Science of the Total Environment 912 (2024) 168789

Contents lists available at ScienceDirect

Science of the Total Environment

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

Long-term exposure to several constituents and sources of $PM_{2.5}$ is associated with incidence of upper aerodigestive tract cancers but not gastric cancer: Results from the large pooled European cohort of the ELAPSE project

Gudrun Weinmayr [a,*], Jie Chen [b], Andrea Jaensch [a], Lea Skodda [a], Sophia Rodopoulou [c], Maciej Strak [b,d], Kees de Hoogh [e,f], Zorana J. Andersen [g], Tom Bellander [h], Jørgen Brandt [i,j], Daniela Fecht [k], Francesco Forastiere [l,m], John Gulliver [k,n], Ole Hertel [o], Barbara Hoffmann [p], Ulla Arthur Hvidtfeldt [q], Klea Katsouyanni [c,k], Matthias Ketzel [i,r], Karin Leander [h], Patrik K.E. Magnusson [s], Göran Pershagen [h], Debora Rizzuto [t,u], Evangelia Samoli [c], Gianluca Severi [v], Massimo Stafoggia [h,l], Anne Tjønneland [q,g], Roel Vermeulen [b], Kathrin Wolf [w], Emanuel Zitt [x,y], Bert Brunekreef [b], George Thurston [z], Gerard Hoek [b], Ole Raaschou-Nielsen [q,i], Gabriele Nagel [a]

[a] *Institute of Epidemiology and Medical Biometry, Ulm University, Ulm, Germany*
[b] *Institute for Risk Assessment Sciences, Utrecht University, Utrecht, the Netherlands*
[c] *Department of Hygiene, Epidemiology and Medical Statistics, Medical School, National and Kapodistrian University of Athens, Athens, Greece*
[d] *National Institute for Public Health and the Environment, Bilthoven, the Netherlands*
[e] *Swiss Tropical and Public Health Institute, Basel, Switzerland*
[f] *University of Basel, Basel, Switzerland*
[g] *Department of Public Health, University of Copenhagen, Copenhagen, Denmark*
[h] *Institute of Environmental Medicine, Karolinska Institutet, Stockholm, Sweden*
[i] *Department of Environmental Science, Aarhus University, Roskilde, Denmark*
[j] *iClimate – interdisciplinary Centre for Climate Change, Aarhus University, Roskilde, Denmark*
[k] *MRC Centre for Environment and Health, School of Public Health, Imperial College London, London, UK*
[l] *Department of Epidemiology, Lazio Region Health Service/ASL Roma 1, Rome, Italy*
[m] *Environmental Research Group, School of Public Health, Faculty of Medicine, Imperial College, London, UK*
[n] *Centre for Environmental Health and Sustainability & School of Geography, Geology and the Environment, University of Leicester, Leicester, UK*
[o] *Faculty of Technical Sciences, Aarhus University, Roskilde, Denmark*
[p] *Institute for Occupational, Social and Environmental Medicine, Centre for Health and Society, Medical Faculty, Heinrich Heine University Düsseldorf, Düsseldorf, Germany*
[q] *The Danish Cancer Institute, Copenhagen, Denmark*
[r] *Global Centre for Clean Air Research (GCARE), University of Surrey, Guildford GU2 7XH, UK*
[s] *Department of Medical Epidemiology and Biostatistics, Karolinska Institutet, Stockholm, Sweden*
[t] *Department of Neurobiology, Care Sciences, and Society, Karolinska Institutet and Stockholm University, Stockholm, Sweden*
[u] *Stockholm Gerontology Research Center, Stockholm, Sweden*
[v] *University Paris-Saclay, UVSQ, Inserm, Gustave Roussy, "Exposome and Heredity" team, CESP UMR1018, 94805, Villejuif, France*
[w] *Institute of Epidemiology, Helmholtz Zentrum München, Neuherberg, Germany*
[x] *Agency for Preventive and Social Medicine (aks), Bregenz, Austria*
[y] *Department of Internal Medicine 3, LKH Feldkirch, Feldkirch, Austria*
[z] *Division of Environmental Medicine, Depts of Medicine and Population Health, New York University Grossman School of Medicine, New York, USA*

Abbreviations: APCA, absolute principal component analysis; BC, Black Carbon; CI, Confidence Interval; HR, Hazard Ratio; NDVI, normalized difference vegetation index; PM, particulate matter; $PM_{2.5}$, particulate matter ≤2.5 μm; PM2.5_Cu etc., denotes the content of the respective chemical element, here copper, in the $PM_{2.5}$ fraction. These elemental constituents are also indicators of specific sources (see Methods); UADT, upper aerodigestive tract.

* Corresponding author at: Institute of Epidemiology and Medical Biometry, Ulm University, Helmholtzstr. 22, 89081 Ulm, Germany.
E-mail address: gudrun.weinmayr@uni-ulm.de (G. Weinmayr).

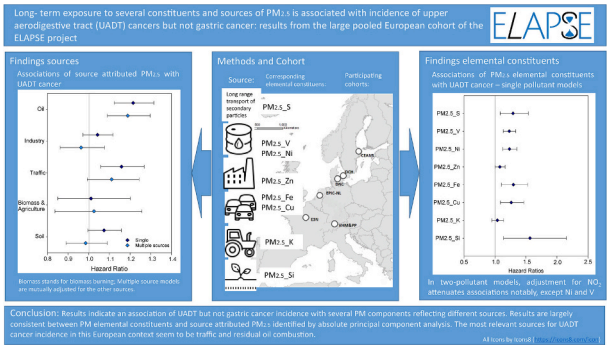
https://doi.org/10.1016/j.scitotenv.2023.168789

Available online 22 November 2023

HIGHLIGHTS

- Pooled large European cohort with exposure levels below EU particulate matter limit values typical for European populations
- First study on gastric and UADT-cancer incidence with PM source-characterization
- Associations of UADT-cancer incidence with several chemical elemental constituents indicative of different sources
- Independent associations of PM source components "residual oil combustion" and "traffic" with UADT cancer incidence
- No association of elements and sources with gastric cancer

GRAPHICAL ABSTRACT



ARTICLE INFO

Editor: Lidia Minguez Alarcon

Keywords:
Air pollution
Upper aerodigestive tract cancer
Gastric cancer
Particulate matter (PM)
PM composition
PM sources
Long-term exposure

ABSTRACT

It is unclear whether cancers of the upper aerodigestive tract (UADT) and gastric cancer are related to air pollution, due to few studies with inconsistent results. The effects of particulate matter (PM) may vary across locations due to different source contributions and related PM compositions, and it is not clear which PM constituents/sources are most relevant from a consideration of overall mass concentration alone. We therefore investigated the association of UADT and gastric cancers with $PM_{2.5}$ elemental constituents and sources components indicative of different sources within a large multicentre population based epidemiological study.

Cohorts with at least 10 cases per cohort led to ten and eight cohorts from five countries contributing to UADT- and gastric cancer analysis, respectively. Outcome ascertainment was based on cancer registry data or data of comparable quality.

We assigned home address exposure to eight elemental constituents (Cu, Fe, K, Ni, S, Si, V and Zn) estimated from Europe-wide exposure models, and five source components identified by absolute principal component analysis (APCA). Cox regression models were run with age as time scale, stratified for sex and cohort and adjusted for relevant individual and neighbourhood level confounders.

We observed 1139 UADT and 872 gastric cancer cases during a mean follow-up of 18.3 and 18.5 years, respectively. UADT cancer incidence was associated with all constituents except K in single element analyses. After adjustment for NO_2, only Ni and V remained associated with UADT. Residual oil combustion and traffic source components were associated with UADT cancer persisting in the multiple source model. No associations were found for any of the elements or source components and gastric cancer incidence.

Our results indicate an association of several PM constituents indicative of different sources with UADT but not gastric cancer incidence with the most robust evidence for traffic and residual oil combustion.

1. Introduction

Gastric and oesophageal cancers are among the most common cancers worldwide (Arnold et al., 2020). Anatomically closely related are other cancers of the upper aerodigestive tract (UADT). While smoking is an established risk factor for these cancers (IARC Working Group on the Evaluation of Carcinogenic Risks to Humans, 2012), evidence on the risk related to ambient air pollution is scarce. However, recent evidence suggests there may be also a relation of air pollution with several cancers and IARC classified outdoor air pollution as carcinogenic in 2013 (Straif et al., 2013).

For cancer-related outcomes, the best evidence to date is available for lung cancer, where several epidemiological studies show associations of lung cancer incidence with particulate matter (PM) (Hamra et al., 2014; Hvidtfeldt et al., 2021b; Raaschou-Nielsen et al., 2013; Turner et al., 2020). Mechanisms are thought to be related to oxidative stress and inflammatory processes which may induce DNA damage and cell proliferation (Straif et al., 2013). These processes occur not only in the lung but can affect also other organs, as inflammatory responses and oxidative stress are transmitted through released circulating mediators including chemokines, cytokines and immune cells (Brook et al., 2018). In addition, ultrafine particles can enter the blood circulation and lymphatic system directly, while larger fine particles can be transported via macrophages and reach other organs (Furuyama et al., 2009; Oberdörster et al., 2005) including the digestive tract. Perhaps even more relevant is the clearance of particles by mucociliary transport, which may lead to subsequent ingestion of particles (Oberdörster et al., 2005).

While these mechanisms give plausibility to the potential effects of PM and its components on cancers other than the lung, epidemiological evidence is still sparse. For gastric and UADT cancers, few studies on PM exist with partly conflicting results (Pritchett et al., 2022). This may be due to differences in the PM compositions across locations. Indeed, PM is a complex mixture which differs according to sources. Indeed, the actual uptake and physiological/toxic effects depend on the particles' characteristics including chemical properties and therefore source (Kelly and Fussell, 2012; Oberdörster et al., 2005). Some sources and constituents of the resulting PM mixture may therefore be more harmful than others to health in general and cancer in particular (Thurston et al., 2013; Turner et al., 2020). The association of PM elemental constituents which are indicative of different sources with gastric and UADT cancer, has only been investigated previously in the European Study of Cohorts for Air Pollution Effects (ESCAPE) (Weinmayr et al., 2018), mainly because, with few exceptions, PM constituents are not routinely measured in regulatory monitoring and bespoke measurements have to be performed. In ESCAPE, we found a robust association of sulphur which is

indicative of long range transport of secondarily formed aerosols with gastric cancer (Weinmayr et al., 2018). Similarly comprehensive studies on different elemental constituents have only been conducted in Europe and the US: on other cancer entities within ESCAPE and the following Effects of Low-level Air Pollution - a Study in Europe (ELAPSE) framework (see e.g. Chen et al., 2022b; Hvidtfeldt et al., 2021a; Raaschou-Nielsen et al., 2016); in the US on overall cancer and lung cancer mortality (Kazemiparkouhi et al., 2022; Thurston et al., 2013). In addition to specific elements, these US-studies investigated specific sources identified by absolute principal component analysis (APCA) (Thurston and Spengler, 1985) and found certain sources to be more harmful than others. Such studies, however, are extremely rare and most reports in the literature focus only on local sources such as certain industrial plants (Fazzo et al., 2016; Lynge et al., 2021). However, for wide-scale prevention it is important to know which sources are most relevant in causing observed health effects.

