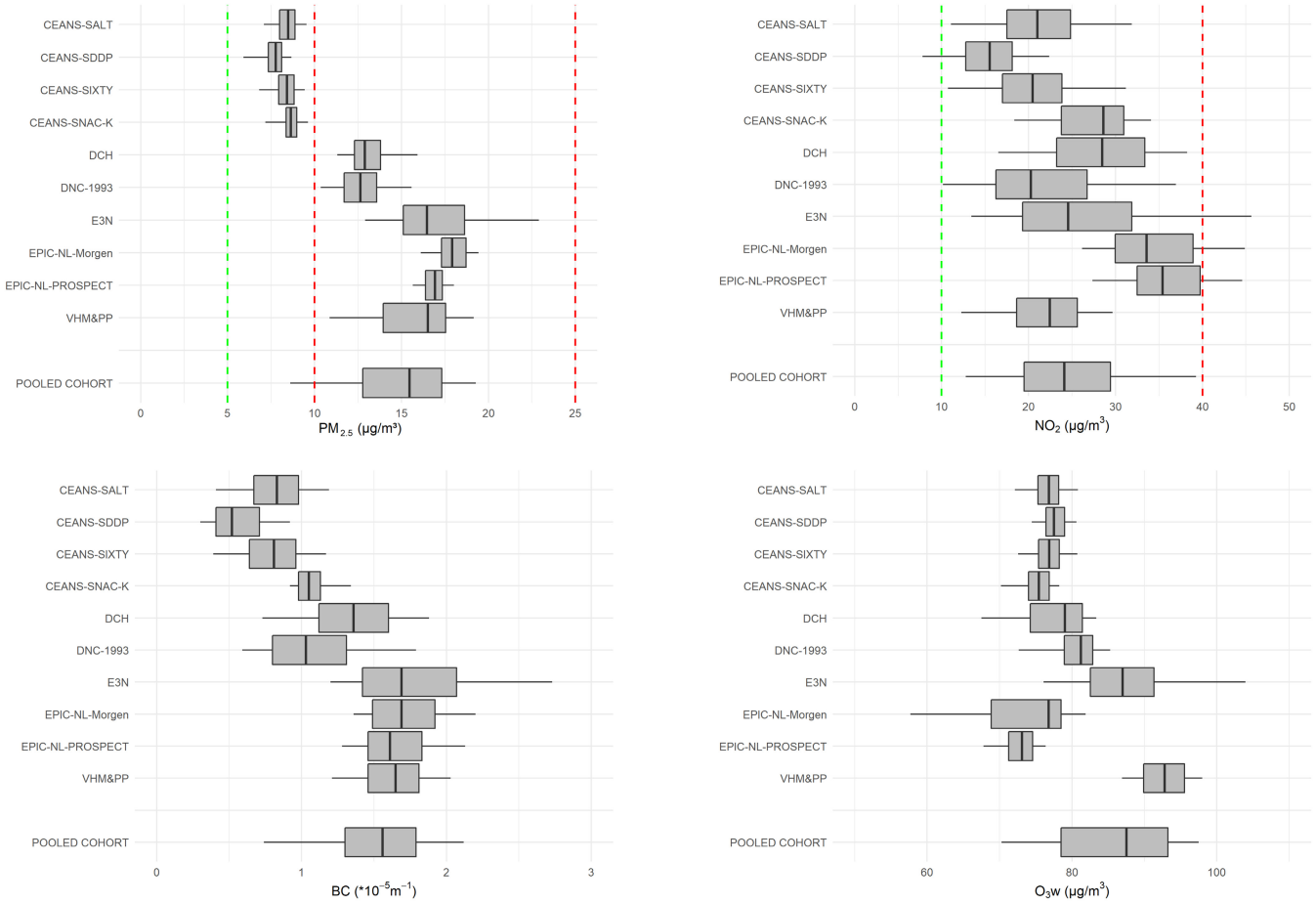

FIGURE 1 Exposure to $PM_{2.5}$, NO_2, BC and O_3 at the warm period at participant address per subcohort for the final data included in model 3 (N = 287,576) green = 2021 WHO guidelines 5 and 10 µg/m^3 $PM_{2.5}$ and NO_2, respectively, red = 2005 WHO guidelines 10 and 40 µg/m^3 $PM_{2.5}$ and NO_2, respectively, and EU ambient air quality limit values, 25 and 40 µg/m^3 $PM_{2.5}$ and NO_2, respectively.

TABLE 2 Cox model estimates for the association between air pollution and risk of gastric and UADT cancer.

