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Long-term exposure to airborne metals and risk of cancer in the French cohort Gazel

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A R T I C L E I N F O

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A B S T R A C T

Background: The specific compounds that make ambient fine particulate matter ($PM_{2.5}$) carcinogen remain poorly identified. Some metals contribute to ambient $PM_{2.5}$ and possibly to its adverse effects. But the challenge of assessing exposure to airborne metals limits epidemiological studies.
Objective: To analyze the relationships between several airborne metals and risk of cancer in a large population.
Methods: We estimated the individual exposure to 12 airborne metals of ~ 12,000 semi-urban and rural participants of the French population-based Gazel cohort using moss biomonitoring data from a 20-year national program. We used principal component analyses (PCA) to derive groups of metals, and focused on six single carcinogenic or toxic metals (arsenic, cadmium, chromium, lead, nickel, and vanadium). We used extended Cox models with attained age as time-scale and time-varying weighted average exposures, adjusted for individual and area-level covariables, to analyze the association between each exposure and all-site combined, bladder, lung, breast, and prostate cancer incidence.
Results: We identified 2,401 cases of all-site cancer between 2001 and 2015. Over the follow-up, median exposures varied from 0.22 (interquartile range (IQR): 0.18–0.28) to 8.68 (IQR: 6.62–11.79) $\mu g.g^{-1}$ of dried moss for cadmium and lead, respectively. The PCA yielded three groups identified as "anthropogenic", "crustal", and "marine". Models yielded positive associations between most single and groups of metal and all-site cancer, with e.g. hazard ratios of 1.08 (95% CI: 1.03, 1.13) for cadmium or 1.06 (95% CI: 1.02,1.10) for lead, per interquartile range increase. These findings were consistent across supplementary analyses, albeit attenuated when accounting for total $PM_{2.5}$. Regarding specific site cancers, we estimated positive associations mostly for bladder, and generally with large confidence intervals.
Conclusion: Most single and groups of airborne metals, except vanadium, were associated with risk of cancer. These findings may help identify sources or components of $PM_{2.5}$ that may be involved in its carcinogenicity.

1. Introduction

Metals and metalloids (referred to as "metals" hereafter) include a wide range of atoms from the nutrient calcium (Ca) to the toxic cadmium (Cd). The human physiology requires nutrients such as Ca or sodium (Na), and other metals such as iron (Fe) or zinc (Zn) in enzymes or metalloproteins. Yet, most metals are toxic beyond a threshold depending on their chemical form (Davidson et al. 2007). The international agency for research on cancer (IARC) classified several metals as carcinogens – such as arsenic (As) and Cd (IARC 2012; Straif et al. 2009). Exposure to metals occurs in the workplace (mining and smelting activities, industrial production, etc), but also in the general environment

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though at much lower concentrations, for example by inhaling ambient airborne metals. Yet the relationship between cancer risk and chronic exposure to airborne metals remains poorly documented. Airborne metals are emitted by natural sources (e.g. soil wind erosion, volcano eruptions) or anthropogenic sources (e.g. industries, traffic), and partly end up in airborne fine particulate matter (with an aerodynamic diameter less than 2.5 µm, referred to as $PM_{2.5}$)(European Environment Agency 2020) – and $PM_{2.5}$ have been classified as carcinogen (Loomis et al. 2013). A few studies focused on the relationships between airborne metals and cancer risk; they found little evidence of increased risks of the upper aero-digestive tract cancer (Weinmayr et al. 2018), and highlighted some evidence of associations between some breast cancers and airborne Cd exposure (Amadou et al. 2019; Liu et al. 2015; White et al. 2019), or between childhood astrocytoma brain tumor and airborne lead (Pb) exposure (von Ehrenstein et al. 2016).

Epidemiologic studies usually face a lack of widely available exposure data for airborne metals. Obtaining fine enough spatial resolution exposure to airborne metals over large territories remains challenging. As an alternative, Coudon et al. (2019) developed an indicator based on the thousands of Cd-emitting industries all over France. Another alternative, applicable to other metals, relies on the biomonitoring of mosses in the wild; these ubiquitous plants do not have roots and take up nutrients from the atmosphere, simultaneously absorbing metals that they can accumulate and tolerate until large concentrations (Markert 2007). Collected over large territories, they can provide data with a sufficiently fine resolution to produce exposure surfaces, and for more metals than classically measured by routine networks. Moss biomonitoring data have now successfully been used in population-based epidemiological studies by investigating individual metals or groups of metals to proxy sources of air pollution (Comess et al. 2021; Lequy et al. 2019).

This study aims to analyze the relationships between airborne metals assessed by moss biomonitoring and incident cancer in the French population-based Gazel cohort.

2. Materials and methods

2.1. Study population

The Gazel cohort included 20,625 participants in 1989 from the national energy company Electricité-de-France-Gaz-de-France (EDF-GDF). Participants completed a detailed self-questionnaire at enrollment, and an annual self-questionnaire ever since, allowing to collect many individual-level data on health, lifestyle, and occupation (Goldberg et al. 2007, 2015). Participants who gave consent have also been followed through national health databases. Their annual residential addresses have been collected since 1989 for most participants, and geocoded (10% at the postal code, 16% at the center of the city or urban unit , 22% at the street-match level, 51% at the exact address thus the number of the street).

Due to the specificities of exposure assessment (cf section hereafter), we excluded all participants residing exclusively in urban areas during their follow-up (Lequy et al. 2019); for participants living only during some years in urban areas after 1996, we excluded the concerned periods. We excluded participants who spent more than 20% of their follow-up abroad mainland France to limit exposure misclassification (Figure S1).

