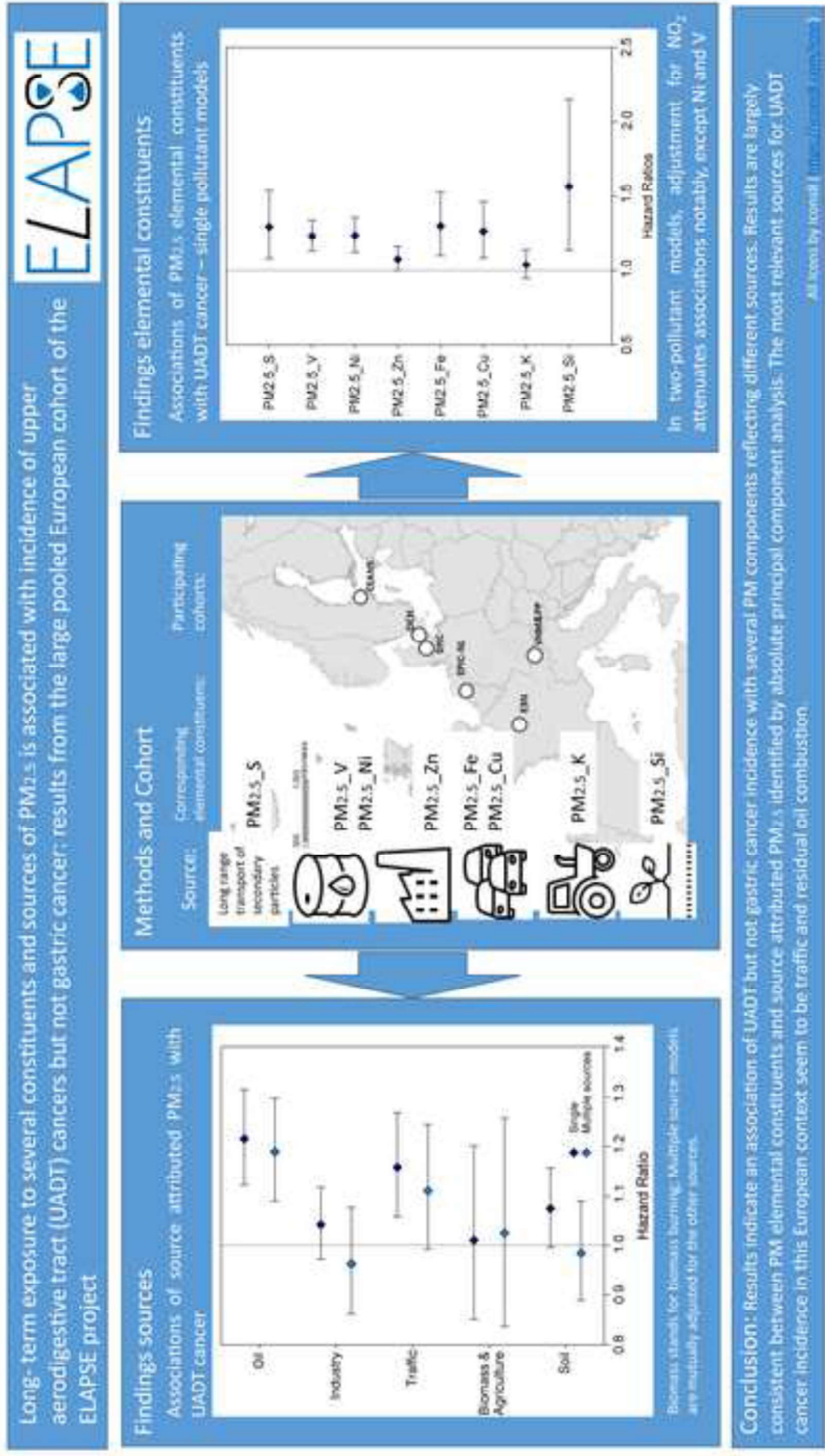




HIGHLIGHTS 3-5 BULLET POINTS

- Pooled large European cohort with exposure levels below current EU particulate matter limit values that are typical for many European populations
- First study on gastric and UADT-cancer incidence with PM source-characterization
- Associations of UADT-cancer incidence with several chemical elements 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

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

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HIGHLIGHTS 3-5 BULLET POINTS