	Model 1[a]	Model 1[a] using the model 3 final data	Model 2[b]	Model 3[c]
	HR (95% CI)	HR (95% CI)	HR (95% CI)	HR (95% CI)
Gastric cancer (N)	333,525	287,576	287,576	287,576
$PM_{2.5}$ (5 µg/m^3)	0.99 (0.87–1.14)	0.97 (0.84–1.12)	0.97 (0.83–1.12)	0.98 (0.85–1.14)
NO_2 (10 µg/m^3)	1.00 (0.90–1.11)	0.98 (0.87–1.09)	0.96 (0.86–1.07)	0.98 (0.88–1.10)
BC (0.5 × 10^{-5} m^{-1})	0.99 (0.89–1.11)	0.97 (0.87–1.09)	0.95 (0.85–1.07)	0.98 (0.87–1.10)
O_{3w} (10 µg/m^3)	1.02 (0.88–1.17)	1.03 (0.88–1.20)	1.06 (0.90–1.23)	1.04 (0.89–1.22)
UADT cancer (N)	343,625	297,406	297,406	297,406
$PM_{2.5}$ (5 µg/m^3)	1.16 (1.02–1.33)	1.24 (1.07–1.44)	1.15 (1.00–1.33)	1.15 (1.00–1.33)
NO_2 (10 µg/m^3)	1.24 (1.14–1.36)	1.29 (1.18–1.41)	1.18 (1.08–1.30)	1.19 (1.08–1.30)
BC (0.5 × 10^{-5} m^{-1})	1.22 (1.11–1.33)	1.24 (1.13–1.37)	1.14 (1.04–1.25)	1.14 (1.04–1.26)
O_{3w} (10 µg/m^3)	0.73 (0.65–0.81)	0.71 (0.63–0.79)	0.81 (0.72–0.91)	0.81 (0.72–0.91)

Abbreviations: CI, confidence interval; HR, hazard ratio; O_{3w}, Ozone in the warm season.
[a]Adjusted for study (strata), sex (strata), age, calendar year of enrolment.
[b]Model 1, further adjusted for individual-level covariates: smoking (status, duration, intensity, intensity^2), marital status and employment status.
[c]Model 2, further adjusted for area-level covariate 2001: mean income at the neighbourhood level.