We defined the end of follow-up as the date of 31st of December 2015, cancer incidence, death or leaving the cohort, whichever occurred first, and censored participants accordingly at the appropriate date.

2.2. Cancer incidence

We ascertained incident cancer cases from three sources: a) French national health administrative databases containing listings of incident cancers during the study period 2001–2016 (Tuppin et al. 2017); b) company records that have systematically recorded all cancers (except nonmelanoma skin cancers) diagnosed among their current employees before retirement (Goldberg et al. 1996); and c) cancer diagnoses self-reported by participants via the follow-up questionnaires from 2008 onwards, when participants started retiring. Participants who gave consent were contacted for collecting medical information to obtain the date of diagnosis and the type of cancer. The French national health administrative database was the priority source and accounted for 81% of the ascertained cases. However, data were available from 2008 onwards only, therefore we used other sources for cancer diagnosed priorly.

The ICD-10 classification system was used to code the type of cancer, with the whole ICD-10 chapter except C77–79 (secondary malignant neoplasms) and C44 (nonmelanoma skin cancers); we used C34, C67, C50, and C61 to identify lung, bladder, breast, and prostate cancer, respectively.

3. Exposure assessment

3.1. Moss biomonitoring data

We used data from moss biomonitoring to estimate exposure to airborne metals as described in Lequy et al. (2019). In France, the French National Museum of Natural History manages a nation-wide moss biomonitoring program dedicated to "background" air pollution, BRAMM (short for moss biomonitoring of atmospheric metal deposition). This program follows the guidelines from the ICP-Vegetation (https://icpvegetation.ceh.ac.uk/get-involved/manuals/moss-survey). At the time of analysis, the BRAMM database included five surveys (1996, 2000, 2006, 2011, and 2016) and focused on 13 metals: aluminum (Al), arsenic (As), calcium (Ca), cadmium (Cd), chromium (Cr), copper (Cu), iron (Fe), mercury (Hg), sodium (Na), nickel (Ni), lead (Pb), vanadium (V), and zinc (Zn). BRAMM monitors background airborne metal levels, mainly in forest sites and away from major industrial, urban, and traffic sources (location of the sampling sites is available in Figure S2). This program and data collection were detailed elsewhere (Lequy et al. 2016): briefly, at each survey, mosses were collected by several trained collectors at approximately 500 sampling sites over mainland France, sent to the laboratory where they were cleaned, gently dried, and grinded. Finally, moss samples were analyzed for their complete metals content. Measurements are given in $\mu g \cdot g^{-1}$ of dry weight: they represent the content of each moss sample at the moment of sampling. Duration of retention of metals in moss has not been definitively established, yet it is generally believed that mosses integrate metals approximately over six months and possibly up to three years (Boquete et al. 2020; Markert et al. 2003). Since mosses were collected in forest to obtain the "background" levels of metals, we considered that this exposure assessment was not suitable for urban dwellers and excluded all the participants who resided in urban areas in 1996, 2000, 2006 and 2011.

3.2. Exposure data

We performed ordinary kriging to develop exposure surfaces for each metal and each survey, with a 2x2 km resolution (Figure S3). We found a median correlation coefficient between the modelled and observed values of 0.88 with an interquartile range (IQR) of 0.75–0.92, attesting a model performance similar to that of PM_{10} or $PM_{2.5}$ in France or Europe (Bentayeb et al. 2014; de Hoogh et al. 2018). The kriging interpolation was performed using R software version 3.3.2 (R Core Team, 2015), and the package GSTAT (Pebesma 2004). After a five-hold-out validation, we obtained Spearman correlation coefficients larger than 0.59 (Supplementary Table S1).

For supplementary analyses, we also estimated individual exposure to ambient $PM_{2.5}$, since airborne metals are partly included in $PM_{2.5}$. We used a land use regression (LUR) model developed over Europe in 2010 from ground-based measurements and land-use variables and rescaled annually between 1990 and 2015 (de Hoogh et al., 2018). The full model explained 72% of $PM_{2.5}$. Further validation using a five-hold-out validation strategy explained 66% of $PM_{2.5}$, indicating its spatial robustness (de Hoogh et al., 2018).

3.3. Creating exposure metrics for each participant

We assigned to each participant and for each residential address at 1996, 2001, 2006, and 2011, airborne metal exposures based on the exposure surface of the corresponding moss-biomonitoring survey (see details in the statistical analyses section, and the location of participants in 1996 and at end of follow-up in Figure S4). Due to missing data in 2000, we imputed exposure to As in 2000 as the mean between 1996 and 2006.

As exposure assessment was not estimated every year, we calculated the single-metal exposure variables as follows: we computed time-weighted cumulated averages for each metal and each survey (i.e. average since 1996 for all available years), accounting for the different time periods between surveys since 1996 for all available surveys until censoring. For consistency in exposure assignment, we also estimated exposure to $PM_{2.5}$ only for years 1996, 2001, 2006, and 2011 using the same calculation method.

Since this exposure assessment might reflect proxy exposures to a set of airborne pollutants emitted by various sources, rather than specific metals, we grouped exposures to metals into markers of more general sources of pollution as a complementary method to the single-metal approach. To do so, we conducted a principal component analysis (PCA) using the above-described exposure variables for all metals except Hg for which there were no data in 1996. The PCA yielded three components which we identified after "oblimin" rotation as "crustal" (two most important metals: Al, Fe), "anthropogenic" (Cd, Pb), and "marine" (Na, Cr) (Table S2), finding similar results as those previously described (Lequy et al. 2019) and explaining respectively 42%, 26%, and 10% of the variability of the dataset. To facilitate interpretation, we multiplied the marine component by −1, meaning "marine" component values increase with increasing Na and Cr.

