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)☆

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1 This paper is dedicated to Rob Beelen who was the coordinating PostDoc of ESCAPE and who died far too early in September 2017. He will live in our memories as a great scientist and precious colleague - and a wonderful person.

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1. Introduction

Long-term exposure to ambient air pollution with particles contributes to increased cancer risk (International Agency for Research on Cancer Monograph Working Group, 2015), with most evidence for lung cancer (Raaschou-Nielsen et al., 2013).

A previous analysis of the large European multicentre ESCAPE study showed an association of particulate matter < 2.5μm (PM2.5) exposure at residence with the incidence of gastric cancer (Nagel et al., 2018). For the incidence of upper aerodigestive tract (UADT) cancer, which may not be strongly correlated with PM mass, we evaluated the association between long-term exposure to elemental components of PM2.5 and PM10 and gastric and UADT cancer incidence in European adults.

Methods: Baseline data were geocoded and exposure was assessed by land-use regression models for copper (Cu), iron (Fe) and zinc (Zn) representing non-tailpipe traffic emissions; sulphur (S) indicating long-range transport; nickel (Ni) and vanadium (V) for mixed oil-burning and industry; silicon (Si) for crustal material and potassium (K) for biomass burning. Cox regression models with adjustment for potential confounders were used for cohort-specific analyses. Combined estimates were determined with random effects meta-analyses.

Results: Ten cohorts in six countries contributed data on 227,044 individuals with an average follow-up of 14.9 years with 633 incident cases of gastric cancer and 763 of UADT cancer.

The combined hazard ratio (HR) for an increase of 200 ng/m3 of PM2.5,S was 1.92 (95%-confidence interval (95%-CI) 1.13;3.27) for gastric cancer, with no indication of heterogeneity between cohorts (I² = 0%), and 1.63 (95%-CI 0.88;3.01) for PM2.5,Zn (I² = 70%). For the other elements in PM2.5 and all elements in PM10 including PM10,S, non-significant HRs between 0.78 and 1.21 with mostly wide CIs were seen. No association was found between any of the elements and UADT cancer. The HR for PM2.5,S and gastric cancer was robust to adjustment for additional factors, including diet, and restriction to study participants with stable addresses over follow-up resulted in slightly higher effect estimates with a decrease in precision. In a two-pollutant model, the effect estimate for total PM2.5 decreased whereas that for PM2.5,S was robust.

Conclusion: This large multicentre cohort study shows a robust association between gastric cancer and long-term exposure to PM2.5,S but not PM10,S, suggesting that S in PM2.5 or correlated air pollutants may contribute to the risk of gastric cancer.
Table 1
Participants, gastric and UADT cancer cases and mean PM$_{2.5}$ concentrations in each cohort.