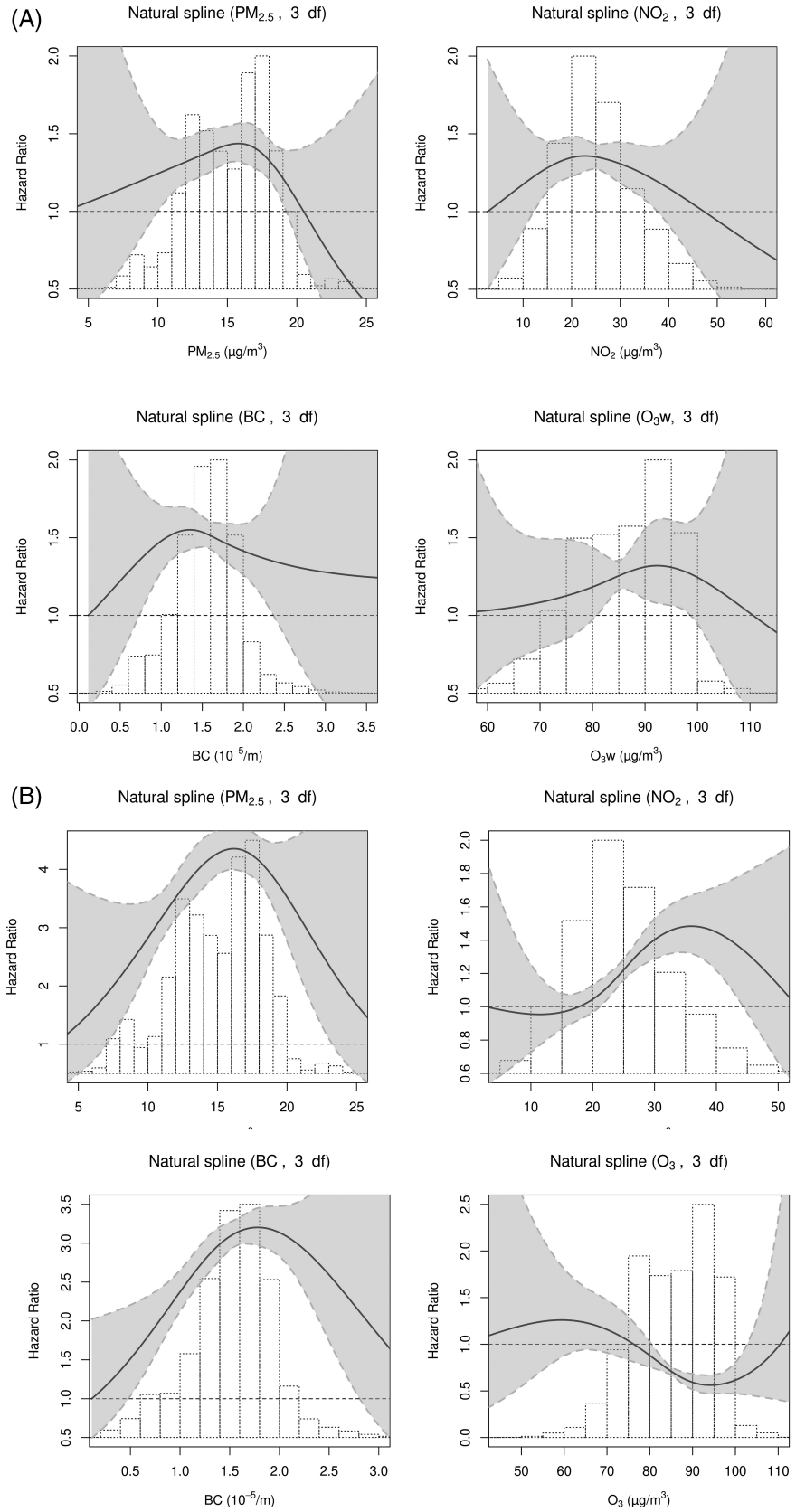

FIGURE 2 (A) Concentration response functions for the association between long-term air pollution exposure and gastric cancer, using natural splines with three degrees of freedom in the main analysis model. (B) Concentration response functions for the association between long-term air pollution exposure and UADT cancer, using natural splines with three degrees of freedom in the main analysis model.

± 13.6 years and 48.1 ± 13.5 years, respectively. Most participants were female, (65% and 66%, respectively), with three subcohorts including only females (DNH, E3N, EPIC-NL Prospect). The prevalence of current smokers was 24% in both study samples. DCH (21.9%) and VHM&PP (49.6%) were the subcohorts contributing most to the study population.

The distribution of the air pollutants by subcohort is presented in Figure 1. Overall, the median levels were 15.5 $\mu g/m^3$ for $PM_{2.5}$, 24.1 $\mu g/m^3$ for NO_2, 1.6×10^{-5} m^{-1} for BC and 87.5 $\mu g/m^3$ for O_{3w} (Table S1). Exposure ranges show a North to South gradient with lower concentrations in the North for PM2.5 and BC and to a lesser extent for NO_2 and O_{3w}. Exposure to $PM_{2.5}$ and NO_2 was generally below annual limit values ($PM_{2.5}$: 25 $\mu g/m^3$; NO_2: 40 $\mu g/m^3$) of the European Air Quality Directive (EU-AAQD) for most of the cohorts, but generally above current WHO guidelines for $PM_{2.5}$ (5 $\mu g/m^3$) and NO_2 (10 $\mu g/m^3$).

The correlation (Spearman correlation coefficient) was strongest between BC and $PM_{2.5}$ (0.76 and 0.78 for the gastric and UADT cancer study, respectively), followed by BC and NO_2 (0.63 and 0.64). $PM_{2.5}$ was moderately correlated with NO_2 (0.47 and 0.48), while O_{3w} was negatively correlated with all other pollutants (Table S2) and more strongly with NO_2 (−0.64 and −0.59).

For gastric cancer we found no association with long-term exposure to $PM_{2.5}$, NO_2, BC or O_{3w} in any of the adjustment models (Table 2). In the main model, the HRs were 0.98 (95% CI: 0.85–1.14) per 5 $\mu g/m^3$ increase in $PM_{2.5}$, 0.98 (95% CI: 0.88–1.10) per 10 $\mu g/m^3$increase in NO_2, 0.98 (0.87–1.10) per 0.5×10^{-5} m^{-1} increase in BC and 1.04 (0.89–1.22) per 10 $\mu g/m^3$ increase in O_{3w}.