3.4. Covariables

Based on the literature, we selected the following individual variables as potential confounders or effect modifiers.

Time-independent variables included sex, education (schooling years: ≤11 years, 12–13 years,14–15 years, Other secondary education, Other diploma), socio-economic status in 1989 (low, medium, high), and occupational exposure to a selection of nine lung carcinogens (asbestos, cadmium, chlorinated solvents, chromium, coal gasification, coal-tar pitch, creosotes, crystalline silica, and hydrazine) during their career (categorized as none, one, two, and three or more). We attributed an area-level deprivation index calculated in 2009 (Rey et al. 2009) categorized as low, medium, and high; since some participants died before 2009, and since this index could not be matched to all municipalities, we used a missing category for the relevant participants.

Time-dependent variables included cumulated smoking pack-years (lifelong), alcohol consumption (abstinent, light drinker, moderate drinker, heavy drinker, unclear), familial status (in a couple or not), body mass index (BMI, categorized in less than 20, 20–25, 25–30, 30–35, greater than 35), fruit and vegetable intake (never or less than once a week; once or twice a week; more than twice a week but not every day; every day or almost). For each participant, we calculated the time-varying cumulative average of distance to the nearest major road over the follow-up.

3.5. Missing values

Except for age and sex, which had no missing data, the amount of missing data ranged between 0.1% and 30%, for socioeconomic status and passive smoking, respectively (Table 1). We used multiple imputations with chained equations to create five complete datasets after five iterations and with good convergence. We longitudinally imputed all variables using all the above-described variables as predictors. The only exceptions were air pollution exposure, distance to the nearest road and area-level deprivation index: we used them as predictors but, because

Table 1
Characteristics of the study population in 1996, in n (%) or median [first quartile, third quartile] for continuous and categorical variables, respectively.

	Diagnosed with cancer between 2001 and 2016		
	No	**Yes**	**P value**
	9354	2401	
Age in 1996 (years)	50.5 [48.0, 53.0]	51.5 [49.0, 55.0]	<0.001
Follow-up time since 1996 (years)	21.0 [21.0, 21.0]	14.2 [10.8, 17.6]	<0.001
Sex (men)	7119 (76.1)	2023 (84.3)	<0.001
Smoking status			<0.001
Never smoker	3951 (42.2)	948 (39.5)	
Former smoker	1772 (18.9)	473 (19.7)	
Current smoker	1190 (12.7)	387 (16.1)	
Missing	2441 (26.1)	593 (24.7)	
Cumulative smoking pack-years[a]	14.0 [7.0, 24.3]	17.0 [7.8, 28.1]	<0.001
Passive smoking			0.689
No	3147 (33.6)	830 (34.6)	
Yes	3408 (36.4)	860 (35.8)	
Missing	2799 (29.9)	711 (29.6)	
Education			0.469
9–11 years	7291 (77.9)	1875 (78.1)	
12–13 years	654 (7.0)	142 (5.9)	
14–15 years	473 (5.1)	133 (5.5)	
Other secondary education	537 (5.7)	144 (6.0)	
Other diploma	199 (2.1)	52 (2.2)	
Missing	200 (2.1)	55 (2.3)	
Occupational exposure[b]			0.013
0	4790 (51.2)	1143 (47.6)	
1	957 (10.2)	251 (10.5)	
2	1307 (14.0)	358 (14.9)	
3	2300 (24.6)	649 (27.0)	
Alcohol use			<0.001
Abstinent	803 (8.6)	183 (7.6)	
Light drinker	3206 (34.3)	783 (32.6)	
Moderate drinker	1525 (16.3)	439 (18.3)	
Heavy drinker	868 (9.3)	291 (12.1)	
Unclear pattern	600 (6.4)	135 (5.6)	
Missing	2352 (25.1)	570 (23.7)	
Marital status			0.042
Single	682 (7.3)	149 (6.2)	
Not single	6327 (67.6)	1683 (70.1)	
Missing	2345 (25.1)	569 (23.7)	
Socioeconomic status			0.013
Low	1998 (21.4)	476 (19.8)	
Middle	5682 (60.7)	1434 (59.7)	
High	1663 (17.8)	490 (20.4)	
Missing	11 (0.1)	1 (0.0)	
BMI			<0.001
<20	244 (2.6)	37 (1.5)	
20–25	2923 (31.2)	703 (29.3)	
25–30	3138 (33.5)	882 (36.7)	
30–35	534 (5.7)	167 (7.0)	
>35	79 (0.8)	18 (0.7)	
Missing	2436 (26.0)	594 (24.7)	
Fruit-vegetable intake			0.144
Never or less than once a week	56 (0.6)	22 (0.9)	
Once or twice a week	721 (7.7)	213 (8.9)	
More than twice a week, not everyday	2001 (21.4)	499 (20.8)	
Every day or almost	4056 (43.4)	1037 (43.2)	
Missing	2520 (26.9)	630 (26.2)	

a: for eversmokers only; b: exposure to nine selected lung carcinogens. Cases of cancer: all ICD-10 chapter of neoplasm except for nonmelanoma skin cancers (C44) and secondary malignant neoplasms (C77–79).

could not predict them from sociodemographic or lifestyle variables, we recreated the initial missing values for them in our final datasets. We used a 2-level model with participant identifiers as 2-level cluster, and the functions "2l.pmm" and "2l.only.pmm" for time-varying and time-independent variables, respectively. We used the packages MICE and MICEADDS for R (van Buuren and Groothuis-Oudshoorn 2011). Model-based estimates were pooled following Rubin's rules (Rubin 1987).