<table>
<thead>
<tr>
<th>Study</th>
<th>Total participants</th>
<th>Baseline period</th>
<th>Baseline mean (SD)</th>
<th>Age at baseline (years)</th>
<th>Incident cases</th>
<th>Exposure PM$_{2.5}$ (μg/m$^3$)</th>
<th>Proportion Proportion among cases</th>
</tr>
</thead>
<tbody>
<tr>
<td>HUBRO, Oslo, Norway</td>
<td>17,958</td>
<td>2000–2001</td>
<td>8.5 (15.0)</td>
<td>47.9</td>
<td>21 (0.12%)</td>
<td>8.9</td>
<td>0.39 (0.39)</td>
</tr>
<tr>
<td>CEANS, Stockholm, Sweden</td>
<td>18,842</td>
<td>1992–2004</td>
<td>10.4 (11.5)</td>
<td>56.2</td>
<td>30 (0.16%)</td>
<td>7.1</td>
<td>0.63 (0.77)</td>
</tr>
<tr>
<td>DCH, Copenhagen, Denmark</td>
<td>37,676</td>
<td>1993–1997</td>
<td>14.8 (4.5)</td>
<td>56.8</td>
<td>120 (0.32%)</td>
<td>11.3</td>
<td>0.86 (0.87)</td>
</tr>
<tr>
<td>EPIC-Netherlands</td>
<td>30,134</td>
<td>1993–1997</td>
<td>11.8 (11.3)</td>
<td>50.4</td>
<td>41 (0.14%)</td>
<td>16.8</td>
<td>n.d. (n.d.)</td>
</tr>
<tr>
<td>VHM&amp;PP, Vorarlberg, Austria</td>
<td>104,713</td>
<td>1985–2005</td>
<td>18.1 (14.9)</td>
<td>42.9</td>
<td>375 (0.36%)</td>
<td>13.6</td>
<td>0.58 (0.74)</td>
</tr>
<tr>
<td>EPIC-Turin, Italy</td>
<td>7946</td>
<td>1993–1998</td>
<td>14.1 (7.5)</td>
<td>50.4</td>
<td>26 (0.33%)</td>
<td>30.1</td>
<td>n.d. (n.d.)</td>
</tr>
<tr>
<td>SIDRIA-Rome, Italy</td>
<td>9775</td>
<td>1999</td>
<td>11.2 (6.0)</td>
<td>44.2</td>
<td>20 (0.20%)</td>
<td>19.4</td>
<td>0.72 (0.70)</td>
</tr>
<tr>
<td>Total</td>
<td>227,044</td>
<td></td>
<td></td>
<td></td>
<td>633</td>
<td></td>
<td>763</td>
</tr>
</tbody>
</table>

Data are n, mean (SD), and n (%). PM$_{2.5}$ = particulate matter with diameter < 2.5 μm. NA = not available. HUBRO = Oslo Health Study. CEANS = Swedish National Study on Aging and Care in Kungsholmen (SNAC-K) + Stockholm Screening Across the Lifespan Twin study and TwinGene (SALT) + Stockholm 60 years old and IMPROVE study (Sixty) + Stockholm Diabetes Prevention Program (SDPP). DCH = Diet, Cancer and Health study. EPIC = European Prospective Investigation into Cancer and Nutrition. VHM&PP = Vorarlberg Health Monitoring and Prevention Programme. SIDRIA = Italian Studies of Respiratory Disorders in Childhood and Environment. n.d. = no data available.

Fig. 1. Location of participating cohorts: Oslo: HUBRO; Stockholm: CEANS (comprising SNAC-K, SALT, Sixty and SDPP); Copenhagen: DCH; Netherlands: EPIC Netherlands; Vorarlberg: VHM&PP; Turin: EPIC Turin; Rome: SIDRIA; For acronyms of cohorts see Methods section.
Fig. 2. Estimated annual mean concentration (ng/m³) of PM_{2.5} elemental components at participants' addresses in each cohort. The solid circles and bars show the median and 25% and 75% percentile concentrations; the x shows the 5% and 95% percentile values.
Recruitment of the cohorts occurred largely in the 1990s. The cohort studies and the use of their data in ESCAPE were approved by the local ethical and data protection authorities.

2.2. Outcome definition

Follow-up was based on linkage to national or local cancer registries, with exception of SIDRIA Rome for which hospital discharge and mortality register data were used. The main outcomes were all cancers of the stomach and of the UADT, respectively. Carcinomas were identified using the International Statistical Classification of Diseases and Related Health Problems, 9th and 10th revision [ICD9 and ICD10]: for gastric cancer C16 [ICD10] and 151 [ICD9], and for UADT cancers: C01-06 and 141-145 (oral cavity), C09, C10 (oropharynx), C12, C13 (hypo-pharynx) and 146 (pharynx), C14, C32 and 161 (larynx), C15 and 150 (esophagus). Lymphomas/myelomas/leukemias were excluded according to the International Classification of Diseases for Oncology (ICDO-3) morphology codes: 9590-9989. We only included primary cancers and only malignant tumors with the fifth digit of the ICDO morphology code being “3”.