For UADT cancer, long-term exposure to $PM_{2.5}$, NO_2 and BC was associated with UADT in the main model (model 3). The HRs were 1.15 (95% CI: 1.00–1.33) per 5 $\mu g/m^3$ increase in $PM_{2.5}$, 1.19 (95% CI: 1.08–1.30) per 10 $\mu g/m^3$ increase in NO_2, 1.14 (1.04–1.26) per 0.5 10^{-5} m^{-1} increase in BC and 0.81 (0.72–0.92) per 10 $\mu g/m^3$ increase in O_{3w}. Cancer incidence in the basic model (model1) HRs were 1.16 (95% CI: 1.02–1.33) per 5 $\mu g/m^3$ increase in $PM_{2.5}$, 1.24 (95% CI: 1.14–1.36) per 10 $\mu g/m^3$increase in NO_2, 1.22 (1.11–1.33) per 0.5 10^{-5} m^{-1} increase in BC and 0.73 (0.65–0.81) per 10 $\mu g/m^3$ increase in O_{3w}. Adjustment for smoking variables (model 2) and area-level SES in model 3 attenuated the associations (Table 2).

The natural cubic splines indicated deviations from linearity in the association between air pollution and gastric cancer (Figure 2A) and UADT cancer (Figure 2B), although at the ends of the distribution. The interpretation of the curve is limited due to the lack of data and associated statistical power. However, in the central area with the majority of the data, the curve for $PM_{2.5}$ and BC indicated linearity with a trend for attenuation at higher concentrations. For NO_2 linearity in the central area was observed with a potential attenuation in the lower and upper regions. A similar pattern but in the opposite direction was observed for O_{3w}.

The two pollutant models (Table S3) showed similar patterns for gastric and UADT cancers. The HRs for NO_2 and BC persisted after adjusting for $PM_{2.5}$ and were slightly attenuated after adjustment for O_{3w}. The HR estimates for $PM_{2.5}$ were attenuated in all two pollutant models. The negative association between O_{3w} and UADT incidence slightly increased after adjustment for NO_2 or BC and remained stable after adjustment for $PM_{2.5}$.

The sensitivity analyses showed similar results to the main findings. Results for $PM_{2.5}$, NO_2, BC and O_{3w}, exposures back-extrapolated to baseline years are shown in the supplemental material (Table S4 for gastric and UADT cancer). The models including different sets of covariates including smoking duration/intensity/ETS and dietary factors revealed similar estimates for the association between air pollutants and gastric (Table S5a) as well as UADT cancer (Table S5b). Furthermore, time-varying analyses resulted (Table S6) in similar estimates for both cancers. Analyses by smoking status suggested no effect modification (Table S7).

Dropping one cohort at time revealed similar results to the pooled cohort's analysis for gastric cancer (Figure S1A). However, UADT cancer analyses estimates were sensitive to the exclusion of DCH (Figure S1B), leading to no associations for all air pollutants.

4 | DISCUSSION

Using data of 297,406 participants from five European countries for the UADT analyses we found long-term exposure to $PM_{2.5}$, NO_2 and BC to be associated with UADT cancer incidence, while O_{3w} was inversely associated. The concentration-response curves appeared mostly linear for all three pollutants in low-middle concentration. For gastric cancer, we observed no association between air pollution and gastric cancer incidence.

Our finding of increased incidence of UADT cancer for $PM_{2.5}$, NO_2 and BC long-term exposure is consistent with previous reports on airborne risk factors from occupation[5,6] indoor air pollution from solid fuel combustion,[30] and smoking.[31] In addition, there is evidence that NO_2 and $PM_{2.5}$ are associated with respiratory health in children and adults,[32] which may contribute to cancer risk due to chronic inflammation.[33] Long-term exposure to $PM_{2.5}$ from wildfires in Brazil showed increased mortality from cancers of the nasopharynx, esophagus and stomach.[7] In this large European study focusing on low level air pollution levels even below current EU standards, the long-term exposure to air pollution increased the incidence of UADT, but no association was found for gastric cancer. Note however, that remains above the recently up-dated WHO air quality guidelines (eg, 10 $\mu g/m^3$ for NO_2 and 5 $\mu g/m^3$ $PM_{2.5}$).[34]

Our observation of no association between long-term air pollution and gastric cancer incidence contrasts to some previous studies.[13,14] A recent meta-analysis on gastrointestinal cancers revealed that most previous studies were on mortality[8] with few exceptions including the studies within the ESCAPE project.[13,14] Overall, in the meta-analysis for gastric cancer, no association was found.[8] However, in the ELAPSE study, we found no association with gastric cancer risk, while in the analyses of the ESCAPE cohort exposure to $PM_{2.5}$ increased gastric cancer incidence by 38%,[13] although, the confidence intervals from both studies overlap. The literature on gastric cancer showed mixed results.[8] The differences between ESCAPE and ELAPSE in effect estimates could be explained by including somewhat different subcohorts and longer follow-up in the ELAPSE project.[26,35] The HRs and confidence interval of the main components overlap widely between ESCAPE and ELAPSE whereas the confidence intervals are considerably smaller in the ELAPSE results. The Europe-wide exposure model increased the number of study-specific participants for three subcohorts because larger areas were covered (DCH, E3N

and VHM&PP). Finally, the exposure models in ELAPSE were refined by developing Europe-wide models using Airbase data and a wider range of predictors.[35]