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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 $\leq 2.5\mu\text{m}$

PM_{2.5}_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

Keywords: Air Pollution; upper aerodigestive tract cancer; gastric cancer; PM composition; PM sources; Long-Term exposure

78 Abstract

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

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

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

94 We observed 1,139 UADT and 872 gastric cancer cases during a mean follow-up of 18.3 and 18.5
95 years, respectively. UADT cancer incidence was associated with all constituents except K in single
96 element analyses. After adjustment for NO₂, only Ni and V remained associated with UADT. Residual
97 oil combustion and traffic source components were associated with UADT cancer persisting in the
98 multiple source model. No associations were found for any of the elements or source components
99 and gastric cancer incidence.

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

103

104

105 KEYWORDS: air pollution; upper aerodigestive tract cancer; gastric cancer; particulate matter (PM)

106 PM composition; PM sources; long-term exposure

107

108 1. Introduction

109 Gastric and oesophageal cancers are among the most common cancers worldwide (Arnold et al.,
110 2020). Anatomically closely related are other cancers of the upper aerodigestive tract (UADT). While
111 smoking is an established risk factor for these cancers (IARC Working Group on the Evaluation of
112 Carcinogenic Risks to Humans, 2012), evidence on the risk related to ambient air pollution is scarce.
113 However, recent evidence suggests there may be also a relation of air pollution with several cancers
114 and IARC classified outdoor air pollution as carcinogenic in 2013 (Straif et al., 2013).

115 For cancer-related outcomes, the best evidence to date is available for lung cancer, where several
116 epidemiological studies show associations of lung cancer incidence with particulate matter (PM)
117 (Hamra et al., 2014; Hvidtfeldt et al., 2021b; Raaschou-Nielsen et al., 2013; Turner et al., 2020).

118 Mechanisms are thought to be related to oxidative stress and inflammatory processes which may
119 induce DNA damage and cell proliferation (Straif et al., 2013). These processes occur not only in the
120 lung but can affect also other organs, as inflammatory responses and oxidative stress are transmitted
121 through released circulating mediators including chemokines, cytokines and immune cells (Brook et
122 al., 2018). In addition, ultrafine particles can enter the blood circulation and lymphatic system
123 directly, while larger fine particles can be transported via macrophages and reach other organs
124 (Furuyama et al., 2009; Oberdörster et al., 2005) including the digestive tract. Perhaps even more
125 relevant is the clearance of particles by mucociliary transport, which may lead to subsequent
126 ingestion of particles (Oberdörster et al., 2005).

127 While these mechanisms give plausibility to the potential effects of PM and its components on
128 cancers other than the lung, epidemiological evidence is still sparse. For gastric and UADT cancers,
129 few studies on PM exist with partly conflicting results (Pritchett et al., 2022). This may be due to
130 differences in the PM compositions across locations. Indeed, PM is a complex mixture which differs
131 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 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), respectively. Gastric cancer was identified by International Classification of Disease and Related Health Problems (ICD) codes 9th revision (151) and 10th revision (C16). 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 five fold hold out validation ranged from 0.41 for Zn to 0.79 for S (Chen et al., 2020).

All models predicted concentrations on a 100m x 100m 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 NO₂, 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/m²); 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 300m or 1km 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 NO₂ 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, 3,251 individuals (3,249 for gastric cancer) were excluded.

3. RESULTS

3.1. Description study population

In the model 3 population 297,406 and 287,576 individuals were 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 1,139 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) (Figure 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 (Figure 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/m³, respectively (Figure 2). In the gastric cancer data set, concentrations were slightly higher (4.1 and 4.0 µg/m³) 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 $\mu\text{g}/\text{m}^3$. Similarly, the exposure contrasts in $\mu\text{g}/\text{m}^3$ for sources were highest for biomass & agriculture followed by traffic and lowest for oil with IQRs of 4.36 $\mu\text{g}/\text{m}^3$, 2.83 $\mu\text{g}/\text{m}^3$ and 0.25 $\mu\text{g}/\text{m}^3$, 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 $\text{PM}_{2.5}$ with 0.49 and 0.52, respectively (Table S2 in the online supplement). Zn was moderately correlated with NO_2 and $\text{PM}_{2.5}$ (medians of 0.57 and 0.47, respectively). K was generally weakly correlated and in different directions. Ni and V showed weak (with $\text{PM}_{2.5}$) and moderate (with NO_2) correlations. Correlations of S with $\text{PM}_{2.5}$ 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 $\text{PM}_{2.5}$ (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 sources 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 $\text{PM}_{2.5}\text{S}$ 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 NO₂, especially for the Cu, Fe, S and Si constituents (Figure 3), after adjustment for NO₂, only Ni, V and S remained associated with UADT (Figure 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 (Figure 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.