2.3. Exposure assessment

Exposures at the residential baseline address of the participants were determined according to a standardized protocol by assigning air pollution exposure estimates derived from land use regression (LUR) models specifically developed for the respective areas (de Hoogh et al., 2013). If a subject moved the new address was not taken into account except for exclusion of these subjects in a sensitivity analyses (see below). A detailed description of the 3-step procedure is found elsewhere. First, dedicated measurement campaigns (three two-week periods over one year) were carried out at 20 locations in each study area for a one-year period between October 2008 and May 2011. Results from the three measurements per site were averaged to a mean annual concentration, adjusting for temporal trends using data from a background monitoring site with continuous data.

Second, we collected information about potential predictor variables relating to nearby traffic intensity, population/household density and land use from Geographic Information Systems (GIS), and evaluated these to explain spatial variation of measured annual average concentrations using regression modelling (Beelen et al., 2013; Eeftens et al., 2012). These LUR models were used to estimate the exposure at the baseline address of each cohort member.

To determine the chemical elements contained in the respective PM fractions, PM filters were sent to Cooper Environmental Services (Portland, OR, USA) to analyse elemental composition using X-Ray Fluorescence (XRF). As indicators mainly of non-tailpipe traffic emissions such as brake and tyre wear, Cu, Fe and zinc (Zn) were selected; sulphur (S) mainly for long-range transport; nickel (Ni) and vanadium (V) for mixed oil-burning and industry; silicon (Si) for crustal material and potassium (K) for biomass burning (de Hoogh et al., 2013; Viana et al., 2008). However, each element can have multiple sources. The LUR model results for all study areas have been shown previously (de Hoogh et al., 2013). Land use regression models for Cu, Fe, and Zn in both fractions (PM_{10} and PM_{2.5}) had average cross-validation explained variance (r^2) between 52% and 84% with a large variability between areas (Raaschou-Nielsen et al., 2016). Models for the other elements performed moderately with average cross-validation r^2 generally between ~50% and ~60%. For PM_{2.5} S the average cross-validation r^2 was 32% with a range from 2 to 67%, consistent with the relatively low spatial variation of PM_{2.5} concentrations within the cohort areas. LUR-models could not be developed for K in PM_{10} (HUBRO), Ni in PM_{10} (HUBRO), Ni in PM_{2.5} (CEANS), V in PM_{2.5} (HUBRO, VHM&PP) and Si in PM_{2.5} (HUBRO).

2.4. Statistical analyses

Cohort-specific analyses were carried out using a common protocol and a centrally developed Stata analysis script (Nagel et al., 2018). In the cases where data of multiple cohorts were pooled (the Swedish and the Dutch cohorts, respectively) the analyses were performed stratifying the Cox Model for a cohort indicator variable.

Cox proportional hazard-regression with age as the underlying time-axis was carried out. The hazard ratio was modeled as an exponential function of continuous exposure. Censoring was applied at the time of death, a diagnosis of any other cancer (except non-melanoma skin cancer) or end of follow-up, whichever came first. Model checks included a test for deviation from proportional hazard assumption and testing the linearity assumption in the relation between each exposure and the lag hazard of the outcome by replacing the linear term with a natural cubic spline with two inner knots placed at the 33rd and 66th percentiles. The model fits of the linear and the spline models were compared using a likelihood-ratio test (Chi-square test with 2df).