Environmental exposures contribute to the development of diseases by various multiple mechanisms such as oxidative stress and inflammation, genetic and epigenetic alterations, altered intracellular and microbiome interaction and impaired nervous system.[36] Of these several potential biological mechanisms for an association between environmental factors and gastric cancer have been hypothesized.[8,37] A recent comprehensive overview revealed that air pollution exposure is associated with metabolic pathways primarily related to oxidative stress, inflammation and steroid metabolism.[38] General mechanisms of carcinogenicity for PM-related cancers include DNA damage due to oxidative stress and inflammation that promotes tumor growth.[8] These pathways were also found to play a role in the association between long-term ambient air pollution and UADT.[2,39] Regarding NO_2, most evidence for different outcomes including mortality comes from epidemiological studies.[40] While the US Environmental Protection Agency review on NO_2 reports findings of an increase in markers of inflammation and oxidative stress in human plasma,[41] experimental studies are still very few and evidence therefrom remains limited.

In the gastrointestinal tract, air pollution may simultaneously impact gastrointestinal and lung health because there is evidence that the gut and lungs can communicate and influence each other via connected blood circulation and lymphatic system.[42,43] This suggests, that the exchange of immune cells, cytokines, chemokines and microbial metabolites between organs may affect health.[44] Besides the mucociliary transport in the upper respiratory tract inhaled pollutants could be forwarded to the gastrointestinal tract including parts of the UADT.[45] In addition, exposure to air pollution has been shown to alter the composition and diversity of gut microbiota.[44] It could be speculated whether long-term air pollution may be associated with alterations in the richness and diversity of human gut microbiota, which may affect immune function.[44]

A possible reason for the inverse association for O_{3w} could be the small exposure contrast for O_{3w} in our study regions with most of the estimated concentrations ranging between 70 and 80 $\mu g/m^3$, in contrast to studies in Canada where ranges of 32 to 128 $\mu g/m^3$[46] and in the United States where 60 to 120 $\mu g/m^3$ were observed. Indeed analyses of other outcomes in the ELAPSE pooled cohort showed also inverse associations for O_{3w} similar to our results.[25] Another reason might be confounding from inversely correlated other pollutants, which are positively associated with cancer.

A strength of this study is the pooling approach of European subcohorts with detailed individual and area-level covariates information such as smoking and indicators of socioeconomic status. The data were harmonized, and Europe-wide air pollution exposure models were developed centrally. Pooling of the subcohorts increased statistical power and facilitated the analysis of less frequent cancer sites. Compared to ESCAPE, the Europe-wide exposure models were improved by incorporating outputs from chemical transport models and satellite data.[26,35] We performed several sensitivity analyses to limit residual confounding, including variables for smoking (smoking status, smoking intensity and smoking duration) and diet (fruit and vegetables, meat). The comparison between the entire study population in model 1 and the sample with set of covariables in model 3 revealed little indication for selection bias. In addition, the quality of the outcome data is based on high-quality European cancer registries following international rules and nomenclature.[47–49]

The following limitations have to be kept in mind when interpreting our findings. The exposure assessment is based on measurements performed in 2010 whereas most of the included subcohorts started in the mid-1990s. However, studies of NO_2 showed that the spatial contrast of air pollution remained stable over the past decades.[50–52] In addition, our study's analyses of back-extrapolated exposures revealed robust associations for $PM_{2.5}$, NO_2, BC and O_{3w}. Another limitation is the residential mobility was only available during follow-up and information on lifestyle factors was only for baseline. Our exposure are partly highly correlated and therefore we cannot disentangle the respective effect. Thus, the observed effects may rather reflect certain air pollution mixtures related to pollution sources for example traffic.[53] Furthermore, we cannot rule out that residual confounding due to missing information on potential covariables of interest such as occupational exposures may have affected the association. However, we were able to adjust for smoking and for indicators of socioeconomic status.

In conclusion, this study showed an indication of that long-term exposure to $PM_{2.5}$, NO_2 and BC at levels well below current EU air pollution limit values could increase UADT cancer incidence, but we found no association between any of the pollutants and gastric cancer. These support the need to aligning the current EU air pollution values fully with the new WHO Air Quality Guidelines published in 2021.