4. Statistical analyses

4.1. Main analyses

To estimate associations between exposure to airborne metals and risk of cancer, we used extended Cox models with attained age as underlying time scale, and with time-varying metal exposure metric, adjusted for all individual sociodemographic and lifestyle covariables, and for calendar year. According to scaled Schoenfeld residuals, our models did not deviate from the proportional hazard assumption except for sex which was therefore included with a strata function.

Since exposure assessment began in 1996 and we implemented a 5-year lag to take into account cancer latency, we excluded participants censored (lost on follow-up, dead, or with site-specific cancer) before 2001 (Figure S1).

Among the available metals, we selected as main exposures (i) As, Cd, Cr, Ni, Pb, and V, with a rationale of carcinogenicity or toxicity to explore their individual associations with cancer, and (ii) the three PCA components, each included in separate Cox models.

For each metal exposure metric and each outcome, we checked for nonlinear relationships by including natural spline functions; we visually assessed any deviation from linearity. In case of a slight deviation and a monotonic relationship, we assumed linearity for the concerned exposure metric, and in case of nonmonotonic relationship, we categorized the exposure metric into quartiles. Therefore, associations are reported as hazard ratios and their 95% confidence intervals either per interquartile range increase for linear relationships, and for each quartile compared to the first quartile for nonlinear relationships.

We selected only women and men for the analyses pertaining to breast and prostate incident cancer, respectively.

4.2. Supplementary analyses

For each outcome and each metal exposure metric, to control potential confounding by $PM_{2.5}$, we followed the method described by Mostofsky and colleagues (2012). This method is based on the residuals of a regression of each metal as dependent variable against $PM_{2.5}$ as independent variable. These residuals were used in separate Cox models as alternative exposure metrics.

As sensitivity analyses for each outcome, we (i) further adjusted for the area-level deprivation index, (ii) used the main Cox model after restricting the study population to the participants geocoded at the address or street-march level, (iii) used the complete cases dataset, and (iv) considered missing data as a category, after categorizing numerical variables into quartiles. To account for the potential residual confounding by occupational exposure, even if we adjusted for the most relevant variable from the available data, we conducted as final sensitivity analysis (v) restricting the study population to participants without any occupational exposure to the above-mentioned list of carcinogens.

To identify any effect modifier, only for all-site combined cancer for reasons of statistical power, we used the main Cox model in population subsets defined by sex, smoking status (never smokers defined as those with zero smoking pack-years), and distance to the nearest major road with a cut-off at the median distance of 1 km. Finally, only for the "marine" PCA3 component, we defined two subsets based on the mean distance to the seashore, with a cut-off at 150 km.

To put the associations between airborne metals and cancer incidence into perspective with those between total $PM_{2.5}$ and cancer incidence, we used the main model and $PM_{2.5}$ as main exposure for each outcome.

5. Results

5.1. Study populations

As study populations, because the number of participants censored for each site of cancer was different (Figure S1), our final study populations included 11,755 participants for the analyses pertaining to all-site cancer (or 40,271 observations, i.e., the total number of participant-exposure pairs from 1996 to censoring), 12,048 for bladder, 12,059 for lung, 2,656 for breast, and 9,321 for prostate. We identified 2,401 cases of primary cancer, all sites combined, in the population of 11,755 participants (Table 1, Table S5); we also identified 220, 232, 208, and 957 cases of primary bladder, lung, breast, and prostate cancer. Participants were aged 50.5 (IQR 48.0–53.0) in 1996 with more than 75% men, 77% of participants had less than 12 years of schooling, and 60% had a medium socioeconomic status. Regarding lifestyle, 34% were light drinkers, 32% were ever smokers who cumulated a median of 16 smoking pack-years until 1996, and 43% ate fruit or vegetable almost every day. Half of the participants had never been exposed to occupational carcinogens. Due to the large number of participants, most of these characteristics differed significantly between cases and non-cases of cancer (except education, passive smoking, and fruit and vegetable intake) but the most striking differences pertained to sex and smoking status.

5.2. Exposure to airborne metals and $PM_{2.5}$ over the follow-up

Over the follow-up, the cumulated average of exposure to metals ranged between medians of 0.22 (IQR 0.18–0.28) to 8.68 (6.62–11.79) $\mu g.g^{-1}$ of dried moss for Cd and Pb, respectively; and of 22.2 (20.1–25.4) $\mu g.m^{-3}$ of $PM_{2.5}$ (Table 2). Most metal exposures were correlated, with Spearman coefficient as high as 0.83 between Cd and Pb (Table S3). Similarly, $PM_{2.5}$ was moderately correlated to Cd, Cr, Pb, and to the group of "anthropogenic" metals with Spearman correlations between 0.46 and 0.51.

5.3. Association between all-site cancer and airborne metals

5.3.1. Main associations using single pollutant models

The Cox models using spline functions revealed nonlinear relationships between most metal exposure metrics and all-site incident cancer (Figure S3). Given the monotonic shape observed for Cd, Cr, Ni, Pb, and the "anthropogenic" PCA2 and "marine" PCA3 components, we approximated these relationships as linear. Yet for As, V, and the "crustal" PCA1 component, which displayed almost bell-shaped relationships, we categorized the exposure variables into quartiles.

We found positive significant associations between all-site incident cancer and Cd, Cr, Pb, and the "anthropogenic" PCA2 and "marine"

Table 2
Airborne metal exposure among the study population from the Gazel cohort at baseline and censoring, and exposure to $PM_{2.5}$ for the same years (median [first quartile, third quartile]). N = 11,755 (40,271 observations).