In the present study, we therefore investigate the association of gastric and UADT cancer incidence with PM components, that are indicators of certain sources of $PM_{2.5}$, specifically several chemical elemental constituents as well as sources identified by the above APCA approach. To our knowledge, this is the first study investigating the relation of gastric and UADT cancer with $PM_{2.5}$ sources by applying two methodologically different source indicators, thereby strengthening the previous approach that was based on individual elemental constituents.

We do this in ELAPSE which constitutes a setting chosen to reflect relatively low air pollution concentrations as they are typical in many parts of Europe and therefore European populations, and thereby also reflect the corresponding characteristic PM mixtures. We furthermore leverage additional advantages of ELAPSE, notably a common pooled dataset of several well-characterised cohorts, which increases statistical power, and a refined exposure assessment by developing hybrid models that in addition to land use variables integrate satellite data and information from chemistry transport models taking account of specific point sources where available (Chen et al., 2020).

In this article, we present in the methods first the participating cohorts, followed by the methods of assessment of the outcome and the exposure to $PM_{2.5}$ indicative of different sources, and finally the statistical analyses undertaken. In the results section, we first present the study population's description and exposure distribution within this population. Then we report on the associations between the cancer incidence and elemental constituents and APCA identified sources of $PM_{2.5}$, respectively. In the discussion, we first highlight the most important finding followed by a brief paragraph pointing out similar studies. In the following largest section, we discuss our findings by source, based on our findings on the related indicators and compare them to similar studies. Finally, we discuss the strengths and limitations of our study and present our conclusions.

2. Methods

2.1. Study population

Ten cohorts (located in five countries) were participating in the pooled cohort of the ELAPSE-study based on the following prerequisites: air pollution at low levels in the study area, ability to transfer data into the common pooled data set, and information on first cancer diagnosis.

The participating cohorts came from Sweden (*Cardiovascular Effects of Air Pollution and Noise in Stockholm* [CEANS], comprising the following four cohorts: Swedish National Study on Aging and Care in Kungsholmen [SNAC-K] (Lagergren et al., 2004), Stockholm Screening Across the Lifespan Twin study [SALT] (Magnusson et al., 2013), Stockholm 60 years old study [Sixty] (Wändell et al., 2007), and Stockholm Diabetes Prevention Program [SDPP] (Eriksson et al., 2008)); Denmark (the *Diet, Cancer and Health cohort* [DCH] (Tjønneland et al., 2007) and the *Danish Nurse Cohort* [DNC] (Hundrup et al., 2012)); 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] (Beulens et al., 2010)); France (*Etude Epidémiologique auprès de femmes de la Mutuelle Générale de l'Education Nationale* [E3N] (Clavel-Chapelon and E3N Study Group, 2015)); Austria (*Vorarlberg Health Monitoring and Prevention Programme* [VHM&PP] (Ulmer et al., 2007)).

Most cohorts represented major cities and their surroundings whereas E3N covered many regions of France and DNC and VHM&PP large areas within the country. Information on potential confounding variables was collected at baseline with recruitment taking place mostly in the 1990s and 2000s. For ELAPSE, confounding variables needed to be harmonized especially regarding life-style factors. More information on the respective procedures can be found in (Brunekreef et al., 2021) and detailed information on the cohorts can be found in (Hvidtfeldt et al., 2021a). Medical ethics committees had approved all cohort studies in their respective countries with details given in Table S12. Anonymized data were transferred to a secure Utrecht University server to build the data set of the pooled cohort.

2.2. Outcome

Outcome data originate from regional/national cancer registries with the exception of E3N, where assessment was based on biannual self-reports confirmed through pathological reports reviewed by an oncologist, or on death certificates. Only first occurrences of primary cancers were considered. Cancer of the upper aerodigestive tract was defined by International Classification of Disease and Related Health Problems (ICD) codes 10th revision and 9th revision, respectively: 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 (oesophagus). Gastric cancer was identified by C16 and 151, respectively. Any prevalent cancers at baseline were excluded (except non-melanoma skin cancers).

2.3. Exposure assessment

Hybrid land use regression models for fine particle elemental composition were developed for Europe and details of model development are given elsewhere (Chen et al., 2020). In brief, in each of the 19 different European study locations of the ESCAPE study, filters from 20 PM measurement stations were obtained. At these sites, three two-week measurements covering three different seasons (cold, warm, intermediate) were carried out from 2008 to 2011. One permanently operating measurement site per study location allowed calculating adjusted annual means for 2010 for the other sites. The $PM_{2.5}$ composition was analysed with energy-dispersive X-ray fluorescence for chemical elements (Tsai et al., 2015). We chose *a priori* eight elements to represent important air pollution sources: copper (Cu), iron (Fe), zinc (Zn) for non-tailpipe traffic emissions, nickel (Ni) and Vanadium (V) for residual oil combustion, potassium (K) for biomass burning, sulphur (S) for secondary inorganic aerosols characterizing long-range transport and silicon (Si) for soil material (de Hoogh et al., 2013; Tsai et al., 2015). Nevertheless, elemental constituents do not necessarily represent single sources, as they may have multiple sources.

Predictors for the exposure models included satellite and chemical transport model data for the regional background component and traffic, industry, land use variables and population density for local variation (Chen et al., 2020). Supervised linear regression (SLR) was used to develop the models, and performance (Pearson R2) using a fivefold hold out validation ranged from 0.41 for Zn to 0.79 for S (Chen et al., 2020).

All models predicted concentrations on a 100 m × 100 m grid scale over Europe. Geocoded participants' addresses were assigned the values of the corresponding grid cell and the resulting exposure values transferred to the Utrecht Server in anonymized form.

Source contributions were determined with APCA (Thurston and

Spengler, 1985) and details can be found in (Chen et al., 2022a). Five sources were identified: Traffic (high loadings on NO_2, black carbon (BC), Cu, and Fe), residual oil combustion (hence also called "oil"; high loadings of Ni and V), crustal/soil material (high loading on Si and moderate loading on Fe), industrial emissions (high loading on Zn), and biomass burning (high loading on K).

2.4. Statistical analysis

We harmonized the data across centres according to a common codebook. Cox regression models with age as time scale were calculated and censoring occurred at event of any other cancer, death, emigration, loss to follow-up or end of follow-up (whichever came first). Exposure values were entered as continuous variables. We introduced strata for sex and cohort to accommodate for different baseline hazards (Samoli et al., 2021). This implies that we analyse predominantly exposure contrasts within cohorts.

Potential confounders were defined *a priori*: Model 1 adjusted for calendar year of enrolment to account for temporal trends. Model 2 additionally adjusted for individual covariates, namely smoking status (never, former, present), smoking intensity (cigarettes or cigarette equivalents per day) and smoking intensity squared, smoking duration (years of smoking), marital status (single, living with a partner, separated, widowed) and occupational status (employed, not employed). Model 3 adjusted in addition for neighbourhood level income in 2001 in € (continuous variable) using data from Eurostat. Neighbourhood areas varied from smaller neighbourhood areas and city districts (CEANS, EPIC-NL, E3N) to municipalities (DNS, DCH, and VHM&PP). Models 1–3 were calculated for individuals that had information for all covariates of model 3 which was the main model of our analysis.

In sensitivity analyses for the PM elements, we considered additional potential confounding variables that were not available in all cohorts, constructing several models to obtain the maximum of cohorts for each analysis.

These models further adjusted for alcohol and fruits; vegetables; meat (all dietary variables harmonized as low, medium and high intake (Brunekreef et al., 2021)); environmental tobacco smoke (ETS) (yes/no); occupational class (blue/white collar); educational level (primary school or less/up to secondary school or equivalent/university degree and more); BMI (<18.5, 18.5–24, 25–29, and 30 + kg/m^2); urbanicity (based on Eurostat Degree of urbanisation dataset: cities or densely populated/towns and suburbs (intermediate population density)/rural areas) and normalized difference vegetation index (NDVI continuous) with a 300 m or 1 km buffer.

The influence of specific cohorts on the overall results was investigated by excluding one cohort at a time.

We furthermore performed two-pollutant models, adjusting the PM-elements for total $PM_{2.5}$ mass, and for NO_2 considered a traffic indicator. For the PM sources we also calculated a model where all sources were mutually adjusted for. All statistical analyses were performed in R software (version 3.4.0).

We only considered cohorts with at least 10 cases which led to the exclusion of the 1999 survey of the DNC (5 gastric and 9 UADT cases). For the gastric cancer analysis, we excluded in addition CEANS-SDPP (3 cases of gastric cancer) and CEANS-SNACK (6 cases). Based on the information at baseline, we dropped 13,374 individuals due to missing exposure (13,364 for gastric cancer) and 42,968 individuals with missing values in individual covariates for model 2 (42,700 for gastric cancer). Because of missing values for the neighbourhood SES indicator in model 3, 3251 individuals (3249 for gastric cancer) were excluded.

3. Results

3.1. Description study population

In the model 3 population 297,406 and 287,576 individuals were

Table 1
Characteristics of the study population.

Cohort	Population size (N)	Persons in model 3 (N)	Baseline period	Years of follow up (Mean)[a]	Age at baseline (Mean ± SD)	Female (%)	Current smokers (%)	(Self-) employed (%)	Married/ cohabiting (%)	Small-area income[b] (Mean ± SD)	Gastric cancer cases (N)	UADT cancer cases (N)
CEANS-SALT	6098	5717	1998–2003	9.90	57.4 ± 10.5	54	21	66	68	25.3 ± 6.6	11	25
CEANS-SDPP	7403	7325	1992–1998	15.34	47.0 ± 4.9	59	26	91	84	24.3 ± 4.2	3	18
CEANS-SIXTY	3856	3660	1997–1999	11.95	60.0 ± 0.0	50	21	68	74	24.7 ± 6.9	14	18
CEANS-SNAC-K	2697	2505	2001–2004	6.93	73.5 ± 11.0	64	14	23	44	28.7 ± 2.2	6	10
DCH	55,401	52,817	1993–1997	16.89	56.7 ± 4.4	53	36	78	71	20.1 ± 3.4	189	452
DNC-1993	17,922	15,664	1993	16.85	56.1 ± 8.4	100	37	70	68	19.2 ± 2.6	35	47
E3N	49,740	38,171	1989–1991	15.85	52.9 ± 6.8	100	13	68	83	11.2 ± 3.0	32	40
EPIC_NL-Morgen	20,096	17,797	1993–1997	16.43	42.7 ± 11.2	54	35	69	65	12.2 ± 1.6	27	48
EPIC_NL-Prospect	15,054	13,651	1993–1998	15.66	57.6 ± 6.0	100	23	51	77	13.1 ± 1.4	46	29
VHM_PP	165,358	140,099	1985–2005	20.97	41.7 ± 14.9	56	20	71	69	22.9 ± 1.7	518	452
Pooled cohort – gastric	333,525[c]	287,576[c]	1985–2005	18.45	48.1 ± 13.5	66	24	71	71	19.6 ± 5.3	872	–
Pooled cohort – UADT	343,625[c]	297,406[c]	1985–2005	18.27	48.3 ± 13.6	65	24	71	72	19.8 ± 5.4	–	1139

CEANS: Cardiovascular Effects of Air Pollution and Noise in Stockholm; SDPP: The Stockholm Diabetes Preventive Program; SIXTY: The Stockholm cohort of 60-yearolds; SALT: Screening Across the Lifespan Twin Study; 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: Étude Épidémiologique auprès de femmes de la Mutuelle Générale de l'Éducation Nationale; VHM&PP: Vorarlberg Health Monitoring and Prevention Programme. SD standard deviation.