AUTHOR CONTRIBUTIONS

Gabriele Nagel: Study conceptualization and design; statistical analysis; article writing. **Jie Chen:** ELAPSE project coordination, preparing pooled data for analyses and providing support with the access to pooled cohort data; contribution of statistical analyses strategy and scripts for the statistical analyses; exposure assessment. **Andrea Jaensch:** Statistical analysis. **Lea Skodda:** Statistical analysis. **Sophia Rodopoulou:** Contribution of statistical analyses strategy and scripts for the statistical analyses. **Maciej Strak:** ELAPSE project coordination, preparing pooled data for analyses and providing support with the access to pooled cohort data. **Kees de Hoogh:** Exposure assessment. **Jørgen Brandt:** Exposure data. **Klea Katsouyanni:** Contribution of statistical analyses strategy and scripts for the statistical analyses. **Evangelia Samoli:** Contribution of statistical analyses strategy and scripts for the statistical analyses. **Massimo Stafoggia:** Contribution of statistical analyses strategy and scripts for the statistical analyses. **Kathrin Wolf:** Contribution of statistical analyses strategy and scripts for the statistical analyses. **Bert Brunekreef:** Principal investigators of the ELAPSE project; supervision, article review and editing; ELAPSE project coordination, preparing pooled data for analyses and providing support with the access to pooled cohort data. **Gerard Hoek:** Principal investigators of the ELAPSE project; supervision, article review and editing; ELAPSE project coordination, preparing pooled data for analyses and providing support with the access to pooled cohort data;

exposure assessment. **Ole Raaschou-Nielsen:** Study conceptualization and design; supervision, article review and editing. **Gudrun Weinmayr:** Study conceptualization and design; statistical analysis; supervision, article review and editing. All authors contributed to the interpretation of the results. All authors read and revised the article for the important intellectual content and approved the final draft. The work reported in the article has been performed by the authors, unless clearly specified in the text.

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CONFLICT OF INTEREST STATEMENT

The authors declare no competing interests.

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 is available from the corresponding author upon request.

ETHICS STATEMENT

This study involved no contact with members of the study population and the published results do not allow identification of individuals. The analyses were undertaken in a secure IT environment where no individual level data can be retrieved. All subcohorts were approved by the medical ethics committees in their respective countries. To build the data set of the pooled cohort anonymized data were transferred to a secure server at Utrecht University.

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REFERENCES

1. Hoffmann B, Boogaard H, de Nazelle A, et al. WHO air quality guidelines 2021—aiming for healthier air for all: a joint statement by medical, public health, scientific societies and patient representative organisations. *Int J Public Health*. 2021;66. doi:10.3389/ijph.2021.1604465
2. Turner MC, Andersen ZJ, Baccarelli A, et al. Outdoor air pollution and cancer: an overview of the current evidence and public health recommendations. *CA Cancer J Clin*. 2020;70:460-479.