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 (1ng/m³ and 200ng/m³, respectively) (Figure 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) (Figure 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 towards 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 (Figure 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 300m or 1km 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 NO₂, 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 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/m³ (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 association 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 content 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 NO₂, 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 NO₂ 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 NO₂ (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 NO₂ 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 NO_x 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 NO₂.

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 NO₂

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 more than 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 (Thurston 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, SO_x 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 NO₂ 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 SO₂ 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.

Author contributions

577 GW, ORN and GN: study conceptualisation and design; GH and BB: principal investigators of the
578 ELAPSE project; GW, GN, AJ, LS: statistical analysis and GW manuscript writing; GN, AJ manuscript
579 review and editing; GH, BB, JC and MStr: ELAPSE project coordination, preparing pooled data for
580 analyses, and providing support with the access to pooled cohort data; SR, ES, KK, MSta, KW,JC:
581 contribution of statistical analyses strategy and scripts for the statistical analyses; KdH, JC, GH and
582 GT: exposure assessment; JB: exposure data. All authors contributed to the interpretation of the
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Table 1: Characteristics of the study population

Cohort	Populatio n size (N)	Persons in model 3 (N)	Baseline period	Years of follow up (Mean) ^a	Age at baseline (Mean±SD)	Fe- male (%)	Current smokers (%)	(Self-) employed (%)	Married/ cohabitin g (%)	Small-area income ^b (Mean±SD)	Gastric cancer cases (N)	UADT cancer cases (N)
CEANS-SALT	6,098	5,717	1998-2003	9.90	57.4 ±10.5	54	21	66	68	25.3±6.6	11	25
CEANS-SDPP	7,403	7,325	1992–1998	15.34	47.0 ±4.9	59	26	91	84	24.3±4.2	3	18
CEANS-SIXTY	3,856	3,660	1997-1999	11.95	60.0±0.0	50	21	68	74	24.7±6.9	14	18
CEANS-SNAC-K	2,697	2,505	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-	20,096	17,797	1993-1997	16.43	42.7±11.2	54	35	69	65	12.2±1.6	27	48
Morgen												
EPIC_NL-	15,054	13,651	1993-1998	15.66	57.6±6.0	100	23	51	77	13.1±1.4	46	29
Prospect												
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	333,525 ^c	287,576 ^c	1985-2005	18.45	48.1 ±13.5	66	24	71	71	19.6±5.3	872	-
– gastric												
Pooled cohort	343,625 ^c	297,406 ^c	1985-2005	18.27	48.3 ±13.6	65	24	71	72	19.8±5.4	-	1,139
– UADT												

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; HNR: Heinz Nixdorf Recall study; E3N: Étude Épidémiologique auprès de femmes de la Mutuelle Générale de l'Éducation Nationale; VHM&PP: Voralberg Health Monitoring and Prevention Programme.

SD standard deviation; ^a for persons in model 3 (as for all the following columns); ^b in Euros × 1,000, year 2001, ^c number of individuals included in the respective analysis.

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/m³, PM_{2.5} Fe—100 ng/m³, PM_{2.5} K—50 ng/m³, PM_{2.5} Ni—1 ng/m³, PM_{2.5} S—200 ng/m³, PM_{2.5} Si—100 ng/m³, PM_{2.5} V—2 ng/m³, PM_{2.5} Zn—10 ng/m³; a Adjusted for study (strata), age, sex (strata), year of baseline visit; b Further adjusted for smoking status, duration, intensity², marital status and employment status; c Further adjusted for 2001 mean income at the neighbourhood level.