Exposure	Unit	At baseline	At censoring[a]
As	**$\mu g.g^{-1}$[b]**	0.42 [0.34, 0.54]	0.44 [0.34, 0.62]
Cd		0.24 [0.19, 0.30]	0.21 [0.17, 0.25]
Cr		4.02 [3.31, 4.86]	2.93 [2.18, 3.71]
Ni		2.75 [2.17, 3.44]	2.76 [2.24, 3.37]
Pb		10.7 [8.2, 15.7]	8.00 [5.94, 10.4]
V		3.20 [2.45, 3.96]	3.28 [2.47, 4.07]
$PM_{2.5}$	**$\mu g.m^{-3}$**	26.4 [23.6, 29.1]	21.1 [19.3, 23.2]

a: Time-weighted cumulative average; b: $\mu g.g^{-1}$ of moss dried at 103 °C.

PCA3 components (Table 3), with HR ranging between 1.07 (1.03–1.12) to 1.16 (1.09–1.25) for an interquartile range increase of each metric. We found positive associations between quartiles of As (for instance with a HR of 1.16 (1.03, 1.30) for the second quartile compared to the first) and the "crustal" PCA1 component (only for the second quartile compared to the first, with a HR of 1.20 (1.07, 1.34)). By comparison, we observed positive and significant associations between all-site incident cancer and $PM_{2.5}$, with HRs of 1.13 (1.07, 1.20), for an interquartile range increase of exposure.

5.3.2. Supplementary analyses

The sensitivity analysis using the residuals of metal exposure metrics as exposures largely attenuated point estimates except for As, Cr, and PCA3 "marine" components (Fig. 1, Figure S6). The other sensitivity analyses yielded similar associations compared to the main result for all metals, except with the analysis restricted to participants geocoded at the address or street-match level, with a substantially reduced point estimate.

Among population subsets, we found no consistent trend by sex or smoking status; indeed, among women, we found slightly smaller associations for Cr and Pb, but higher associations for "marine" PCA3 component (Fig. 2). We even found negative associations among women for V and "crustal" PCA1 component. We found slightly higher associations among never-smokers for Cd, Pb, "anthropogenic" PCA2 and "marine" PCA3 components; but we found no differences for As, and "crustal" PCA1 component. We estimated a smaller association for Cr among never-smokers than among ever-smokers. We obtained consistently higher associations between exposure to metals and incident all-site cancer among participants living within 1 km from the nearest major road; conversely, we obtained reduced and often no longer statistically significant associations among participants living further. In particular for Ni, the association was completely reversed for participants living far from major roads. For information, we also estimated higher associations for $PM_{2.5}$ among participants living close to major roads. Finally, for the "marine" PCA3 component, we found a substantially attenuated association among participants living less than 150 km far from sea shore, with a HR of 1.15 (1.09, 1.22) compared to 1.29 (1.18, 1.41) among participants living more than 150 km far from seashore.

5.4. Associations between specific site incident cancers and airborne metals

The main models estimated positive and significant associations between bladder cancer and Cr, As, and V and "crustal" PCA1 component (Table 3), with for instance a HR of 1.20 (1.03, 1.40) for an interquartile increase of Cr. The main models yielded a positive association between lung cancer and "crustal" PCA1 component (second quartile compared to the first, with a HR of 1.61 (1.11, 2.34)). We estimated no statistically significant association with breast cancer. We estimated positive and statistically significant associations between prostate cancer and "crustal" PCA1 (Q2 compared to Q1) and "marine" PCA3 components. For prostate, we estimated also positive associations with Cd and Pb, though with relatively large confidence intervals. For these outcomes and all exposures, the sensitivity analyses estimated fairly similar associations as the main analyses (Figure S8). For information, we estimated a positive association between $PM_{2.5}$ and prostate cancer incidence (HR of 1.17 (1.07, 1.28) for one IQR increase), but the point estimates pertaining to other site-specific cancers were close to the null with large confidence intervals (Table S6).

6. Discussion

6.1. Principal findings

We estimated positive associations between most metal exposure metrics and all-site cancer in a French general-population based cohort mainly composed of men over 50 years old at the beginning of the study period. We also estimated mainly positive associations between airborne metals and specific site cancer, albeit with large interval confidences.

These results were robust to most sensitivity analyses. Associations with exposures to airborne As, Cr, and "marine" PCA3 components were not reduced in the sensitivity analyses using the residuals against $PM_{2.5}$. Airborne As and "marine" PCA3 components were not correlated with $PM_{2.5}$ (Table S3), which quite likely explains why the analysis using the residuals did not change the associations; Cr was correlated to $PM_{2.5}$ with a Spearman coefficient of 0.5, as high as the correlations between Cd or Pb to $PM_{2.5}$. For this reason, identifying mechanisms or sources traced by Cr in mosses could help understand the associations between Cr exposure and risk of cancer.

We found no substantial effect modification by sex or smoking status.

Table 3
Associations between exposure to metals (as single metals or PCA components) and $PM_{2.5}$ and incident cancer.