[a] For persons in model 3 (as for all the following columns).

[b] In Euros × 1000, year 2001.

[c] Number of individuals included in the respective analysis.

included for the UADT- and gastric cancer analysis, respectively, with a mean follow-up of 18.27 and 18.45 years, respectively (5,434,843 and 5,305,133 person years) (Table 1). We observed 1139 and 872 incident cases of UADT- and gastric cancer, respectively.

Individual cohorts varied in size with VHM&PP and DCH contributing most to the overall study population. Recruitment was mainly in the 1990'ies. The percentage of women in the pooled cohort was 65 % and 66 % for UADT and gastric cancer, respectively, with three female only cohorts (DNC, E3N, EPIC-NL Prospect). Cohort-specific mean age at baseline ranged from 42 (VHM&PP) to 74 years (CEANS – SNAC-K), with mean age of 48 years and 7.3 % being older than 65 years in the pooled cohort. Smoking prevalence ranged from 13 to 37 % in E3N and DNC-1993, respectively, with a mean prevalence of 24 %.

3.2. Description of the exposure

For K and Zn, concentrations were clearly lower in the Scandinavian countries, for Zn also in Vorarlberg (Austria) (Fig. 1). Except for Si, a similar tendency for a North-South gradient was seen for the other elements, with the exception of low concentrations for S and especially Ni and V in Vorarlberg.

The pattern of lower concentrations in Scandinavia also holds for the oil and industry components, however with low exposures also in Vorarlberg (Fig. 2). A similar tendency for a North-South gradient is seen for agriculture and traffic, but not for the soil component which did not show any clear pattern by latitude.

In the UADT cancer data set, the highest median source related $PM_{2.5}$ concentration in the pooled cohort was found for traffic and biomass & agriculture with 4.1 and 3.8 μg/m^3, respectively (Fig. 2). In the gastric cancer data set, concentrations were slightly higher (4.1 and 4.0 μg/m^3) for these two sources due to the two missing Swedish cohorts, whereas for the other sources median concentrations remained unchanged. The lowest concentration was seen for residual oil with a median of 0.1 μg/m^3. Similarly, the exposure contrasts in μg/m^3 for sources were highest for biomass & agriculture followed by traffic and lowest for oil with IQRs of 4.36 μg/m^3, 2.83 μg/m^3 and 0.25 μg/m^3, respectively.

Fe and Cu were highly correlated with NO_2 with median Spearman correlations of 0.83 and 0.88, and only moderately correlated with $PM_{2.5}$ with 0.49 and 0.52, respectively (Table S2 in the online supplement). Zn was moderately correlated with NO_2 and $PM_{2.5}$ (medians of 0.57 and 0.47, respectively). K was generally weakly correlated and in different directions. Ni and V showed weak (with $PM_{2.5}$) and moderate (with NO_2) correlations. Correlations of S with $PM_{2.5}$ and NO_2 were also generally moderate (medians of 0.45 and 0.48, respectively). Si was highly correlated with NO_2 (median of 0.76) and moderately with $PM_{2.5}$ (median of 0.41). Highest median correlations between sources (Table S3) are found between traffic and soil (0.69), residual oil and industry (0.56) and in negative direction between traffic and agriculture & biomass burning (−0.60).

3.3. Associations

No association was observed for any of the constituents or source components with gastric cancer (Table 2) in any of the models. We also run models 1 and 2 in the datasets with all individuals that had information on model 1 and model 2 covariates, respectively, as opposed to having information on all model 3 covariates in the *a priori* prespecified main analysis. These analyses yielded the same results (Table S4 in the online supplement).

For UADT cancer, effect estimates across the different model datasets were also similar, with the largest difference found for model 1: for $PM_{2.5}$S with 1.35 (1.16–1.57) vs. 1.49 (1.25–1.77) in the model 3 population, or $PM_{2.5}$Si with 2.16 (1.61–2.89) vs. 2.31 (1.69–3.16) (Table S4 in the online supplement).

With UADT cancer, all $PM_{2.5}$ constituents, except for K, show a statistically significant positive association (borderline for Zn). The highest HR for an increase by interquartile range (IQR), which provides a more comparable metric over different pollutants, was observed for S with 1.31 (1.09–1.58), whereas the HRs for the other elements were between 1.19 for Ni followed by 1.18 for Cu and Ni on one side, and 1.08 for Zn on the other (Table S5 in online supplement). These results were essentially robust to adjustment with $PM_{2.5}$ whereas greater changes were observed upon adjustment with NO_2, especially for the Cu, Fe, S and Si constituents (Fig. 3). After adjustment for NO_2, only Ni, and V remained statistically significantly associated with UADT (Fig. 3 and Table S7 in the online supplement).

Regarding sources, there was no association with particles from biomass & agriculture, an elevated non-significant association with soil and industry, and a clear association with traffic and oil (Fig. 4). Traffic and oil were only slightly attenuated by the mutual adjustment of all sources, whereas none of the other three sources showed an association in this multisource model.

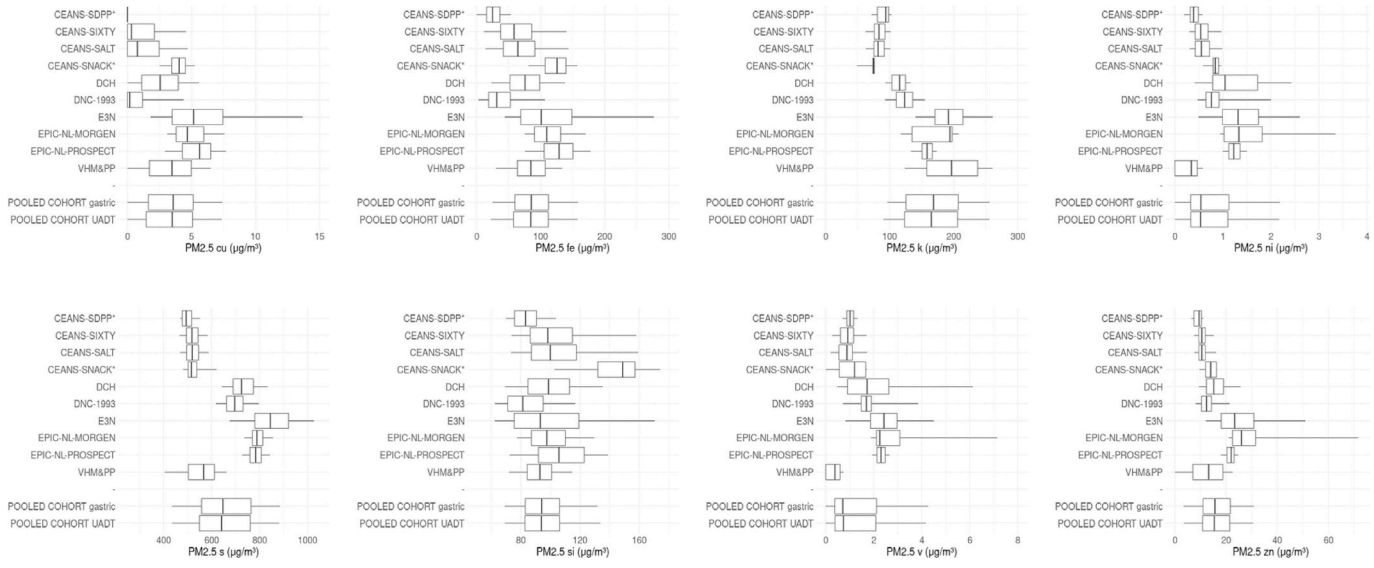


Fig. 1. Exposure distribution of concentrations of $PM_{2.5}$ elemental constituents at participants' baseline residential addresses.
Sub-cohorts are shown from North to South; the boundary of the box closest to zero indicates P25; the boundary of the box furthest from zero, P75; the bold vertical line inside the box, P50; and the whiskers, P5 and P95.

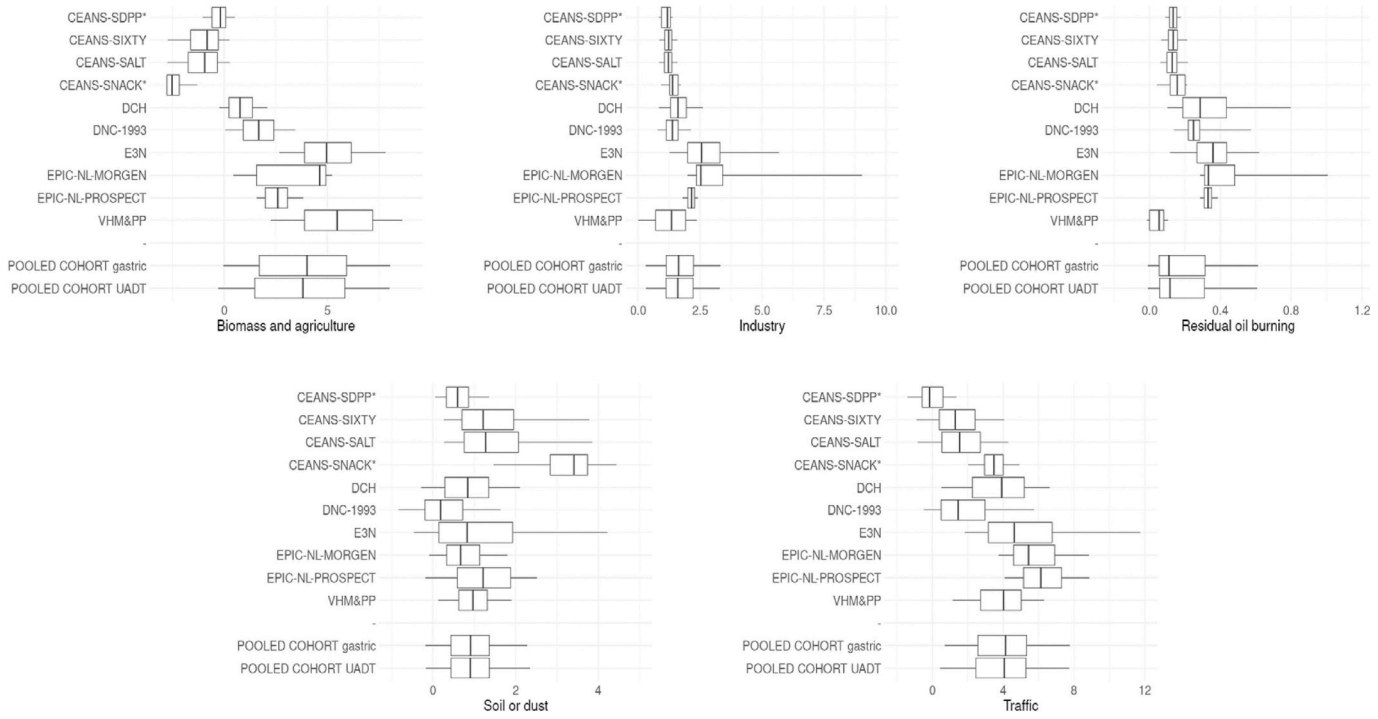


Fig. 2. Expopsure distribution of source-specific $PM_{2.5}$ concentrations at participants' baseline residential addresses.
Sub-cohorts are shown from North to South; the boundary of the box closest to zero indicates P25; the boundary of the box furthest from zero, P75; the bold vertical line inside the box, P50; and the whiskers, P5 and P95.