Figure 2

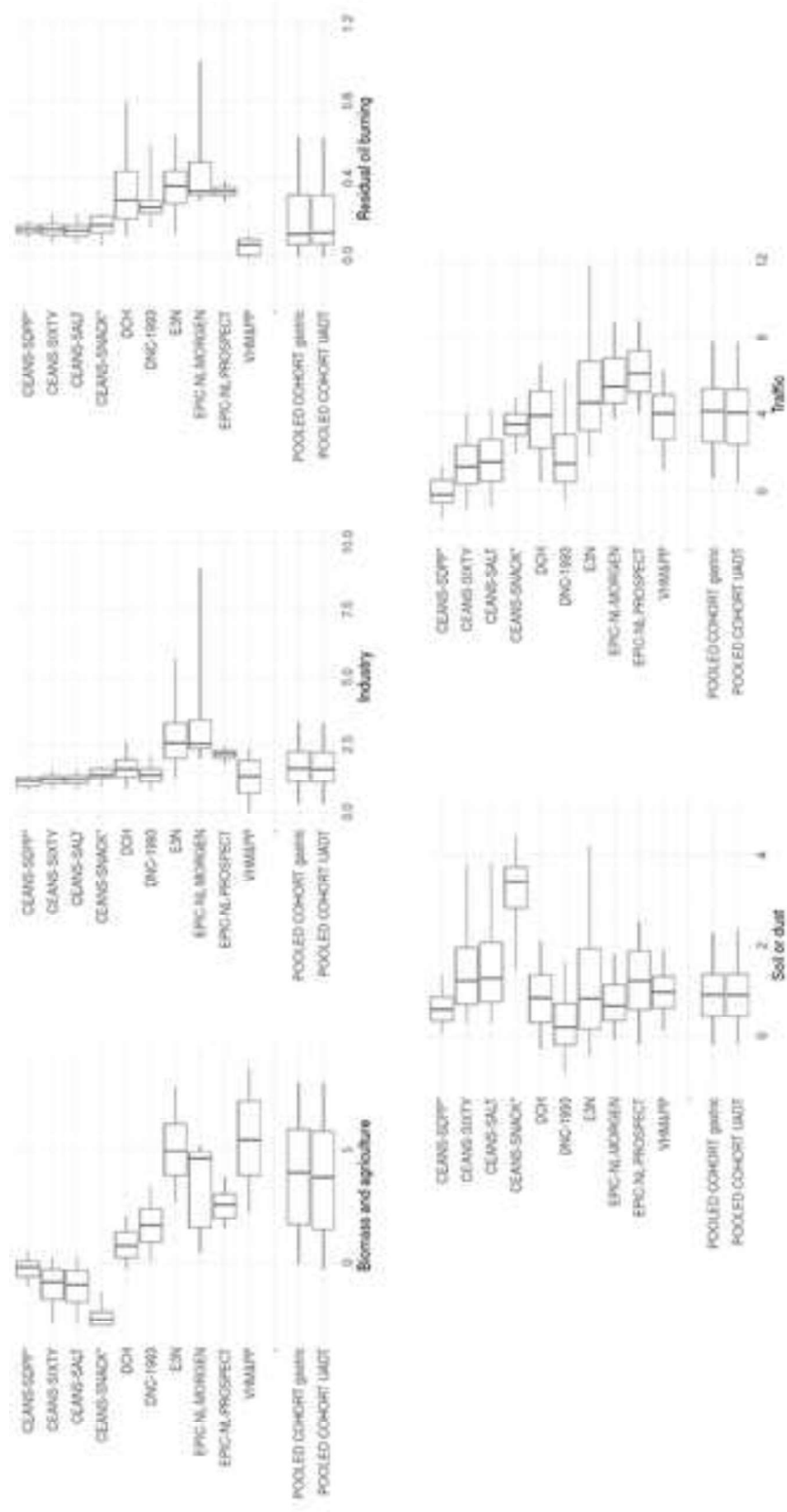


Figure 2: Exposure distribution of source-specific $PM_{2.5}$ concentrations at participants' baseline residential addresses

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 indicates P75; the bold vertical line inside the box, P50; and the whiskers, P5 and P95.