Confounder sets were determined a priori with increasing levels of adjustment, following the procedures of previous ESCAPE studies (Nagel et al., 2018). Model 1 was adjusted for age (time scale), calendar year of enrolment and sex. Model 2 was additionally adjusted for baseline information on smoking status, smoking intensity, smoking duration, occupational exposure, employment status and educational level. Model 3 (the main model) was in addition adjusted for area-level (residential neighborhood or similar) socio-economic status (SES). The availability of these variables varied slightly between cohorts (Nagel et al., 2018). Only complete case analyses were performed. In the few cases where one variable was missing entirely, the cohort was nevertheless analysed using the available confounders. In sensitivity analyses we included additional potential confounders (alcohol consumption, environmental tobacco smoke (ETS), intake of fruit, intake of meat and marital status), restricted the analysis to participants with stable residence during follow-up or for at least 10 years, and included an indicator for urban/rural environment to the main model.

All cohort-specific analyses were done in Stata versions 10 to 14 (StataCorp, College Station, TX).

The results obtained from the cohort-specific analyses were combined with random effects meta-analysis (DerSimonian and Laird, 1986). Heterogeneity between cohorts was tested by the χ^2 test from Cochran’s Q statistic and quantified with the I^2 (Higgins and Thompson, 2002). Stata version 14 (StataCorp) was used for meta-analyses.

3. Results

The cohorts contributed together data on 227,044 individuals with an average follow-up time of 14.9 years. 633 incident cases of gastric cancer and 763 of UADT cancer occurred. DCH and VHM&PP contributed with most of the cases (Table 1). Mean age at baseline in the cohorts ranged from 43 years (VHM&PP) to 57 years (DCH). The details of each cohort including participants characteristics and availability of variables have been reported previously (Nagel et al., 2018).

There was a wide range of annual mean concentrations of PM elements concentrations within and between study cohorts. Generally, the Nordic countries showed the lowest and the Southern countries the highest levels of PM (Table 1) and similarly for most of the elements, less consistent for Ni, V and Zn. Ni had relatively high values in Sweden, S in the Netherlands, and Austria showed high levels of K in PM_{2.5} (Fig. 2 and Figure in the online Supplementary Material). For PM_{2.5} differences in individual exposures were highest in SIDRIA (Rome) for Cu, Fe, K, in EPIC Turin and Netherlands for Ni and S, in EPIC-Netherlands for V and Zn and in CEANS (Stockholm) for Si. The pattern for PM_{10} was very similar. Correlations of PM elements with total PM_{2.5} and PM_{10} varied between location with median correlation coefficients largely between 0.4 and 0.6 (Raaschou-Nielsen et al., 2016).

In the tests of linearity of the dose-response, the p-value of only 4
were ≤ 0.05 and only 8 ≤ 0.1, p-values of < 0.05 were observed for
DCH for PM_{10,S}, for EPIC-Turin for PM_{10,K} and for VHMM&PP and
SIDRIA for PM_{10,SI}. Therefore we took over the results for the linear
models for all cohorts and pollutants and consider that this is a valid
approximation.

The meta-analysis results from the main model for PM_{2.5,S}
components showed effect estimates above and below unity. Only the positive
association of PM_{2.5,S} with gastric cancer incidence was statistically
significant with a hazard ratio (HR) of 1.93 (95%-confidence interval
(95%-CI) 1.13;3.27) for an increase of 200 ng/m^3 (Table 2, Fig. 3) with
no heterogeneity in cohort results.

The second highest HR was seen for PM_{2.5,Zn} with 1.63 (95%-CI
0.88;3.01) for an increase of 10 ng/m^3 with heterogeneity between
cohorts (I^2 = 70%) No clear association was found with UADT cancers
for any of the PM_{2.5,S} elements. Effect estimates from the age-sex adjusted
and fully adjusted confounder model did not differ substantially. Also no clear association could be seen between any of the PM_{10,}
components and gastric or UADT cancer incidence (Table in the online
Supplementary Material). The association for PM_{10,S} with gastric cancer
was 0.97 (95%-CI 0.67;1.41) for an increase of 200 ng/m^3, also
with no heterogeneity between cohorts. Excluding VHMM&PP which had a
weight of 66% and 71%, in the meta-analysis of PM_{2.5,S} and PM_{10,S},
respectively, yielded a combined HR of 2.75 (95%-CI 1.10;6.86) and
1.43 (95%-CI 0.72;2.85), respectively. Excluding the three cohorts
(HUBRO, CEANS, EPIC-Netherlands) with a leave-one-out cross-vali-
dation (LOOCV) R^2 below 0.3 for the LUR-models yielded a HRR of 1.74
(95%-CI 0.90;3.33) for PM_{2.5,S}.