Table 2
Association of PM elemental constituents with UADT and gastric cancer.

Pollutant	UADT model 1[a] HR (95 % CI)	UADT model 2[b] HR (95 % CI)	UADT model 3[c] HR (95 % CI)	Gastric model 1[a] HR (95 % CI)	Gastric model 2[b] HR (95 % CI)	Gastric model 3[c] HR (95 % CI)
$PM_{2.5}$Cu	1.46 (1.26–1.69)	1.26 (1.09–1.46)	1.26 (1.09–1.46)	0.98 (0.83–1.16)	0.95 (0.80–1.13)	0.99 (0.83–1.17)
$PM_{2.5}$Fe	1.56 (1.33–1.83)	1.30 (1.10–1.53)	1.30 (1.10–1.53)	0.95 (0.79–1.16)	0.91 (0.75–1.11)	0.95 (0.78–1.16)
$PM_{2.5}$K	1.06 (0.97–1.17)	1.04 (0.95–1.14)	1.04 (0.95–1.14)	1.00 (0.91–1.09)	0.99 (0.91–1.09)	1.01 (0.92–1.11)
$PM_{2.5}$Ni	1.34 (1.24–1.45)	1.23 (1.12–1.35)	1.23 (1.12–1.35)	0.97 (0.83–1.14)	0.94 (0.80–1.10)	0.93 (0.79–1.10)
$PM_{2.5}$S	1.49 (1.25–1.77)	1.29 (1.08–1.54)	1.29 (1.08–1.54)	0.99 (0.82–1.19)	0.96 (0.80–1.16)	0.98 (0.82–1.18)
$PM_{2.5}$Si	2.31 (1.69–3.16)	1.56 (1.13–2.14)	1.57 (1.14–2.15)	1.08 (0.73–1.59)	0.96 (0.64–1.44)	0.99 (0.66–1.48)
$PM_{2.5}$V	1.33 (1.23–1.44)	1.22 (1.13–1.32)	1.23 (1.13–1.33)	0.98 (0.85–1.13)	0.95 (0.83–1.10)	0.94 (0.82–1.09)
$PM_{2.5}$Zn	1.14 (1.07–1.22)	1.08 (1.00–1.16)	1.08 (1.00–1.16)	1.03 (0.94–1.13)	1.01 (0.92–1.11)	1.03 (0.94–1.13)

HR: hazard ratio; CI: confidence interval; HRs are given for the following increments: $PM_{2.5}$ Cu—5 ng/m^3, $PM_{2.5}$ Fe—100 ng/m^3, $PM_{2.5}$ K—50 ng/m^3, $PM_{2.5}$ Ni—1 ng/m^3, $PM_{2.5}$ S—200 ng/m^3, $PM_{2.5}$Si—100 ng/m^3, $PM_{2.5}$ V—2 ng/m^3, $PM_{2.5}$ Zn—10 ng/m^3.
[a] Adjusted for study (strata), age, sex (strata), year of baseline visit.
[b] Further adjusted for smoking status, duration, intensity, intensity^2, marital status and employment status.
[c] Further adjusted for 2001 mean income at the neighbourhood level.

3.3.1. Sensitivity analyses

When omitting one cohort at a time, results for UADT cancers were robust except when omitting DCH which led to null associations for all elements with HRs ranging from 0.94 for Ni to 1.08 for S for the chosen increment (1 ng/m^3 and 200 ng/m^3, respectively) (Fig. S1 online supplement). Indeed, DCH had comparably strong positive associations with the respective elements in contrast to the other cohorts, except for CEANS showing associations similar to DCH (except for Ni) (Fig. S1 in the online Supplement). Regarding the sources, a similar picture emerged with associations for UADT cancer being driven mainly by the DCH cohort, except for biomass & agriculture. The corresponding associations tended toward the null but overlap of CIs was substantial for soil and industry. Positive associations similar to DCH were observed in CEANS for traffic, biomass & agriculture and soil (Fig. S2 in the online Supplement). For gastric cancer, omitting one cohort at a time, did not change the HRs.

Adjustment for additional confounders (alcohol and fruits; ETS; vegetables; meat; occupational class; educational level; BMI) did not change the effect estimates (Tables S8 to S11 in the online supplement). HRs were also robust to adjustment for urbanicity and NDVI, where the strongest change in estimate was seen for Si with a change in HR from 1.56 to 1.45 and 1.67, depending on whether NDVI in a 300 m or 1 km buffer was used.

4. Discussion

In this large cohort study, we found no association for gastric cancer but positive associations for UADT with all $PM_{2.5}$-elemental constituents, except K, as well as for all APCA identified sources, except biomass & agriculture and industry. Results for elements were generally stable upon adjustment to $PM_{2.5}$ but not NO_2, with only Ni and V representing mixed oil burning/industry remaining statistically significant. In multisource models, only associations with oil and traffic remained stable and positive. Results were robust in the numerous sensitivity

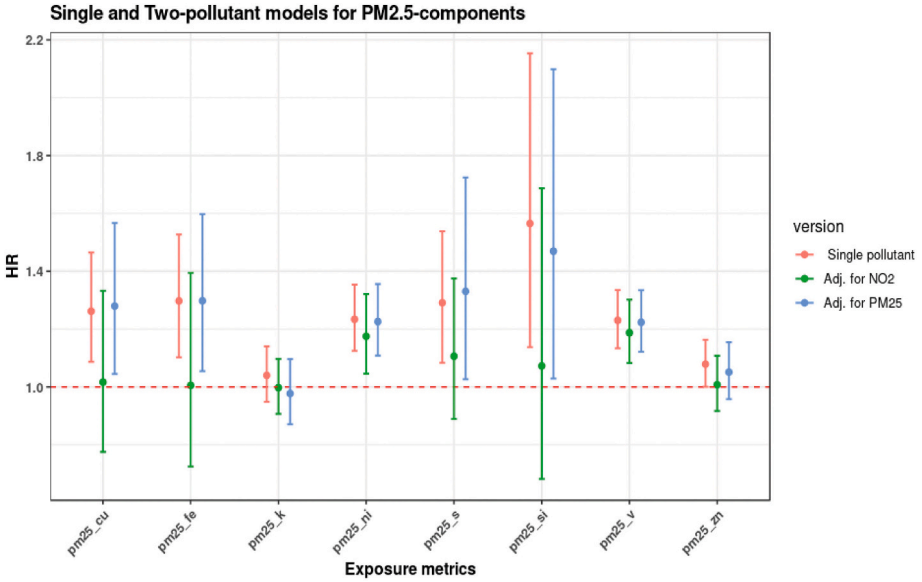


Fig. 3. Associations of PM elemental constituents with UADT in single and two-pollutant models (adjusted for NO_2 or $PM_{2.5}$).
Results are shown for model 3 adjusted for study (strata), age, sex (strata), year of baseline visit, smoking status, duration, intensity, intensity^2, marital status, employment status, and 2001 mean income at the neighbourhood level; HRs are given for the following increments: $PM_{2.5}$ Cu—5 ng/m^3, $PM_{2.5}$ Fe—100 ng/m^3, $PM_{2.5}$ K—50 ng/m^3, $PM_{2.5}$ Ni—1 ng/m^3, $PM_{2.5}$ S—200 ng/m^3, $PM_{2.5}$ Si—100 ng/m^3, $PM_{2.5}$ V—2 ng/m^3, $PM_{2.5}$ Zn—10 ng/m^3; high correlation (median across cohorts >0.7) between the two pollutants in the model were observed for Fe, Cu, Zn with NO_2 and K with $PM_{2.5}$.

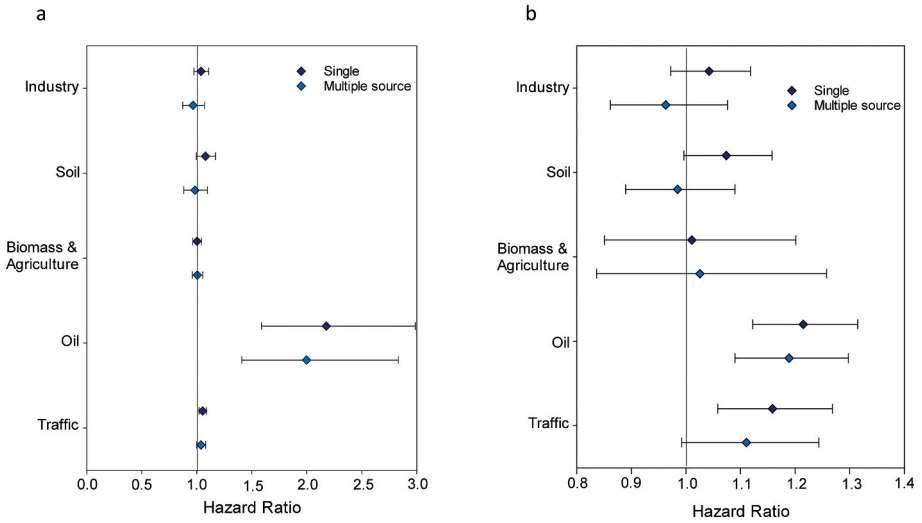


Fig. 4. Associations of source-specific $PM_{2.5}$ with UADT cancer.
Hazard ratios are shown per 1 μg/m^3 (a) and per IQR (b) respectively; Multipollutant models are mutually adjusted; Results are shown for model 3 adjusted for study (strata), age, sex (strata), year of baseline visit, smoking status, duration, intensity, intensity^2, marital status, employment status, and 2001 mean income at the neighbourhood level.

analyses, except for exclusion of the influential DCH cohort.

Our results differ from the previous ESCAPE-analysis where we found no relation with UADT and an association of S with gastric cancer. However, for most pollutants CIs overlap widely between ESCAPE and ELAPSE and are considerably smaller in the ELAPSE results. The reason for differences may be the longer follow-up and further improved exposure models in ELAPSE. Larger areas could be covered for three cohorts due to the Europe-wide exposure model, thereby increasing the number of study participants (notably for DCH, E3N and VHM&PP). While the results for DCH largely drive results there is considerable overlap of the CI from DCH with those of the other cohorts.

To our knowledge, only a previous ESCAPE analysis has looked at PM elemental constituents and gastric or UADT cancers, and our present study is the first one reporting on these specific $PM_{2.5}$ effects by source. Similar analyses on sources are essentially restricted to analyses on lung cancer mortality or mortality for all cancers from North America (namely the American Cancer Society Cancer Prevention Study-II (ACS CPS-II) cohort analysed within the National Particle Toxicity Component Initiative (NPACT) (Thurston et al., 2013) and a study in the Medicare cohort (Kazemiparkouhi et al., 2022)) and previous analyses within the ELAPSE framework (Chen et al., 2022a). The following discussion therefore has to rely largely on a comparison with these other outcomes, although they are not directly comparable due to different types of cancer included and because mortality outcomes also include survival after incidence.