Cancer site			All-site	Bladder	Lung	Breast	Prostate
Cases/observations		By quartiles or by IQR	2,401/40,271	220/43,936	232/42,685	208/9,493	957/32,857
Single metal (μg.g^{-1})	As	<0.34	1.00 (Ref.)	1.00 (Ref.)	1.00 (Ref.)	1.00 (Ref.)	1.00 (Ref.)
		0.34, 0.43	**1.17 (1.04, 1.31)**	**1.64 (1.07, 2.51)**	0.98 (0.67, 1.44)	1.27 (0.83, 1.94)	1.13 (0.95, 1.36)
		0.43, 0.59	**1.16 (1.03, 1.30)**	**1.89 (1.26, 2.85)**	1.37 (0.95, 1.96)	1.44 (0.95, 2.18)	1.10 (0.91, 1.32)
		0.59, 2.33	**1.11 (0.99, 1.25)**	**1.69 (1.12, 2.55)**	1.13 (0.78, 1.62)	1.35 (0.88, 2.07)	1.00 (0.83, 1.20)
	V	<2.5	1.00 (Ref.)	1.00 (Ref.)	1.00 (Ref.)	1.00 (Ref.)	1.00 (Ref.)
		2.5, 3.3	1.09 (0.97, 1.22)	**1.67 (1.11, 2.51)**	1.12 (0.77, 1.62)	1.02 (0.68, 1.52)	1.14 (0.95, 1.36)
		3.3, 4.1	1.02 (0.91, 1.15)	1.31 (0.85, 2.00)	1.03 (0.71, 1.49)	1.01 (0.68, 1.50)	0.98 (0.82, 1.17)
		4.1, 8.3	0.98 (0.87, 1.10)	1.62 (1.09, 2.42)	1.02 (0.71, 1.48)	0.91 (0.60, 1.37)	0.83 (0.69, 1.01)
	Cd	per IQR	**1.08 (1.03, 1.13)**	**1.08 (0.92, 1.26)**	1.02 (0.87, 1.19)	1.03 (0.86, 1.23)	1.07 (1.00, 1.15)
	Cr	per IQR	**1.08 (1.03, 1.14)**	**1.20 (1.03, 1.40)**	1.04 (0.89, 1.23)	1.05 (0.88, 1.24)	1.06 (0.98, 1.15)
	Ni	per IQR	1.01 (0.95, 1.06)	1.08 (0.91, 1.29)	1.00 (0.84, 1.19)	1.00 (0.84, 1.19)	0.99 (0.91, 1.07)
	Pb	per IQR	**1.06 (1.02, 1.10)**	1.03 (0.90, 1.18)	0.97 (0.84, 1.11)	0.99 (0.86, 1.15)	1.06 (1.00, 1.12)
PCA (unitless)	PCA1	<-0.7	1.00 (Ref.)	1.00 (Ref.)	1.00 (Ref.)	1.00 (Ref.)	1.00 (Ref.)
		−0.7, −0.1	1.03 (0.91, 1.15)	1.18 (0.77, 1.79)	1.15 (0.78, 1.69)	0.92 (0.61, 1.38)	1.02 (0.85, 1.22)
		−0.1, 0.7	**1.20 (1.07, 1.34)**	**1.66 (1.11, 2.47)**	**1.61 (1.11, 2.34)**	1.05 (0.71, 1.55)	**1.23 (1.03, 1.46)**
		0.7, 2.9	1.01 (0.90, 1.14)	**1.56 (1.06, 2.30)**	1.21 (0.83, 1.76)	0.93 (0.62, 1.40)	0.84 (0.69, 1.01)
	PCA2	per IQR	**1.07 (1.02, 1.13)**	1.08 (0.91, 1.29)	1.01 (0.84, 1.20)	1.01 (0.82, 1.23)	1.06 (0.98, 1.15)
	PCA3	per IQR	**1.19 (1.12, 1.27)**	1.03 (0.84, 1.28)	1.00 (0.81, 1.23)	1.20 (0.97, 1.49)	**1.16 (1.05, 1.28)**

Extended Cox models with attained age as time-scale and time-varying exposure to airborne metals, adjusted for time-varying cumulative smoking pack-years, alcohol use, marital status, fruit and vegetable intake, calendar year, and for sex, socio-economic status, education as static variables. Associations are expressed as hazard ratios and their 95% confidence intervals, for one interquartile range increase (Table S6). Numbers in bold highlight statistically significant associations (alpha = 5%). IQR: interquartile range. Exposures were lagged 5 years.