The results for the association of PM_{2.5,S} with gastric cancer were
robust to further adjustment for dietary variables and ETS showing no
change in the HR, obtained for the respective cohorts in this analysis, of
1.83 (95%-CI 1.05;3.20), (Fig. 4, additional confounder data available for
6 cohorts). Similarly, adjustment for the rural indicator yielded very
similar effect estimates (information available in 5 cohorts). Restriction
to the population with a stable residence, which is less subject to mis-
classification of long-term exposure at the residence, resulted in slightly
increased effect estimates, however with wider CIs.

In two-pollutant models, the effect estimated for total PM_{2.5}
changed from 1.36 (95%-CI 0.97;1.90) to 1.07 (95%-CI 0.70;1.64)
when adjusted for PM_{2.5,S} and to 1.42 (95%-CI 0.68;2.95) when ad-
justed for PM_{2.5,Zn}. The effect estimated for PM_{2.5,S} changed from 1.93
(95%-CI 1.13;3.27) to 1.79 (95%-CI 0.96;3.37) when adjusted for total
PM_{2.5} and the estimate for PM_{10,S} was not affected.

4. Discussion

This study including cohorts from 6 European countries shows a
statistically significant robust association of PM_{2.5,S} with gastric cancer
incidence. The effect estimate for PM_{2.5,S} decreased markedly when ad-
justed for PM_{2.5,S} whereas the estimate for the latter changed little. No
further statistically significant association of the elementary compo-
unds with gastric or UADT cancer was observed, including PM_{10,S}.

The identification of PM_{2.5,S} as the element most strongly asso-
ciated with gastric cancer is in agreement with previous analyses within
the ESCAPE study on all-cause mortality (Beelen et al., 2015) and lung
cancer incidence (Raaschou-Nielsen et al., 2016). In our analysis of
gastric cancer, the HR for PM_{2.5,S} was larger than for all-cause mor-
tality (HR 1.14 and lung cancer (HR 1.34). In contrast to lung cancer,
our estimate for gastric cancer was robust when additionally adjusted
for smoking status, smoking intensity, smoking duration, occupational
exposure, employment status, educational level, and for area-level
(residential neighbourhood or similar) socio-economic status (area
SES). However, it is of concern that there was no corresponding asso-
ciation seen for PM_{10,S} in contrast to PM_{2.5,S}. In general, PM_{2.5}
component mass makes up large amount of PM_{10} component mass and
sulphates are mainly present in the PM_{2.5} fraction (Tsai et al., 2015).
Indeed, the actual concentrations measured at the monitoring sites used
to develop the LUR models were highly correlated (median within area
r = 0.8) (Tsai et al., 2015). At the cohort address, we found a moderate
correlation (median = 0.57) between predicted PM_{2.5,S} and PM_{10,S}
exposures from the LUR. In the large VHMM&PP cohort, the correlation
was identical for measured and modeled concentrations. The lower
correlation is likely due to relatively moderate performance of the LUR