3. Morgan E, Arnold M, Camargo MC, et al. The current and future incidence and mortality of gastric cancer in 185 countries, 2020-40: a population-based modelling study. *EClinicalMedicine*. 2022;47:101404.
4. GBD 2019 Cancer Risk Factors Collaborators. The global burden of cancer attributable to risk factors, 2010–19: a systematic analysis for the global burden of disease study 2019. *Lancet*. 2022;400:563-591.
5. Lynge E, Holmsgaard HA, Holmager TLF, Lophaven S. Cancer incidence in Thyborøn-Harboøre, Denmark: a cohort study from an industrially contaminated site. *Sci Rep*. 2021;11:13006.
6. Richiardi L, Corbin M, Marron M, et al. Occupation and risk of upper aerodigestive tract cancer: the ARCAGE study. *Int J Cancer*. 2012;130:2397-2406.
7. Yu P, Xu R, Li S, et al. Exposure to wildfire-related PM2.5 and site-specific cancer mortality in Brazil from 2010 to 2016: a retrospective study. *PLoS Med*. 2022;19:e1004103.
8. Pritchett N, Spangler EC, Gray GM, et al. Exposure to outdoor particulate matter air pollution and risk of gastrointestinal cancers in adults: a systematic review and meta-analysis of epidemiologic evidence. *Environ Health Perspect*. 2022;130:36001.
9. Ancona C, Badaloni C, Mataloni F, et al. Mortality and morbidity in a population exposed to multiple sources of air pollution: a retrospective cohort study using air dispersion models. *Environ Res*. 2015;137:467-474.
10. Coleman NC, Burnett RT, Ezzati M, Marshall JD, Robinson AL, Pope CA. Fine particulate matter exposure and cancer incidence: analysis of SEER cancer registry data from 1992-2016. *Environ Health Perspect*. 2020;128:107004.
11. Ethan CJ, Mokoena KK, Yu Y, et al. Association between PM2.5 and mortality of stomach and colorectal cancer in Xi'an: a time-series study. *Environ Sci Pollut Res*. 2020;27:22353-22363.
12. Guo C, Chan T-C, Teng Y-C, et al. Long-term exposure to ambient fine particles and gastrointestinal cancer mortality in Taiwan: a cohort study. *Environ Int*. 2020;138:105640.
13. Nagel G, Stafoggia M, Pedersen M, et al. Air pollution and incidence of cancers of the stomach and the upper aerodigestive tract in the European Study of Cohorts for Air Pollution Effects (ESCAPE). *Int J Cancer*. 2018;143:1632-1643.
14. Weinmayr G, Pedersen M, Stafoggia M, et al. Particulate matter air pollution components and incidence of cancers of the stomach and the upper aerodigestive tract in the European Study of Cohorts of Air Pollution Effects (ESCAPE). *Environ Int*. 2018;120:163-171.
15. Brunekreef B, Strak M, Chen J, et al. Mortality and morbidity effects of long-term exposure to low-level $PM_{2.5}$, BC, NO_2, and O_3: an analysis of European cohorts in the ELAPSE project. *Res Rep Health Eff Inst*. 2021;2021:1-127.
16. Lagergren M, Fratiglioni L, Hallberg IR, et al. A longitudinal study integrating population, care and social services data. The Swedish National study on Aging and Care (SNAC). *Aging Clin Exp Res*. 2004;16:158-168.
17. Magnusson PKE, Almqvist C, Rahman I, et al. The Swedish Twin Registry: establishment of a biobank and other recent developments. *Twin Res Hum Genet*. 2013;16:317-329.
18. Wändell P-E, Wajngot A, de Faire U, Hellénius M-L. Increased prevalence of diabetes among immigrants from non-European countries in 60-year-old men and women in Sweden. *Diabetes Metab*. 2007;33:30-36.
19. Eriksson A-K, Ekbom A, Granath F, Hilding A, Efendic S, Ostenson C-G. Psychological distress and risk of pre-diabetes and type 2 diabetes in a prospective study of Swedish middle-aged men and women. *Diabet Med*. 2008;25:834-842.
20. Tjønneland A, Olsen A, Boll K, et al. Study design, exposure variables, and socioeconomic determinants of participation in diet, cancer and health: a population-based prospective cohort study of 57,053 men and women in Denmark. *Scand J Public Health*. 2007;35:432-441.
21. Hundrup YA, Simonsen MK, Jørgensen T, Obel EB. Cohort profile: the Danish nurse cohort. *Int J Epidemiol*. 2012;41:1241-1247.
22. Beulens JWJ, Monninkhof EM, Verschuren WMM, et al. Cohort profile: the EPIC-NL study. *Int J Epidemiol*. 2010;39:1170-1178.
23. Clavel-Chapelon F; E3N Study Group. Cohort profile: the French E3N cohort study. *Int J Epidemiol*. 2015;44:801-809.
24. Ulmer H, Kelleher CC, Fitz-Simon N, Diem G, Concin H. Secular trends in cardiovascular risk factors: an age-period cohort analysis of 698,954 health examinations in 181,350 Austrian men and women. *J Intern Med*. 2007;261:566-576.
25. Hvidtfeldt UA, Chen J, Andersen ZJ, et al. Long-term exposure to fine particle elemental components and lung cancer incidence in the ELAPSE pooled cohort. *Environ Res*. 2021;193:110568.
26. de Hoogh K, Chen J, Gulliver J, et al. Spatial PM2.5, NO2, O3 and BC models for Western Europe – evaluation of spatiotemporal stability. *Environ Int*. 2018;120:81-92.
27. Eeftens M, Beelen R, de Hoogh K, et al. Development of land use regression models for PM(2.5), PM(2.5) absorbance, PM(10) and PM(coarse) in 20 European study areas; results of the ESCAPE project. *Environ Sci Technol*. 2012;46:11195-11205.
28. Stafoggia M, Oftedal B, Chen J, et al. Long-term exposure to low ambient air pollution concentrations and mortality among 28 million people: results from seven large European cohorts within the ELAPSE project. *Lancet Planet Health*. 2022;6:e9-e18.
29. Crouse DL, Erickson AC, Christidis T, et al. Evaluating the sensitivity of PM2.5-mortality associations to the spatial and temporal scale of exposure assessment. *Epidemiology*. 2020;31:168-176.
30. Josyula S, Lin J, Xue X, et al. Household air pollution and cancers other than lung: a meta-analysis. *Environ Health*. 2015;14:24.
31. Macfarlane TV, Macfarlane GJ, Oliver RJ, et al. The aetiology of upper aerodigestive tract cancers among young adults in Europe: the ARCAGE study. *Cancer Causes Control*. 2010;21:2213-2221.
32. Boogaard H, Patton AP, Atkinson RW, et al. Long-term exposure to traffic-related air pollution and selected health outcomes: a systematic review and meta-analysis. *Environ Int*. 2022;164:107262.
33. Greten FR, Grivennikov SI. Inflammation and cancer: triggers, mechanisms, and consequences. *Immunity*. 2019;51:27-41.
34. WHO global air quality guidelines: particulate matter (PM2.5 and PM10), ozone, nitrogen dioxide, sulfur dioxide and carbon monoxide [Internet]. https://iris.who.int/handle/10665/345329
35. Chen J, de Hoogh K, Gulliver J, et al. Development of Europe-wide models for particle elemental composition using supervised linear regression and random forest. *Environ Sci Technol*. 2020;54:15698-15709.
36. Peters A, Nawrot TS, Baccarelli AA. Hallmarks of environmental insults. *Cell*. 2021;184:1455-1468.
37. Kayamba V, Kelly P. Environmental factors associated with gastric carcinogenesis. *Curr Opin Gastroenterol*. 2022;38:156-161.
38. Jin L, Godri Pollitt KJ, Liew Z, et al. Use of untargeted metabolomics to explore the air pollution-related disease continuum. *Curr Environ Health Rep*. 2021;8:7-22.
39. Loomis D, Grosse Y, Lauby-Secretan B, et al. International Agency for Research on Cancer monograph working group IARC. The carcinogenicity of outdoor air pollution. *Lancet Oncol*. 2013;14:1262-1263.
40. Forastiere F, Peters A. Invited perspective: the NO_2 and mortality dilemma solved? Almost there! *Environ Health Perspect*. 2021;129:121304.
41. Assessment UENC for E. Integrated Science Assessment (ISA) for Oxides of Nitrogen – Health Criteria (Final Report, Jan 2016) | ISA: Integrated Science Assessments | Environmental Assessment | US EPA [Internet]. https://assessments.epa.gov/isa/document/&deid=310879
42. Enaud R, Prevel R, Ciarlo E, et al. The gut-lung axis in health and respiratory diseases: a place for inter-organ and inter-kingdom crosstalks. *Front Cell Infect Microbiol*. 2020;10:9.