4.1. Indicators of oil combustion

We observed the strongest association with residual oil combustion, especially on a mass concentration basis, where the HR was by far larger than that of traffic with the second highest HR. This estimate was stable in the multisource model. This is in line with the results for lung cancer mortality in previous ELAPSE analyses of the pooled cohort where the oil source also had the highest HR per 1 μg/m^3 (Chen et al., 2022a).

The association with oil is backed up by the positive associations for Ni and V which were both selected originally as tracers of mixed oil burning (de Hoogh et al., 2013; Tsai et al., 2015). Ni and V originate from fossil fuel burning in heating and notably shipping. Associations with V and Ni were also found in other ELAPSE analyses, i.e. for lung cancer incidence in the pooled cohort, and lung cancer mortality in the Danish administrative cohort in single-pollutant models (Hvidtfeldt et al., 2021a; So et al., 2023).

Contrary to our results, the studies in North America on total cancer mortality and lung cancer mortality found no positive association with long-term exposure to oil nor V and Ni (Kazemiparkouhi et al., 2022; Thurston et al., 2013).

Exposure contrasts related to oil and related elemental constituents are generally low and may make it more difficult to detect effects. Our large cohort together with the high spatial resolution of our exposure models may have allowed us to detect such associations more easily (Chen et al., 2022a). Related to the high risk per mass unit this association deserves further attention. The relatively higher risk compared to other sources seems plausible given that PM from fossil fuel contains high contents of toxic metals in relation to other particles (Maciejczyk et al., 2021).

4.2. Indicators of industry

We did not observe an association with the industrial source component, especially not in the multisource model similar to the results from the previous ELAPSE lung cancer mortality analyses (Chen et al., 2022a). While Zn had originally been selected as indicator for non-tailpipe traffic emissions, the APCA analysis found that Zn loaded most strongly on the industry factor, as compared to its loading on other factors (Chen et al., 2022a). Furthermore, industrial Zn-emissions reflected a large part of measured Zn-variability in LUR-models, including those of ports (Chen et al., 2021, 2020).

This may explain why our results show that the pattern of association is similar for industry and Zn: while Zn was borderline associated with UADT cancer incidence in the single-pollutant model, the association weakened moderately and became statistically non-significant when adjusting for $PM_{2.5}$ mass. In other ELAPSE analyses, Zn was associated with lung cancer mortality, but not incidence (Hvidtfeldt et al., 2021a; So et al., 2023).

Our findings are broadly in line with results from the North American context, where Zn was an indicator of industry processing non-ferrous metals in ACS CPS-II (Thurston et al., 2013) and indicator for "metals" in the Medicare cohort (Kazemiparkouhi et al., 2022). No positive associations were observed in ACS CPS-II with lung cancer mortality, neither with the metals source nor Zn. In the Medicare cohort, Zn was not associated with all cancer nor lung cancer mortality and the "metals" source was weakly, however statistically significantly associated with all cancer mortality.

Other studies on industrial emissions investigated rather cancer clusters in relation to proximity to specific industrial sources (Fazzo et al., 2016; Lynge et al., 2021) making comparisons impossible.

4.3. Indicators of traffic

Traffic is the second source where the observed association with UADT cancer persisted in the multisource model. This aligns with associations with the elements Cu and Fe related to non-tailpipe traffic emissions. Also, adjustment with $PM_{2.5}$ mass does not change substantially the estimates. In contrast, after adjustment for NO_2, which is mainly related to traffic (tailpipe emissions), the HR for Cu and Fe are very close to 1.0. However, these effect sizes have to be viewed with caution as NO_2 and these elements are highly correlated.

In the ELAPSE analysis on lung cancer mortality (Chen et al., 2022a), the effect estimate for the traffic factor per IQR was slightly smaller and attenuated toward null upon multisource adjustment. In the Medicare cohort, mortality from all cancers was statistically significantly associated with the traffic source. The association with lung cancer mortality was slightly weaker and not statistically significant (Kazemiparkouhi et al., 2022). In ACS CPS-II, the traffic factor was not associated with lung cancer mortality after adjustment for ecological variables (Thurston et al., 2013). However, in a nation-wide Danish study, a factor indicating local sources of $PM_{2.5}$ (including traffic) was associated with higher lung cancer mortality (Raaschou-Nielsen et al., 2023).

Regarding Cu and Fe, previous ELAPSE analyses found no associations with lung cancer incidence (Hvidtfeldt et al., 2021a) but with lung cancer mortality when not adjusted for NO_2 (So et al., 2023), the latter similar to our results. Negative associations with Fe and Cu were found in Medicare (mortality from lung cancer and all cancers) (Kazemiparkouhi et al., 2022) and no association was found between Fe and lung cancer mortality in ACS CPS-II (Thurston et al., 2013). This suggests that effects of traffic may depend not only on the type of cancer, but also on the air pollution mix related to traffic in different regions. It may also be difficult, to locally varying degrees, to disentangle the effects of tailpipe i.e. combustion related and non-tailpipe traffic emissions, the latter being related to mainly brake and tyre wear. In contrast to Fe and Cu, the traffic source component analysed here encompasses both tailpipe and non-tailpipe emissions (Chen et al., 2022a).

Further evidence for a role of traffic related air pollution in UADT cancer incidence comes from our previous results of a positive association with NO_2 and BC, both combustion-related pollutants, mostly indicative of traffic (Nagel et al. submitted) in our setting. Furthermore, a hypothesis generating study from Denmark investigating NOx and traffic indicators found non-significant but elevated HR for oesophageal cancer but not for gastric cancer (Raaschou-Nielsen et al., 2011) – which is in line with our findings. To our knowledge, no other studies have looked at specifically UADT or gastric cancer and traffic-related air pollution PM components.

4.4. Indicators of crustal material/soil

The observed association of this source with UADT cancer did not persist in the multisource model and the association with Si weakened upon adjustment with $PM_{2.5}$ and turned not statistically significant after adjustment for NO_2.

In ELAPSE, lung cancer incidence showed an association with Si that became not significant upon adjustment with $PM_{2.5}$ (Hvidtfeldt et al., 2021a) and lung cancer mortality was associated with soil in the single but not the multisource model (Chen et al., 2022a). However, in the Danish cohort, Si was associated with lung cancer mortality, even in two-pollutant models. The two US-Studies investigating sources showed no association of soil with mortality from lung cancer but a positive one with all cancers (Kazemiparkouhi et al., 2022; Thurston et al., 2013). Associations with Si were positive for mortality from all cancers in Medicare (Kazemiparkouhi et al., 2022) but no clear association was observed with lung cancer mortality in neither of the two US-cohorts.

Thus, the picture is unclear, which may also be related to whether this source originates from natural soils or road dust suspension. Indeed Si is a tracer for crustal material that may originate from both. Previous associations, e.g., in the Californian Teachers Study for cardiovascular outcomes, have been interpreted to reflect rather road dust or other traffic-related pollutants. In our study, this may also be the case as seen by the attenuations in the multisource model and upon adjustment with NO_2.

4.5. Indicators of biomass & agriculture

We found no association for the source biomass & agriculture nor K, not even in the single source/pollutant models. This is in contrast to the ELAPSE results for lung cancer, where positive associations were found for lung cancer incidence with K (Hvidtfeldt et al., 2021a) and lung cancer mortality with K and the source (Chen et al., 2022a; So et al., 2023).

On the contrary, in the two US-studies the results for their outcomes (all cancer mortality (Kazemiparkouhi et al., 2022) and lung cancer mortality (Kazemiparkouhi et al., 2022; Thurston et al., 2013)) showed weak inverse, partly even statistically significant, associations with biomass combustion, and a small inverse or null association with K.

Overall, this seems in contrast to reports on elevated UADT cancer in case-control studies (Okello et al., 2019) and a cohort study (Sheikh et al., 2020) on indoor biomass and wood burning. However, a large case-control study in Eastern Europe found relations with wood burning only when used for >50 years and was less clear in participants who did not use coal, an important confounder in their analysis (Sapkota et al., 2013). Nevertheless, a study in Brazil reported an elevated relative risk in relation to wildfire related $PM_{2.5}$ on UADT cancer (Yu et al., 2022). However, concentrations are higher in this context than in usual chronic real-life exposures.

Still, without specific markers for biomass burning such as levoglucosan, our results must be interpreted with caution.

4.6. Indicators of long-range transport, secondary pollutants

Sulphur had been chosen as a marker for long range transport: in the atmosphere SO_2 is transformed to sulphuric acid which by further reaction can form secondary PM-particles such as sulphates and, by photochemical reaction with organic vapours, secondary organic aerosols. These particles can persist over time and be transported long distances (Kelly and Fussell, 2012).

Our association of UADT cancer risk with sulphur is in line with the ELAPSE findings for lung cancer incidence (Hvidtfeldt et al., 2021a), and lung cancer mortality in the single-pollutant model (So et al., 2023). A nationwide Danish study showed higher lung cancer mortality in association with concentrations of sulphate but not with other secondary inorganic particles (Raaschou-Nielsen et al., 2023). Early investigations from ACS CPS-II showed also relations of lung cancer mortality to sulphate particles (Pope III, 2002) as did the recent Medicare study for lung and all cancer mortality in relation to S (Kazemiparkouhi et al., 2022). However, in the more recent analysis of the ACS CPS-II within the NPACT project, S was not related to lung cancer mortality (Thurston et al., 2013).

In these two studies (Kazemiparkouhi et al., 2022; Thurston et al., 2013), S was an indicator for coal combustion in the source apportionment, and the results for coal identified by factor analyses mirrored the results found for S. However, Thurston et al. (2013) report a higher correlation of S with oil compared to coal and S is considered a general marker for fossil fuel combustion (Maciejczyk et al., 2021). Indeed, in the ELAPSE source analysis, the highest correlation of S was with the oil source, which was more correlated only with Ni and V. Our findings of an association between S and UADT cancer, are therefore in line with our findings above for oil combustion.

The toxicity of S itself is generally considered as not relevant. However, it may have indirect effects via solubilizing metal ions influencing thereby their bioavailability (Cassee et al., 2013) and the resulting oxidative potential of the particles (Kelly and Fussell, 2012; Maciejczyk et al., 2021). Furthermore, sulphates are precursors of secondary organic particles (Kelly and Fussell, 2012).

4.7. Strengths and limitations

A strength of our investigation is the relatively large study size considering the rarity of the outcomes, with inclusion of cohorts from several locations in Europe into a pooled data set which increased statistical power. Nevertheless, the sample size may still be limited to detect associations with gastric cancer. Detailed information of individual and neighbourhood/community level covariates including smoking and socioeconomic status was available and harmonized across the cohorts.

The exposure models had high spatial resolution allowing individual exposure estimates. As they were developed Europe-wide and then applied to cohort participants, exposure assessment is the same for all locations. Still the model may perform less well in individual study locations, which may be relevant as cohort is included in the strata statement and we therefore consider mainly intra-location contrasts. While our results are mainly driven by positive effect estimates in DCH, with overlap in CIs of estimates with and without DCH, we can probably exclude that this is due to differences in exposure assessment procedures. Furthermore, the DCH cohort has many participants and covers large areas of Denmark, so the Europe-wide model may work particularly well for this population. In addition, we were able to include additional source-relevant data based on satellite-model estimates of sulphate, organic matter, black carbon and mineral dust in $PM_{2.5}$, as well as emissions from major industrial point sources providing information on Cu, Ni, SOx and Zn. Therefore, we think the hybrid models perform better than the previous models from the ESCAPE cohort. Importantly we could also investigate sources as defined by APCA, which resolves the problem of high correlations between PM constituents and found consistency of results.