<table>
<thead>
<tr>
<th>Table 2</th>
</tr>
</thead>
<tbody>
<tr>
<td>Results of the random effects meta-analyses of associations between PM_{2.5} elemental components and the risk for gastric and UADT cancer.</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Fixed increase (ng/m^3)</th>
<th>Number of cohorts</th>
<th>Number of cases</th>
<th>HR (95% CI)</th>
<th>Measures of heterogeneity between cohorts (model 3)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Gastric cancer</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>PM_{2.5,Cu} 5</td>
<td>7</td>
<td>633</td>
<td>1.00 (0.73–1.38)</td>
<td>37.0% 0.15</td>
</tr>
<tr>
<td>PM_{2.5,Fe} 100</td>
<td>7</td>
<td>633</td>
<td>1.04 (0.80–1.35)</td>
<td>22.5% 0.26</td>
</tr>
<tr>
<td>PM_{2.5,Ni} 50</td>
<td>7</td>
<td>633</td>
<td>1.10 (0.88–1.37)</td>
<td>28.1% 0.21</td>
</tr>
<tr>
<td>PM_{2.5,S} 200</td>
<td>7</td>
<td>633</td>
<td>2.07 (1.23–3.47)</td>
<td>60.3% 0.03</td>
</tr>
<tr>
<td>PM_{2.5,Si} 100</td>
<td>6</td>
<td>612</td>
<td>0.97 (0.54–1.75)</td>
<td>45.2% 0.10</td>
</tr>
<tr>
<td>PM_{2.5,Zn} 2</td>
<td>5</td>
<td>237</td>
<td>0.95 (0.47–1.89)</td>
<td>87% 0.87</td>
</tr>
<tr>
<td>PM_{2.5,Zn} 10</td>
<td>7</td>
<td>633</td>
<td>1.54 (0.80–2.97)</td>
<td>70.2% &lt; 0.01</td>
</tr>
<tr>
<td>UADT cancer</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>PM_{2.5,Cu} 5</td>
<td>6</td>
<td>763</td>
<td>1.08 (0.83–1.40)</td>
<td>0.0% 0.64</td>
</tr>
<tr>
<td>PM_{2.5,Fe} 100</td>
<td>6</td>
<td>763</td>
<td>0.97 (0.79–1.28)</td>
<td>0.0% 0.73</td>
</tr>
<tr>
<td>PM_{2.5,K} 50</td>
<td>6</td>
<td>763</td>
<td>1.13 (0.78–1.65)</td>
<td>22.9% 0.26</td>
</tr>
<tr>
<td>PM_{2.5,Ni} 1</td>
<td>5</td>
<td>706</td>
<td>0.97 (0.56–1.67)</td>
<td>11.6% 0.34</td>
</tr>
<tr>
<td>PM_{2.5,S} 200</td>
<td>6</td>
<td>763</td>
<td>0.90 (0.46–1.75)</td>
<td>54.9% 0.05</td>
</tr>
<tr>
<td>PM_{2.5,Si} 100</td>
<td>5</td>
<td>740</td>
<td>0.75 (0.54–1.04)</td>
<td>99% 0.99</td>
</tr>
<tr>
<td>PM_{2.5,Si} 2</td>
<td>4</td>
<td>429</td>
<td>0.78 (0.48–1.28)</td>
<td>0.0% 0.63</td>
</tr>
<tr>
<td>PM_{2.5,Zn} 10</td>
<td>6</td>
<td>763</td>
<td>1.09 (0.87–1.37)</td>
<td>25.6% 0.24</td>
</tr>
</tbody>
</table>

PM_{2.5} = particulate matter with diameter < 2.5 μm. We included only participants without missing data in any of the variables included in model 3, so the datasets were identical for analyses with all three models. HR = hazard ratio. CI = confidence interval. UADT = upper aerodigestive tract.

Model 1: age (timescale in Cox model, sex, calendar time.
Model 2: model 1 + smoking status, smoking intensity, smoking duration, occupational exposure, employment status and educational level.
Model 3: model 2 + area-level (residential neighbourhood or similar) socio-economic status. 1: without CEANS. 2: without HUBRO. 3: without HUBRO, VHMM&PP.
models for S (de Hoogh et al., 2013) and possibly the over-representation of traffic locations at the monitoring sites compared to the cohort addresses. Overall, the explained variance of PM$_{10}$S models was slightly higher than for PM$_{2.5}$S LUR models (de Hoogh et al., 2013). The low variability of S within study areas likely has contributed to moderate performance (de Hoogh et al., 2013). In both the mortality and lung cancer studies (Beelen et al., 2015; Raaschou-Nielsen et al., 2016), HRs for PM$_{10}$S, were above unity, but smaller and less consistent than for PM$_{2.5}$S.