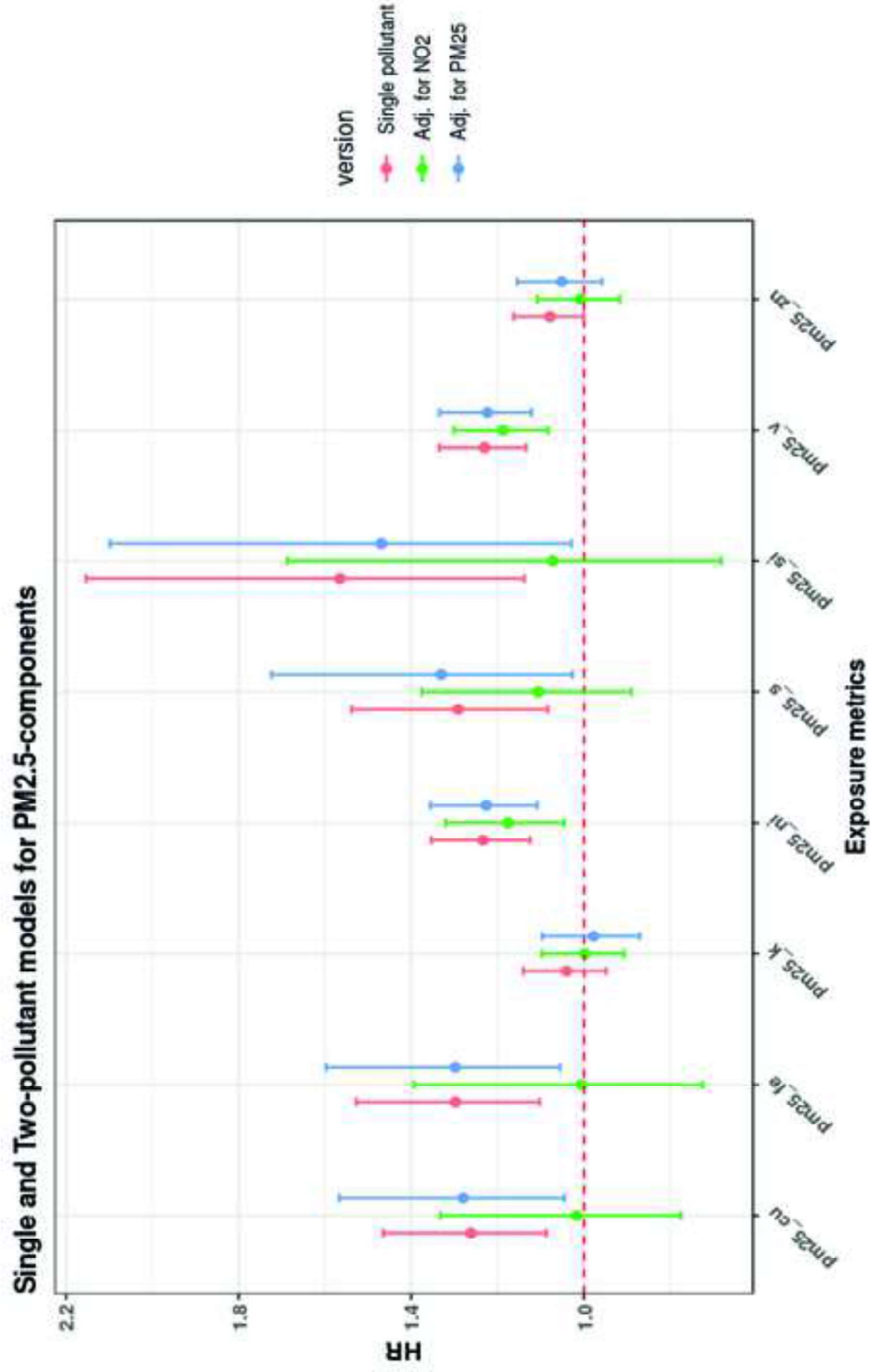


Figure 3: associations of PM elemental constituents with UADT in single and two-pollutant models (adjusted for NO₂ or PM_{2.5}). Results are shown for model 3 adjusted for study (strata), age, sex (strata), year of baseline visit, smoking status, duration, intensity, marital status, and 2001 mean income at the neighbourhood level; HRs are given for the following increments: PM_{2.5} Cu—5 ng/m³, PM_{2.5} Fe—100 ng/m³, PM_{2.5} Ni—1 ng/m³, PM_{2.5} S—50 ng/m³, PM_{2.5} Si—100 ng/m³, PM_{2.5} V—2 ng/m³, PM_{2.5} Zn—10 ng/m³; high correlation (median across cohorts >0.7) between the two pollutants in the model were observed for Fe, Cu, Zn with NO₂ and K with PM_{2.5}.