When studying sources, it is at present virtually impossible to incorporate personal mobility data, however it has been reported that epidemiological studies taking only into account exposure at residence have no severe bias (Hoek, 2017). Especially in the absence of a systematic bias, such as people living in clean areas working more frequently in more polluted sites than others, we expect an attenuation of the association due to non-differential measurement error which was indeed reported in two studies that could incorporate work/school address and commuting (Hoek, 2017). Another limitation is that measurements were taken after the recruitment of cohort individuals, mostly approximately a decade earlier. However, spatial contrasts rather than temporal changes are most relevant in epidemiological studies on long-term exposures. In addition, studies on spatial pattern of contrast of NO_2 have shown that these remain stable over similarly long time periods. Indeed, major patterns of emissions sources are not likely to change dramatically over time (Belis et al., 2013; Viana et al., 2008) and this is probably even less the case for substances that are not regulated, which applies to most of the investigated $PM_{2.5}$ constituents. Changes would therefore have occurred most likely for S with SO_2 having been regulated resulting in decreased emissions over time (EEA (European Environment Agency), 2015) which may have inflated the observed HR.

4.8. Conclusion

Our results indicate an association of UADT but not gastric cancer incidence with several PM elemental constituents reflecting different PM sources. A limitation is that the second largest cohort strongly influences the results. Nevertheless, results are largely consistent between two types of indicators for PM sources: PM elemental constituents and sources identified by APCA. Traffic and residual oil combustion are the most relevant sources for UADT cancer incidence in this European context, which points to a higher toxicity of fossil fuel related combustion particles in comparison to some other sources as it has been also observed in the US with regard to mortality (Thurston, 2022). This is of even more concern as these associations were found in a population that is exposed to moderate to low $PM_{2.5}$ exposure, almost entirely to concentrations below the limit values of the current European Union Air Quality Directive. In terms of prevention, these results add to the importance of transforming the transport and energy systems.

Nevertheless, other similar studies should further strengthen the evidence base underpinning the relationships specifically with gastric and UADT cancers.

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.

The analyses on gastric and UADT cancers were supported by the German Cancer Aid (Project No. 70114601).

CRediT authorship contribution statement

Gudrun Weinmayr: Conceptualization, Formal analysis, Writing – original draft. **Jie Chen:** Data curation, Formal analysis, Project administration, Writing – review & editing. **Andrea Jaensch:** Formal analysis, Writing – review & editing. **Lea Skodda:** Formal analysis, Writing – review & editing. **Sophia Rodopoulou:** Formal analysis, Writing – review & editing. **Maciej Strak:** Project administration, Writing – review & editing. **Kees de Hoogh:** Writing – review & editing, Data curation. **Zorana J. Andersen:** Writing – review & editing. **Tom Bellander:** Writing – review & editing. **Jørgen Brandt:** Data curation, Writing – review & editing. **Daniela Fecht:** Writing – review & editing. **Francesco Forastiere:** Writing – review & editing. **John Gulliver:** Writing – review & editing. **Ole Hertel:** Writing – review & editing. **Barbara Hoffmann:** Writing – review & editing. **Ulla Arthur Hvidtfeldt:** Writing – review & editing. **Klea Katsouyanni:** Formal analysis, Writing – review & editing. **Matthias Ketzel:** Writing – review & editing. **Karin Leander:** Writing – review & editing. **Patrik K.E. Magnusson:** Writing – review & editing. **Göran Pershagen:** Writing – review & editing. **Debora Rizzuto:** Writing – review & editing. **Evangelia Samoli:** Formal analysis, Writing – review & editing. **Gianluca Severi:** Writing – review & editing. **Massimo Stafoggia:** Writing – review & editing, Formal analysis. **Anne Tjønneland:** Writing – review & editing. **Roel Vermeulen:** Writing – review & editing. **Kathrin Wolf:** Formal analysis, Writing – review & editing. **Emanuel Zitt:** Writing – review & editing. **Bert Brunekreef:** Data curation, Investigation, Writing – review & editing. **George Thurston:** Data curation, Writing – review & editing. **Gerard Hoek:** Data curation, Investigation, Project administration, Writing – review & editing. **Ole Raaschou-Nielsen:** Conceptualization, Writing – review & editing. **Gabriele Nagel:** Conceptualization, Formal analysis, Writing – review & editing.

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 data that has been used is confidential.

Acknowledgements

The authors would like to thank all participants in the pooled cohort studies and the respective study teams of the ELAPSE project for their hard work and effort. We thank Marjan Tewis for the data management tasks in creating the pooled cohort database.

Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.scitotenv.2023.168789.

References

Arnold, M., Abnet, C.C., Neale, R.E., Vignat, J., Giovannucci, E.L., McGlynn, K.A., Bray, F., 2020. Global burden of 5 major types of gastrointestinal cancer. Gastroenterology 159, 335–349.e15. https://doi.org/10.1053/j.gastro.2020.02.068.

Belis, C.A., Karagulian, F., Larsen, B.R., Hopke, P.K., 2013. Critical review and meta-analysis of ambient particulate matter source apportionment using receptor models in Europe. Atmos. Environ. 69, 94–108. https://doi.org/10.1016/j.atmosenv.2012.11.009.

Beulens, J.W.J., Monninkhof, E.M., Monique Verschuren, W.M., van der Schouw, Y.T., Smit, J., Ocke, M.C., Jansen, E.H.J.M., van Dieren, S., Grobbee, D.E., Peeters, P.H.M., Bueno-de-Mesquita, H.B., 2010. Cohort profile: the EPIC-NL study. Int. J. Epidemiol. 39, 1170–1178. https://doi.org/10.1093/ije/dyp217.

Brook, R.D., Newby, D.E., Rajagopalan, S., 2018. Air pollution and Cardiometabolic disease: an update and call for clinical trials. Am. J. Hypertens. 31, 1–10. https://doi.org/10.1093/ajh/hpx109.

Brunekreef, B., Strak, M., Chen, J., Andersen, Z.J., Atkinson, R., Bauwelinck, M., Bellander, T., Boutron, M.-C., Brandt, J., Carey, I., Cesaroni, G., Forastiere, F., Fecht, D., Gulliver, J., Hertel, O., Hoffmann, B., de Hoogh, K., Houthuijs, D., Hvidtfeldt, U., Janssen, N., Jorgensen, J., Katsouyanni, K., Ketzel, M., Klompmaker, J., Hjertager Krog, N., Liu, S., Ljungman, P., Mehta, A., Nagel, G., Oftedal, B., Pershagen, G., Peters, A., Raaschou-Nielsen, O., Renzi, M., Rodopoulou, S., Samoli, E., Schwarze, P., Sigsgaard, T., Stafoggia, M., Vienneau, D., Weinmayr, G., Wolf, K., Hoek, G., 2021. Mortality and Morbidity Effects of Long-Term Exposure to Low-Level PM2.5, BC, NO2, and O3: An Analysis of European Cohorts in the ELAPSE Project. Res. Rep. Health. Eff. Inst, pp. 1–127.

Cassee, F.R., Héroux, M.-E., Gerlofs-Nijland, M.E., Kelly, F.J., 2013. Particulate matter beyond mass: recent health evidence on the role of fractions, chemical constituents and sources of emission. Inhal. Toxicol. 25, 802–812. https://doi.org/10.3109/08958378.2013.850127.

Chen, J., de Hoogh, K., Gulliver, J., Hoffmann, B., Hertel, O., Ketzel, M., Weinmayr, G., Bauwelinck, M., van Donkelaar, A., Hvidtfeldt, U.A., Atkinson, R., Janssen, N.A.H., Martin, R.V., Samoli, E., Andersen, Z.J., Oftedal, B.M., Stafoggia, M., Bellander, T., Strak, M., Wolf, K., Vienneau, D., Brunekreef, B., Hoek, G., 2020. Development of Europe-wide models for particle elemental composition using supervised linear regression and random Forest. Environ. Sci. Technol. 54, 15698–15709. https://doi.org/10.1021/acs.est.0c06595.

Chen, J., Rodopoulou, S., de Hoogh, K., Strak, M., Andersen, Z.J., Atkinson, R., Bauwelinck, M., Bellander, T., Brandt, J., Cesaroni, G., Concin, H., Fecht, D., Forastiere, F., Gulliver, J., Hertel, O., Hoffmann, B., Hvidtfeldt, U.A., Janssen, N.A.H., Jöckel, K.-H., Jørgensen, J., Katsouyanni, K., Ketzel, M., Klompmaker, J.O., Lager, A., Leander, K., Liu, S., Ljungman, P., MacDonald, C.J., Magnusson, P.K.E., Mehta, A., Nagel, G., Oftedal, B., Pershagen, G., Peters, A., Raaschou-Nielsen, O., Renzi, M., Rizzuto, D., Samoli, E., van der Schouw, Y.T., Schramm, S., Schwarze, P., Sigsgaard, T., Sørensen, M., Stafoggia, M., Tjønneland, A., Vienneau, D., Weinmayr, G., Wolf, K., Brunekreef, B., Hoek, G., 2021. Long-Term Exposure to Fine Particle Elemental Components and Natural and Cause-Specific Mortality—A Pooled Analysis of Eight European Cohorts within the ELAPSE Project. Environ. Health Perspect. 129, EHP8368. https://doi.org/10.1289/EHP8368.

Chen, J., Hoek, G., de Hoogh, K., Rodopoulou, S., Andersen, Z.J., Bellander, T., Brandt, J., Fecht, D., Forastiere, F., Gulliver, J., Hertel, O., Hoffmann, B., Hvidtfeldt, U.A., Verschuren, W.M.M., Jöckel, K.-H., Jørgensen, J.T., Katsouyanni, K., Ketzel, M., Méndez, D.Y., Leander, K., Liu, S., Ljungman, P., Faure, E., Magnusson, P.K.E., Nagel, G., Pershagen, G., Peters, A., Raaschou-Nielsen, O., Rizzuto, D., Samoli, E., van der Schouw, Y.T., Schramm, S., Severi, G., Stafoggia, M., Strak, M., Sørensen, M., Tjønneland, A., Weinmayr, G., Wolf, K., Zitt, E., Brunekreef, B., Thurston, G.D., 2022a. Long-term exposure to source-specific fine particles and mortality—a pooled analysis of 14 European cohorts within the ELAPSE project. Environ. Sci. Technol. 56, 9277–9290. https://doi.org/10.1021/acs.est.2c01912.