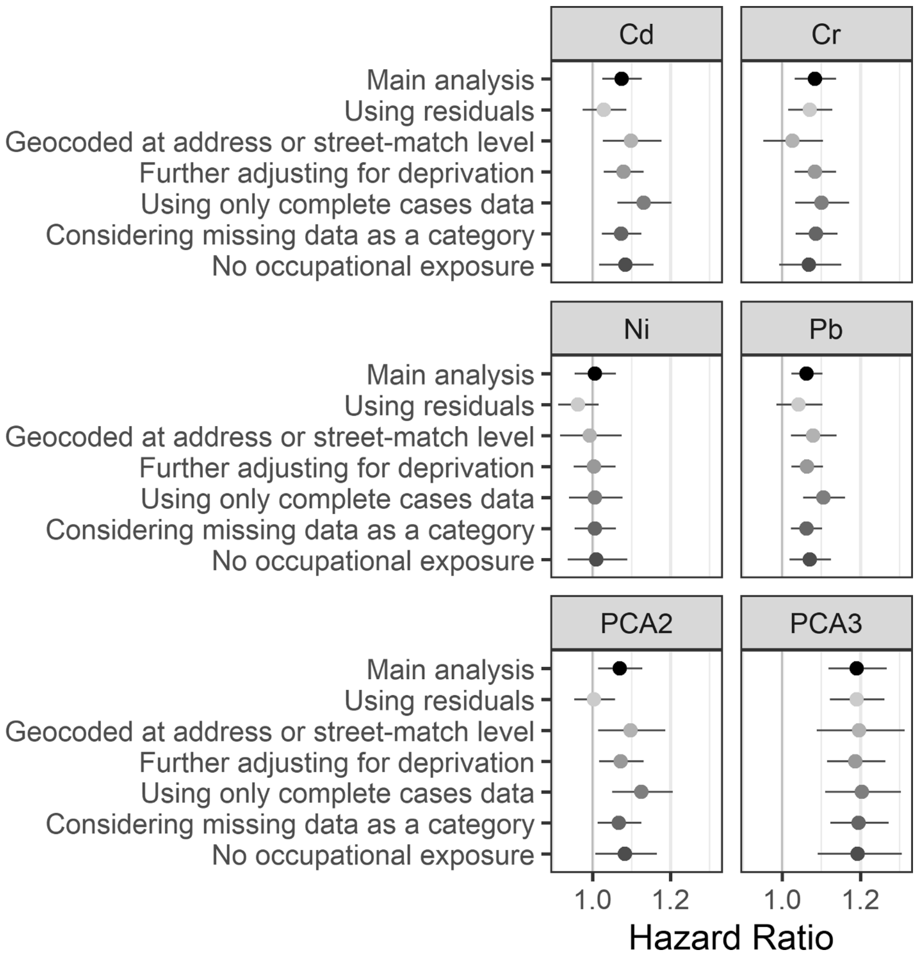

Fig. 1. Linear associations estimated by the main and sensitivity analyses for all-site cancer and Cd, Cr, Ni, Pb, the "anthropogenic" PCA2 and "marine" PCA3 components, using single-pollutant extended Cox models with attained age as time-scale and time-varying exposure, adjusted for sex, cumulative smoking pack-years, alcohol consumption, socio-economic status, education, marital status, fruit and vegetable intake, calendar year, and occupational exposure (except for the analysis excluding participants with occupational exposures). Associations are expressed as hazard ratios and their 95% confidence intervals, for one interquartile range increase (Table S4). The corresponding figures for the other metal exposure metrics available in Figure S6, and all numeric values in Table S6. Number of cases/observations: 2,401/40,271 for the main analysis, using residuals, further adjusting for deprivation, and considering missing data as category; 1,092/18,723 for the analysis restricting the study participants to those geocoded at address or street-match level; 1,451/23,428 for the complete cases data analysis; 1,143/20,288 for the analysis restricting the study participants to those without occupational exposure.

However, the distance to the nearest major road modified most associations, with higher point estimates for participants living closer to major roads (except for the "marine" PCA3 component). This would indicate an influence of traffic-related metals on risk of cancer. We found unexpected associations between all-site and prostate incident cancer and the "marine" PCA3 component, which includes Na and Cr as two first contributing metals. In addition, this association depended on the distance to the seashore with a smaller association among those living close to the seashore than among those living further away. Apart from chance, a source of pollution remaining to be identified may explain these findings, as well as beneficial effects of living close to the seashore.

6.2. Comparison with the literature

Some metals contained in $PM_{2.5}$ have been positively associated with all-site cancer mortality in the USA between 2000 and 2008 (Kazemiparkouhi et al. 2021), in particular the PCA-derived components identified by Kazemiparkouhi and colleagues as 'crustal' (silicon and Ca), 'metal' (Pb, Zn, As) or 'traffic-related' (organic carbon, As) components; these authors estimated no significant association with lung cancer mortality. Although Kazemiparkouhi and colleagues used another exposure assessment method, and although the PCA components differed from those obtained in the present study, their findings showed similarities with this study, such as a positive HR of 1.007 (1.003, 1.010) with all-site cancer mortality for an interquartile range of airborne Pb exposure, or a HR of 1.003 (1.001, 1.004) for the 'metal' PCA component. Among adults, and in relation to airborne metals, breast cancer is one of the most studied sites of cancer to date. Liu and colleagues (2015) estimated positive and nonlinear associations between estrogen and progesterone receptor negative breast cancers and airborne inorganic As and Cd exposure in never-smokers. This is consistent with our findings, with the limit that we could not distinguish between the types of breast cancers and the physico-chemical form or the degree of oxidation of the metals. White and colleagues (2019) found positive associations mostly with postmenopausal breast cancer and Cd, Pb, and Hg. Amadou et al (2019) estimated a positive association between breast cancer and airborne Cd, from an exposure assessment method based on industrial sites. Our methodology focuses on background pollution levels, and the breast cancer analyses in the present study lacked statistical power. We also estimated positive associations between breast cancer and As, although the relatively wide confidence intervals included the null. Weinmayr and colleagues (2018) found a positive association between Zn and gastric cancer (1.63 (95%-CI 0.88;3.01) for an increase of 10 ng.m^{-2} but we had not enough participants to examine this outcome.

6.3. Mechanisms

We chose to treat several metals as single exposures in this study because they are classified as class1 carcinogens, except for Pb which is known to be toxic (Davidson et al. 2007). Furthermore, Pb exposure had large spatial contrasts offered by good-quality exposure surfaces, and high correlation with $PM_{2.5}$ that is classified carcinogen (Loomis et al. 2013). "Anthropogenic" metals are included in the smaller fraction of particulate matter (Nerriere et al. 2007), therefore they can penetrate deeply in lungs, and they seem soluble in lung fluids (Wiseman and Zereini 2014). They may reach the bloodstream (Nemmar et al. 2002), penetrate cells (Steiner et al. 2016), and affect different organs and cause mortality, as shown for some of $PM_{2.5}$ metal components (Comess