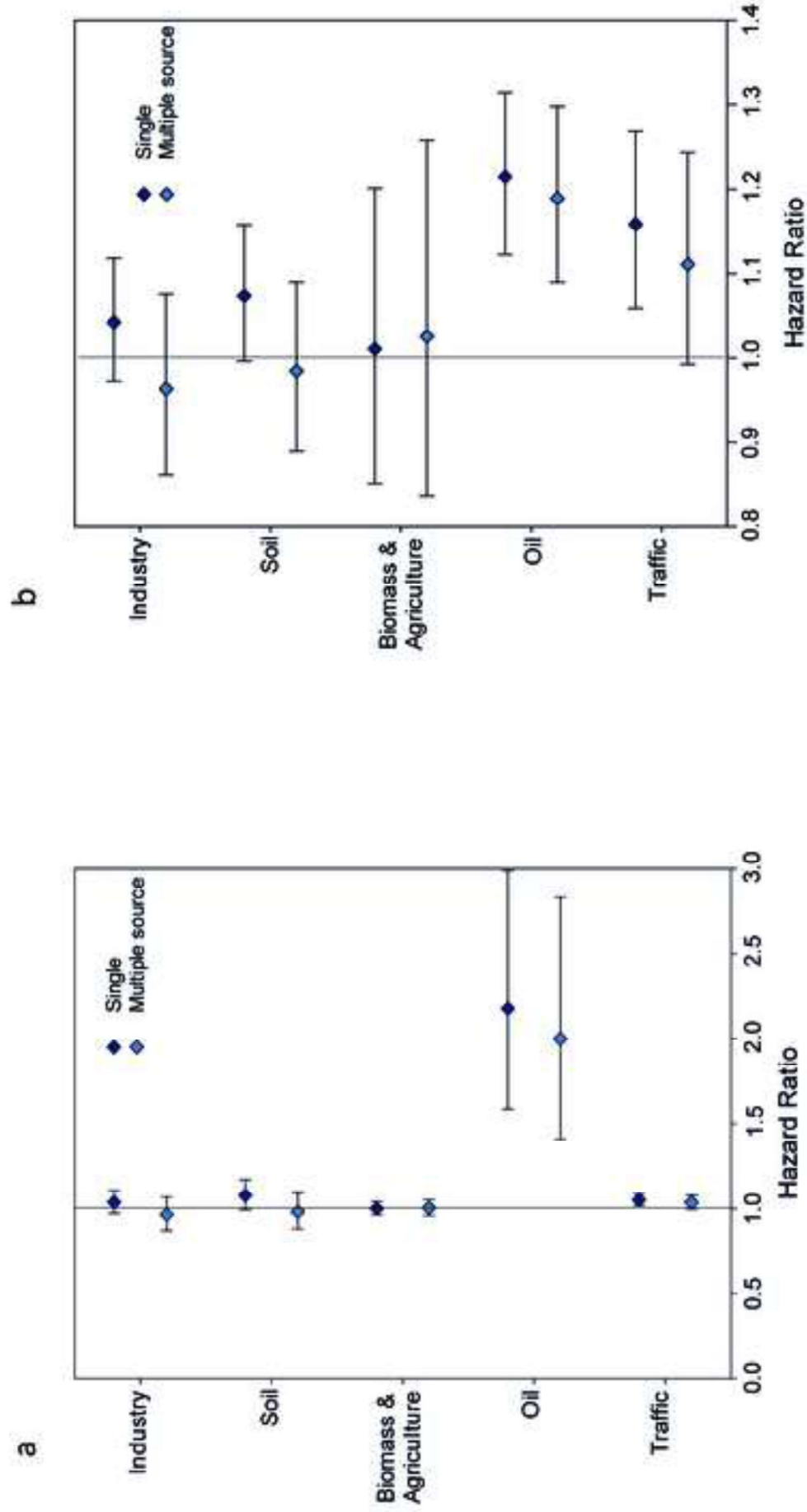


Figure 4: Associations of source-specific PM_{2.5} with UADT cancer.

Hazard ratios are shown per 1 µg/m³ (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, intensity², marital status, employment status, and 2001 mean income at the neighbourhood level.