Chen, J., Rodopoulou, S., Strak, M., de Hoogh, K., Taj, T., Poulsen, A.H., Andersen, Z.J., Bellander, T., Brandt, J., Zitt, E., Fecht, D., Forastiere, F., Gulliver, J., Hertel, O., Hoffmann, B., Hvidtfeldt, U.A., Verschuren, W.M.M., Jørgensen, J.T., Katsouyanni, K., Ketzel, M., Lager, A., Leander, K., Liu, S., Ljungman, P., Severi, G., Boutron-Ruault, M.-C., Magnusson, P.K.E., Nagel, G., Pershagen, G., Peters, A., Rizzuto, D., van der Schouw, Y.T., Samoli, E., Sørensen, M., Stafoggia, M., Tjønneland, A., Weinmayr, G., Wolf, K., Brunekreef, B., Raaschou-Nielsen, O., Hoek, G., 2022b. Long-term exposure to ambient air pollution and bladder cancer incidence in a pooled European cohort: the ELAPSE project. Br. J. Cancer 126, 1499–1507. https://doi.org/10.1038/s41416-022-01735-4.

Clavel-Chapelon, F., E3N Study Group, for the E.S, 2015. Cohort profile: the French E3N cohort study. Int. J. Epidemiol. 44, 801–809. https://doi.org/10.1093/ije/dyu184.

de Hoogh, K., Wang, M., Adam, M., Badaloni, C., Beelen, R., Birk, M., Cesaroni, G., Cirach, M., Declercq, C., Dėdelė, A., Dons, E., de Nazelle, A., Eeftens, M., Eriksen, K., Eriksson, C., Fischer, P., Gražulevičienė, R., Gryparis, A., Hoffmann, B., Jerrett, M., Katsouyanni, K., Iakovides, M., Lanki, T., Lindley, S., Madsen, C., Mölter, A., Mosler, G., Nádor, G., Nieuwenhuijsen, M., Pershagen, G., Peters, A., Phuleria, H., Probst-Hensch, N., Raaschou-Nielsen, O., Quass, U., Ranzi, A., Stephanou, E., Sugiri, D., Schwarze, P., Tsai, M.-Y., Yli-Tuomi, T., Varró, M.J., Vienneau, D.,

Weinmayr, G., Brunekreef, B., Hoek, G., 2013. Development of land use regression models for particle composition in twenty study areas in Europe. Environ. Sci. Technol. 47, 5778–5786. https://doi.org/10.1021/es400156t.

EEA (European Environment Agency), 2015. n.d. Sulphurdioxide (SO2) emissions [WWW Document]. URL. https://www.eea.europa.eu/data-and-maps/indicators/eea-32-sulphur-dioxide-so2-emissions-1/assessment-3.

Eriksson, A.-K., Ekbom, A., Granath, F., Hilding, A., Efendic, S., Ostenson, C.-G., 2008. Psychological distress and risk of pre-diabetes and type 2 diabetes in a prospective study of Swedish middle-aged men and women. Diabet. Med. 25, 834–842. https://doi.org/10.1111/j.1464-5491.2008.02463.x.

Fazzo, L., Carere, M., Tisano, F., Bruno, C., Cernigliaro, A., Cicero, M.R., Comba, P., Contrino, M.L., De Santis, M., Falleni, F., Ingallinella, V., Madeddu, A., Marcello, I., Regalbuto, C., Sciacca, G., Soggiu, M.E., Zona, A., 2016. Cancer incidence in Priolo, Sicily: a spatial approach for estimation of industrial air pollution impact. Geospat. Health 11, 320. https://doi.org/10.4081/gh.2016.320.

Furuyama, A., Kanno, S., Kobayashi, T., Hirano, S., 2009. Extrapulmonary translocation of intratracheally instilled fine and ultrafine particles via direct and alveolar macrophage-associated routes. Arch. Toxicol. 83, 429–437. https://doi.org/10.1007/s00204-008-0371-1.

Hamra, G.B., Guha, N., Cohen, A., Laden, F., Raaschou-Nielsen, O., Samet, J.M., Vineis, P., Forastiere, F., Saldiva, P., Yorifuji, T., Loomis, D., 2014. Outdoor particulate matter exposure and lung cancer: a systematic review and meta-analysis. Environ. Health Perspect. 122, 906–911. https://doi.org/10.1289/ehp/1408092.

Hoek, G., 2017. Methods for assessing long-term exposures to outdoor air pollutants. Curr. Environ. Heal. Rep. 4, 450–462. https://doi.org/10.1007/s40572-017-0169-5.

Hundrup, Y.A., Simonsen, M.K., Jørgensen, T., Obel, E.B., 2012. Cohort profile: the danish nurse cohort. Int. J. Epidemiol. 41, 1241–1247. https://doi.org/10.1093/ije/dyr042.

Hvidtfeldt, U.A., Chen, J., Andersen, Z.J., Atkinson, R., Bauwelinck, M., Bellander, T., Brandt, J., Brunekreef, B., Cesaroni, G., Concin, H., Fecht, D., Forastiere, F., van Gils, C.H., Gulliver, J., Hertel, O., Hoek, G., Hoffmann, B., de Hoogh, K., Janssen, N., Jørgensen, J.T., Katsouyanni, K., Jöckel, K.-H., Ketzel, M., Klompmaker, J.O., Lang, A., Leander, K., Liu, S., Ljungman, P.L.S., Magnusson, P.K.E., Mehta, A.J., Nagel, G., Oftedal, B., Pershagen, G., Peter, R.S., Peters, A., Renzi, M., Rizzuto, D., Rodopoulou, S., Samoli, E., Schwarze, P.E., Severi, G., Sigsgaard, T., Stafoggia, M., Strak, M., Vienneau, D., Weinmayr, G., Wolf, K., Raaschou-Nielsen, O., 2021a. Long-term exposure to fine particle elemental components and lung cancer incidence in the ELAPSE pooled cohort. Environ. Res. 193, 110568 https://doi.org/10.1016/j.envres.2020.110568.

Hvidtfeldt, U.A., Severi, G., Andersen, Z.J., Atkinson, R., Bauwelinck, M., Bellander, T., Boutron-Ruault, M.-C., Brandt, J., Brunekreef, B., Cesaroni, G., Chen, J., Concin, H., Forastiere, F., van Gils, C.H., Gulliver, J., Hertel, O., Hoek, G., Hoffmann, B., de Hoogh, K., Janssen, N., Jöckel, K.-H., Jørgensen, J.T., Katsouyanni, K., Ketzel, M., Klompmaker, J.O., Krog, N.H., Lang, A., Leander, K., Liu, S., Ljungman, P.L.S., Magnusson, P.K.E., Mehta, A.J., Nagel, G., Oftedal, B., Pershagen, G., Peter, R.S., Peters, A., Renzi, M., Rizzuto, D., Rodopoulou, S., Samoli, E., Schwarze, P.E., Sigsgaard, T., Simonsen, M.K., Stafoggia, M., Strak, M., Vienneau, D., Weinmayr, G., Wolf, K., Raaschou-Nielsen, O., Fecht, D., 2021b. Long-term low-level ambient air pollution exposure and risk of lung cancer – a pooled analysis of 7 European cohorts. Environ. Int. 146, 106249 https://doi.org/10.1016/j.envint.2020.106249.

IARC Working Group on the Evaluation of Carcinogenic Risks to Humans, 2012. Personal habits and indoor combustions. In: IARC Monogr. Eval. Carcinog. Risks to Humans, 100, pp. 1–538.

Kazemiparkouhi, F., Honda, T., Eum, K.-D., Wang, B., Manjourides, J., Suh, H.H., 2022. The impact of long-term PM2.5 constituents and their sources on specific causes of death in a US Medicare cohort. Environ. Int. 159, 106988 https://doi.org/10.1016/j.envint.2021.106988.

Kelly, F.J., Fussell, J.C., 2012. Size, source and chemical composition as determinants of toxicity attributable to ambient particulate matter. Atmos. Environ. 60, 504–526. https://doi.org/10.1016/j.atmosenv.2012.06.039.

Lagergren, M., Fratiglioni, L., Hallberg, I.R., Berglund, J., Elmståhl, S., Hagberg, B., Holst, G., Rennemark, M., Sjölund, B.M., Thorslund, M., Wiberg, I., Winblad, B., Wimo, A., 2004. A longitudinal study integrating population, care and social services data. The Swedish National study on Aging and Care (SNAC). Aging Clin. Exp. Res. 16, 158–168. https://doi.org/10.1007/BF03324546.

Lynge, E., Holmsgaard, H.A., Holmager, T.L.F., Lophaven, S., 2021. Cancer incidence in Thyborøn-Harbøøre, Denmark: a cohort study from an industrially contaminated site. Sci. Rep. 11, 13006. https://doi.org/10.1038/s41598-021-92446-y.

Maciejczyk, P., Chen, L.-C., Thurston, G., 2021. The role of fossil fuel combustion metals in PM2.5 air pollution health associations. Atmosphere (Basel) 12, 1086. https://doi.org/10.3390/atmos12091086.

Magnusson, P.K.E., Almqvist, C., Rahman, I., Ganna, A., Viktorin, A., Walum, H., Halldner, L., Lundström, S., Ullén, F., Långström, N., Larsson, H., Nyman, A., Gumpert, C.H., Råstam, M., Anckarsäter, H., Cnattingius, S., Johannesson, M., Ingelsson, E., Klareskog, L., de Faire, U., Pedersen, N.L., Lichtenstein, P., 2013. The Swedish twin registry: establishment of a biobank and other recent developments. Twin Res. Hum. Genet. 16, 317–329. https://doi.org/10.1017/thg.2012.104.

Oberdörster, G., Oberdörster, E., Oberdörster, J., 2005. Nanotoxicology: an emerging discipline evolving from studies of ultrafine particles. Environ. Health Perspect. 113, 823–839. https://doi.org/10.1289/ehp.7339.

Okello, S., Akello, S.J., Dwomoh, E., Byaruhanga, E., Opio, C.K., Zhang, R., Corey, K.E., Muyindike, W.R., Ocama, P., Christiani, D.D., 2019. Biomass fuel as a risk factor for esophageal squamous cell carcinoma: a systematic review and meta-analysis. Environ. Health 18, 60. https://doi.org/10.1186/s12940-019-0496-0.

Pope III, C.A., 2002. Lung Cancer, cardiopulmonary mortality, and long-term exposure to fine particulate air pollution. JAMA 287, 1132. https://doi.org/10.1001/jama.287.9.1132.

Pritchett, N., Spangler, E.C., Gray, G.M., Livinski, A.A., Sampson, J.N., Dawsey, S.M., Jones, R.R., 2022. 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. 130 https://doi.org/10.1289/EHP9620.

Raaschou-Nielsen, O., Andersen, Z.J., Hvidberg, M., Jensen, S.S., Ketzel, M., Sørensen, M., Hansen, J., Loft, S., Overvad, K., Tjønneland, A., 2011. Air pollution from traffic and cancer incidence: a Danish cohort study. Environ. Health 10, 67. https://doi.org/10.1186/1476-069X-10-67.