For gastric cancer, the null finding for PM$_{10}$S parallels the null-finding for total PM$_{10}$ that we have found in our previous ESCAPE analysis (Nagel et al., 2018).

Overall, our results for PM$_{2.5}$S were robust as sensitivity analyses did not notably change the effect estimate. Restricting the analyses to persons who lived at least 10 years at their baseline address resulted in slightly increased HRs, which would be expected if the association is true and causal because the degree of non-differential misclassification of exposure is expected to be lower in this sub-population. Excluding the most influential cohort, VHM&PP with a weight of 66%, increased the HR. Although two-pollutant models should be interpreted with caution (Mostofsky et al., 2012), our finding that the HR in association with PM$_{2.5}$S is robust when adjusting for PM$_{2.5}$, which in turn is reduced to virtually no effect, is strengthening our result. Even more so, because in contrast to earlier studies where S and PM were strongly correlated, the moderate correlation in our study (mean of 0.55) allows us to be more confident to disentangle effects.

Nevertheless, PM$_{2.5}$S may also be seen as a marker of a certain pollutant mix. Sources of S are coal, residual oil and motor vehicle fuels. In the NPACT project, the coal combustion source category showed the strongest associations of all investigated sources with long-term effects (mortality in humans and aortic plaque progression in mice) (Lippmann et al., 2013).

Ashely et al. reported a correlation between SO$_2$ exposure and gastric cancer mortality in the UK (Ashley, 1969). This study showed that regions with coal and textile industry had higher gastric cancer mortality. Another study showed that workers exposed to SO$_2$ in the pulp and paper industry had no increased risk of gastric cancer, but mortality from gastric cancer showed a positive dose-response with increasing exposure, however, with very imprecise estimates (Lee et al., 2002).

While an earlier review on toxicological results postulated that there is little evidence that sulphate in ambient concentration is toxicologically relevant (Schlesinger and Cassee, 2003), recent reviews acknowledge that it is unclear which effects are related to sulphates contained in the PM-mixture: the cationic elements (H$^+$, and therefore acidity, and notably (transition) metals) or adsorbed compounds like polyaromatic hydrocarbons (PAH) may explain the observed epidemiological associations (Cassee et al., 2013; Reiss et al., 2007). A study in Hong Kong (Wong et al., 2012) that investigated the effects of limiting the sulphur content in fuel found that natural mortality was reduced, however the reduction in SO$_2$ was highly correlated with reductions in V and Ni and was not statistically significant after adjustment. In our study these metals (V and Ni from residual oil combustion e.g. from industry) were not associated with gastric cancer incidence, although one might argue that the corresponding LUR-models suffered from a lack of sufficiently specific predictors (Beelen et al., 2015).

The possible pathomechanisms of carcinogenicity of sulphate in ambient air for gastric cancer are not clear. Results from experimental research with human bronchial epithelial cells, support the hypothesis that SO$_2$ derivatives could by activation of pro-oncogenes and the inactivation of tumour suppressor genes play a role in the pathogenesis of cancer (Qin and Meng, 2009). It can also be speculated whether the formation of sulphuric acid, which is formed from oxidation from SO$_2$, increases the risk of gastric cancer (Bernatsky et al., 2017). As pointed out above, sulphate may indirectly affect health by e.g. co-occurring primary text.}

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**Fig. 3.** Risk for gastric cancer associated with PM$_{2.5}$S in each cohort study. Hazard ratios according to PM$_{2.5}$S in each of the cohort studies, based on confounder model 3. Weights are from random effects analysis. Data points show HR; lines show 95% CI, boxes show the weight with which each cohort contributed to the overall HR; vertical bold line shows overall HR. HR = hazard ratio. PM$_{2.5}$ = particulate matter with diameter < 2.5 μm.
transition metals. The bioavailability of these metals may increase (Cassee et al., 2013) and they can lead to the formation of reactive oxygen species (ROS) which in turn may result in oxidative DNA-damage (Møller et al., 2008; Risom et al., 2005).