43. Dang AT, Marsland BJ. Microbes, metabolites, and the gut-lung axis. *Mucosal Immunol*. 2019;12:843-850.
44. Filardo S, di Pietro M, Protano C, Antonucci A, Vitali M, Sessa R. Impact of air pollution on the composition and diversity of human gut microbiota in general and vulnerable populations: a systematic review. *Toxics*. 2022;10:579.
45. Vignal C, Guilloteau E, Gower-Rousseau C, Body-Malapel M. Review article: epidemiological and animal evidence for the role of air pollution in intestinal diseases. *Sci Total Environ*. 2021;757:143718.
46. Bai L, Shin S, Burnett RT, et al. Exposure to ambient air pollution and the incidence of congestive heart failure and acute myocardial infarction: a population-based study of 5.1 million Canadian adults living in Ontario. *Environ Int*. 2019;132:105004.
47. Barlow DH. What is the optimal policy for osteoporosis management? *Maturitas*. 2008;60:3-9.
48. Gjerstorff ML. The Danish cancer registry. *Scand J Public Health*. 2011;39:42-45.
49. Hackl M, Waldhoer T. Estimation of completeness of case ascertainment of Austrian cancer incidence data using the flow method. *Eur J Public Health*. 2013;23:889-893.
50. Eeftens M, Beelen R, Fischer P, Brunekreef B, Meliefste K, Hoek G. Stability of measured and modelled spatial contrasts in NO(2) over time. *Occup Environ Med*. 2011;68:765-770.
51. Cesaroni G, Porta D, Badaloni C, et al. Nitrogen dioxide levels estimated from land use regression models several years apart and association with mortality in a large cohort study. *Environ Health*. 2012;11:48.
52. Gulliver J, de Hoogh K, Hansell A, Vienneau D. Development and back-extrapolation of NO_2 land use regression models for historic exposure assessment in Great Britain. *Environ Sci Technol*. 2013;47:7804-7811.
53. Weinmayr G, Chen J, Jaensch A, et al. Long-term exposure to several constituents and sources of PM2.5 is associated with incidence of upper aerodigestive tract cancers but not gastric cancer: results from the large pooled European cohort of the ELAPSE project. *Sci Total Environ*. 2023;912:168789.

SUPPORTING INFORMATION

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

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