Raaschou-Nielsen, O., Andersen, Z.J., Beelen, R., Samoli, E., Stafoggia, M., Weinmayr, G., Hoffmann, B., Fischer, P., Nieuwenhuijsen, M.J., Brunekreef, B., Xun, W.W., Katsouyanni, K., Dimakopoulou, K., Sommar, J., Forsberg, B., Modig, L., Oudin, A., Oftedal, B., Schwarze, P.E., Nafstad, P., De Faire, U., Pedersen, N.L., Ostenson, C.-G., Fratiglioni, L., Penell, J., Korek, M., Pershagen, G., Eriksen, K.T., Sørensen, M., Tjønneland, A., Ellermann, T., Eeftens, M., Peeters, P.H., Meliefste, K., Wang, M., Bueno-de-Mesquita, B., Key, T.J., de Hoogh, K., Concin, H., Nagel, G., Vilier, A., Grioni, S., Krogh, V., Tsai, M.-Y., Ricceri, F., Sacerdote, C., Galassi, C., Migliore, E., Ranzi, A., Cesaroni, G., Badaloni, C., Forastiere, F., Tamayo, I., Amiano, P., Dorronsoro, M., Trichopoulou, A., Bamia, C., Vineis, P., Hoek, G., 2013. Air pollution and lung cancer incidence in 17 European cohorts: prospective analyses from the European Study of Cohorts for Air Pollution Effects (ESCAPE). Lancet Oncol. 14, 813–822. https://doi.org/10.1016/S1470-2045(13)70279-1.

Raaschou-Nielsen, O., Beelen, R., Wang, M., Hoek, G., Andersen, Z.J., Hoffmann, B., Stafoggia, M., Samoli, E., Weinmayr, G., Dimakopoulou, K., Nieuwenhuijsen, M., Xun, W.W., Fischer, P., Eriksen, K.T., Sørensen, M., Tjønneland, A., Ricceri, F., de Hoogh, K., Key, T., Eeftens, M., Peeters, P.H., Bueno-de-Mesquita, H.B., Meliefste, K., Oftedal, B., Schwarze, P.E., Nafstad, P., Galassi, C., Migliore, E., Ranzi, A., Cesaroni, G., Badaloni, C., Forastiere, F., Penell, J., De Faire, U., Korek, M., Pedersen, N., Östenson, C.-G., Pershagen, G., Fratiglioni, L., Concin, H., Nagel, G., Jaensch, A., Ineichen, A., Naccarati, A., Katsoulis, M., Trichpoulou, A., Keuken, M., Jedynska, A., Kooter, I.M., Kukkonen, J., Brunekreef, B., Sokhi, R.S., Katsouyanni, K., Vineis, P., 2016. Particulate matter air pollution components and risk for lung cancer. Environ. Int. 87, 66–73. https://doi.org/10.1016/j.envint.2015.11.007.

Raaschou-Nielsen, O., Antonsen, S., Agerbo, E., Hvidtfeldt, U.A., Geels, C., Frohn, L.M., Christensen, J.H., Sigsgaard, T., Brandt, J., Pedersen, C.B., 2023. PM2.5 air pollution components and mortality in Denmark. Environ. Int. 171, 107685 https://doi.org/10.1016/j.envint.2022.107685.

Samoli, E., Rodopoulou, S., Hvidtfeldt, U.A., Wolf, K., Stafoggia, M., Brunekreef, B., Strak, M., Chen, J., Andersen, Z.J., Atkinson, R., Bauwelinck, M., Bellander, T., Brandt, J., Cesaroni, G., Forastiere, F., Fecht, D., Gulliver, J., Hertel, O., Hoffmann, B., de Hoogh, K., Janssen, N.A.H., Ketzel, M., Klompmaker, J.O., Liu, S., Ljungman, P., Nagel, G., Oftedal, B., Pershagen, G., Peters, A., Raaschou-Nielsen, O., Renzi, M., Kristoffersen, D.T., Severi, G., Sigsgaard, T., Vienneau, D., Weinmayr, G., Hoek, G., Katsouyanni, K., 2021. Modeling multi-level survival data in multi-center epidemiological cohort studies: applications from the ELAPSE project. Environ. Int. 147, 106371 https://doi.org/10.1016/j.envint.2020.106371.

Sapkota, A., Zaridze, D., Szeszenia-Dabrowska, N., Mates, D., Fabiánová, E., Rudnai, P., Janout, V., Holcatova, I., Brennan, P., Boffetta, P., Hashibe, M., 2013. Indoor air pollution from solid fuels and risk of upper aerodigestive tract cancers in central and Eastern Europe. Environ. Res. 120, 90–95. https://doi.org/10.1016/j.envres.2012.09.008.

Sheikh, M., Poustchi, H., Pourshams, A., Khoshnia, M., Gharavi, A., Zahedi, M., Roshandel, G., Sepanlou, S.G., Fazel, A., Hashemian, M., Abaei, B., Sotoudeh, M., Nikmanesh, A., Merat, S., Etemadi, A., Moghaddam, S.N., Islami, F., Kamangar, F., Pharoah, P.D., Dawsey, S.M., Abnet, C.C., Boffetta, P., Brennan, P., Malekzadeh, R., 2020. Household fuel use and the risk of gastrointestinal cancers: the Golestan Cohort Study. Environ. Health Perspect. 128, 067002 https://doi.org/10.1289/EHP5907.

So, R., Chen, J., Stafoggia, M., de Hoogh, K., Katsouyanni, K., Vienneau, D., Samoli, E., Rodopoulou, S., Loft, S., Lim, Y.-H., Westendorp, R.G.J., Amini, H., Cole-Hunter, T., Bergmann, M., Shahri, S.M.T., Zhang, J., Maric, M., Mortensen, L.H., Bauwelinck, M., Klompmaker, J.O., Atkinson, R.W., Janssen, N.A.H., Oftedal, B., Renzi, M., Forastiere, F., Strak, M., Brunekreef, B., Hoek, G., Andersen, Z.J., 2023. Long-term exposure to elemental components of fine particulate matter and all-natural and cause-specific mortality in a Danish nationwide administrative cohort study. Environ. Res. 224, 115552 https://doi.org/10.1016/j.envres.2023.115552.

Straif, K., Cohen, A., Samet, J., Cancer, I.A. for R. on, 2013. IARC scientific publication NO. 161: air pollution and cancer. Lyon Int. Agency Res. Cancer.

Thurston, G.D., 2022. Fossil fuel combustion and PM2.5 mass air pollution associations with mortality. Environ. Int. 160, 107066 https://doi.org/10.1016/j.envint.2021.107066.

Thurston, G.D., Spengler, J.D., 1985. A quantitative assessment of source contributions to inhalable particulate matter pollution in metropolitan Boston. Atmos. Environ. 19, 9–25. https://doi.org/10.1016/0004-6981(85)90132-5.

Thurston, G., Ito, K., Lall, R., Burnett, R., Turner, M., Krewski, D., Shi, Y., Jerrett, M., Gapstur, S.M., Diver, W.R., et al., 2013. Study 4: Mortality and long-term exposure to PM2.5 and its components in the American Cancer Society's CPS-II cohort. In: Lippmann, M., Chen, L.-C., Gordon, T., Ito, K., Thurston, G.D. (Eds.), National Particle Component Toxicity (NPACT) Initiative: Integrated Epidemiologic and Toxicologic Studies of the Health Effects of P Articulate Matter Components. Health Effects Institute, Boston, MA, pp. 127–166. Research Report 177.

Tjønneland, A., Olsen, A., Boll, K., Stripp, C., Christensen, J., Engholm, G., Overvad, K., 2007. 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 35, 432–441. https://doi.org/10.1080/14034940601047986.

Tsai, M.-Y., Hoek, G., Eeftens, M., de Hoogh, K., Beelen, R., Beregszászi, T., Cesaroni, G., Cirach, M., Cyrys, J., De Nazelle, A., de Vocht, F., Ducret-Stich, R., Eriksen, K., Galassi, C., Gražuleviciene, R., Gražulevicius, T., Grivas, G., Gryparis, A., Heinrich, J., Hoffmann, B., Iakovides, M., Keuken, M., Krämer, U., Künzli, N., Lanki, T., Madsen, C., Meliefste, K., Merritt, A.-S., Mölter, A., Mosler, G., Nieuwenhuijsen, M.J., Pershagen, G., Phuleria, H., Quass, U., Ranzi, A., Schaffner, E., Sokhi, R., Stempfelet, M., Stephanou, E., Sugiri, D., Taimisto, P., Tewis, M., Udvardy, O., Wang, M., Brunekreef, B., 2015. Spatial variation of PM elemental composition between and within 20 European study areas — results of the ESCAPE project. Environ. Int. 84, 181–192. https://doi.org/10.1016/j.envint.2015.04.015.

Turner, M.C., Andersen, Z.J., Baccarelli, A., Diver, W.R., Gapstur, S.M., Pope, C.A., Prada, D., Samet, J., Thurston, G., Cohen, A., 2020. Outdoor air pollution and cancer: an overview of the current evidence and public health recommendations. CA Cancer J. Clin. 70, 460–479. https://doi.org/10.3322/caac.21632.

Ulmer, H., Kelleher, C.C., Fitz-Simon, N., Diem, G., Concin, H., 2007. Secular trends in cardiovascular risk factors: an age-period cohort analysis of 6 98 954 health examinations in 1 81 350 Austrian men and women. J. Intern. Med. 261, 566–576. https://doi.org/10.1111/j.1365-2796.2007.01779.x.

Viana, M., Kuhlbusch, T.A.J., Querol, X., Alastuey, A., Harrison, R.M., Hopke, P.K., Winiwarter, W., Vallius, M., Szidat, S., Prévôt, A.S.H., Hueglin, C., Bloemen, H., Wåhlin, P., Vecchi, R., Miranda, A.I., Kasper-Giebl, A., Maenhaut, W., Hitzenberger, R., 2008. Source apportionment of particulate matter in Europe: a review of methods and results. J. Aerosol Sci. 39, 827–849. https://doi.org/10.1016/j.jaerosci.2008.05.007.

Wändell, P.-E., Wajngot, A., de Faire, U., Hellénius, M.-L., 2007. Increased prevalence of diabetes among immigrants from non-European countries in 60-year-old men and women in Sweden. Diabetes Metab. 33, 30–36. https://doi.org/10.1016/j.diabet.2006.07.001.

Weinmayr, G., Pedersen, M., Stafoggia, M., Andersen, Z.J., Galassi, C., Munkenast, J., Jaensch, A., Oftedal, B., Krog, N.H., Aamodt, G., Pyko, A., Pershagen, G., Korek, M., De Faire, U., Pedersen, N.L., Östenson, C.-G., Rizzuto, D., Sørensen, M., Tjønneland, A., Bueno-de-Mesquita, B., Vermeulen, R., Eeftens, M., Concin, H., Lang, A., Wang, M., Tsai, M.-Y., Ricceri, F., Sacerdote, C., Ranzi, A., Cesaroni, G., Forastiere, F., de Hoogh, K., Beelen, R., Vineis, P., Kooter, I., Sokhi, R., Brunekreef, B., Hoek, G., Raaschou-Nielsen, O., Nagel, G., 2018. 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. 120, 163–171. https://doi.org/10.1016/j.envint.2018.07.030.

Yu, P., Xu, R., Li, S., Yue, X., Chen, G., Ye, T., Coêlho, M.S.Z.S., Saldiva, P.H.N., Sim, M. R., Abramson, M.J., Guo, Y., 2022. Exposure to wildfire-related PM2.5 and site-specific cancer mortality in Brazil from 2010 to 2016: a retrospective study. PLoS Med. 19, e1004103 https://doi.org/10.1371/journal.pmed.1004103.