4.1. Strengths and limitations

Our study comprises data from several cohorts from 7 geographical areas, and constitutes the largest data set to date for the analysis of PM-elements in relation to gastric cancer. A strength is the common standardized exposure assessment protocol that estimates local concentrations with a small scale resolution. Our analysis was able to take into account important individual confounders, especially smoking. We could also adjust for nutritional variables in 4 of the 7 study-specific effect estimates, but cannot rule out residual confounding. While we cannot exclude the possibility of some misclassification due to the measurement campaigns taking place after recruitment of cohort participants, we were, however, able to take into account information on residential stability, which would tend to decrease the degree of exposure misclassification.

We were not able to take into account the mobility of the individuals, but had to rely on exposure estimates for the residential address at enrolment into the cohorts. Also, the LUR-model approach does involve some degree of misclassification, and especially the performance of the models for PM$_{2.5}$S were among the lowest when evaluated by leave-one-out cross-validation, presumably because of the small measured within-study area contrasts. The average leave-one-out cross-validation (LOOCV) $R^2$ in the present study with data from 7 geographical areas ranged between 7 and 61% for PM$_{2.5}$S, with the highest values in DCH (61%) and VHM&PP (53%) and the lowest in HUBRO. The sensitivity analyses excluding studies with a (LOOCV) $R^2$ yielded an only mildly attenuated effect estimate with a widened confidence interval, resulting from the exclusion of three of the seven cohorts. It is not clear whether the mild change is related to the LOOCV or other characteristics of the cohorts. We further note that the $I^2$ statistic of the overall analysis is 0%, suggesting that the variability in estimates across cohorts is mostly due to random error.

![Fig. 4. Results of sensitivity analyses for the association of gastric cancer with PM$_{2.5}$S. Hazard ratios (HR) with 95% confidence intervals are shown. N = number. The additional confounders were alcohol consumption, environmental tobacco smoke (ETS), intake of fruit, intake of meat and marital status where available.](image-url)
Overall, we would expect the misclassification related to low LOOCV $R^2$ to be non-differential and therefore to induce a bias towards the null-effect. Also the relatively poor model fit would not contribute to an erroneously increased effect estimate in the two-pollutant model: indeed, if two pollutants are of similar influence, the pollutant for which the concentrations are more precisely estimated would yield the higher effect estimate. This is unlikely to be the case here, because the model fit for PM$_{2.5}$ mass was better than for PM$_{2.5-4}$ S with validation $R^2$ ranging from 42% to 78%.

In this analysis we tested 32 outcome-exposure combinations, so a chance finding due to multiple testing cannot be fully excluded. Nevertheless, the robustness of the results and the fact that 6 of the 7 cohort estimates were greater than one indicates that the result for S in PM$_{2.5}$ is probably not due to chance. However, clearly additional specific studies are needed.

Taken together, our results indicate that S in the PM$_{2.5}$ fraction, or correlated air pollutants, may contribute to increased risk of cancer of the stomach.

Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.envint.2018.07.030.

References


Eeftens, M., Beelen, R., de Hoogh, K., 2012. Development of Land Use Regression models for PM$_{2.5}$, PM$_{2.5-4}$ Absorbance, PM$_{10}$ and PM$_{2.5-4}$ in 20 European Study Areas; Results of the ESCAPE Project. Environ. Sci. Technol. 46, 11195–11205. https://doi.org/10.1021/es301948k.