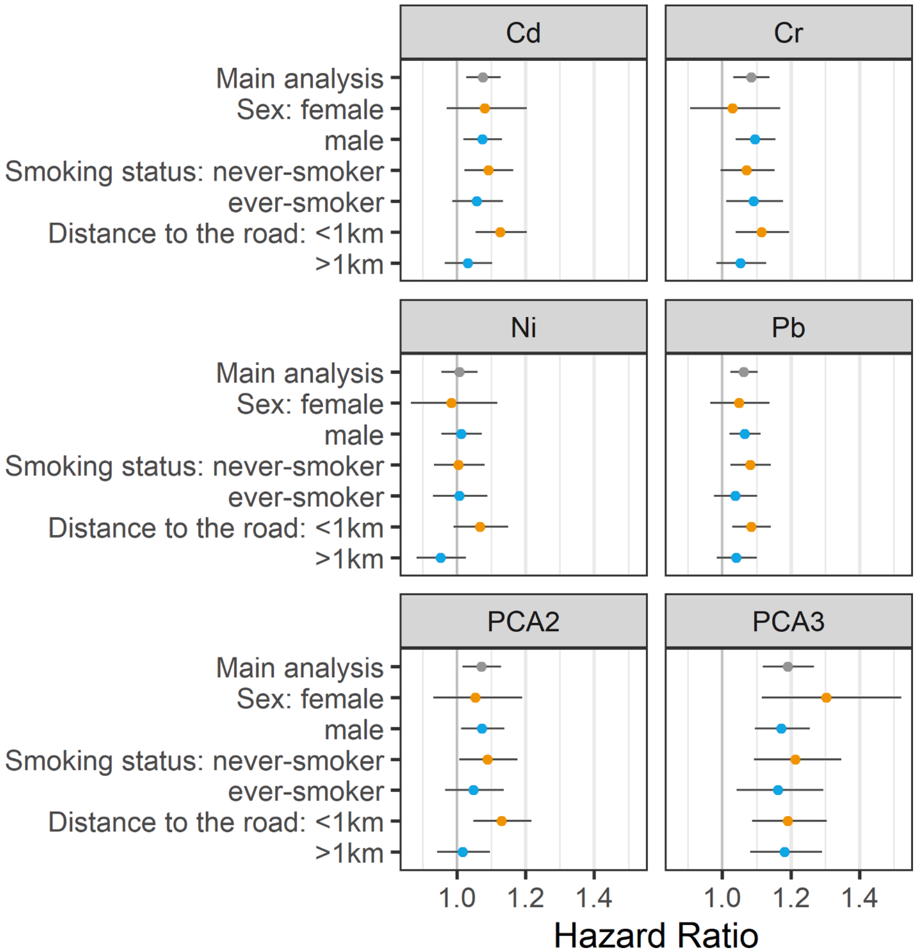

Fig. 2. Linear associations estimated by the main analyses and analyses by subgroups (among women, men, never-smokers, ever-smokers, and participants living close or far from the nearest major road with a cut-off at 1 km) for all-site cancer and Cd, Cr, Ni, Pb, and the "anthropogenic" PCA2 and "marine" PCA3 components, using single-pollutant extended Cox models with attained age as time-scale and time-varying exposure, adjusted for sex, cumulative smoking pack-years, alcohol consumption, socio-economic status, education, marital status, fruit and vegetable intake, and calendar year. Associations are expressed as hazard ratios and their 95% confidence intervals, for one interquartile range increase (Table S4). The corresponding figure for the other metal exposure metrics is available in Figure S7, and all numeric values in Table S6. Number of cases/observations; 378/9,112 for women, 2,023/31,159 for men, 1,233/19,585 for never-smokers, 1,168/20,686 for ever-smokers, 1,178/19,765 for participants living close to the nearest major road, and 1,199/20,190 for those far from the nearest major road.

et al. 2021; Lavigne et al. 2019; Lequy et al. 2019). "Crustal" metals are likely included in the coarser fraction of particulate matter, which does not penetrate as deeply as finer particles, and might explain some nonlinear plateauing associations observed for crustal exposures ("crustal" PCA component, As, or V). As, Cd, and Cr were the most associated with cancer incidence (all-site, bladder, prostate), and these metals are known genotoxicants. Yet Ni in this study, despite the carcinogenicity of Ni compounds (IARC 2012), was associated positively only to all-site cancer among participants living close to a major road. This may be due to the chemical form of metals, which moss biomonitoring does not allow to distinguish, as mentioned above. For these reasons, these results and the limits of the exposure assessment led us to interpret single-metal exposures as tracer of sources of pollutants rather than associations with single-metal exposures per se.

6.4. *Strengths*

This sub-cohort of semi-urban and rural dwellers from the Gazel cohort included more than 10,000 participants followed over 15 years. Therefore, we had longitudinal data for many variables and could use extended Cox models with time-varying variables. Participants hold a large variety of jobs, including both workers and executives. Cancer cases were ascertained mainly from national registries; therefore, we are confident we identified cases exhaustively with credible dates of diagnosis. The BRAMM data allowed to analyze associations with ambient airborne metals, including some seldom studied, such as Cr. We handled confounding by $PM_{2.5}$ with the method from Mostofsky and colleagues (2012) to try disentangling associations with metals from those with $PM_{2.5}$. For information, we also found mostly positive associations between $PM_{2.5}$ and risk of cancer.

6.5. *Limits*

In terms of exposure assessment, some uncertainties remain regarding moss biomonitoring, such as the period of time mosses accumulate metals. One limit of passive moss biomonitoring is that is cannot provide metal concentrations in the air as ng.m^{-3} as $PM_{2.5}$ speciation can do. Rather, moss biomonitoring outputs are concentrations in mosses, here in µg.g^{-1} of dry moss Then, we favor the interpretation according to which the associations we estimated are not due to airborne metal exposures per se, but rather that these exposures proxy sources of pollution – global sources for PCA components and more specific sources for single metals. Indeed, the exposure surfaces provided meaningful spatial contrasts explainable by plausible sources, and metal concentrations were correlated to LUR-modelled $PM_{2.5}$. The results yielded by the analyses using residuals must be interpreted with caution: the regressions providing the residuals combined moss biomonitoring to LUR modeling based on $PM_{2.5}$ measurements obtained from classical devices, and these different exposure assessment methods need more cross-comparison. For Cr, the IARC classified only hexavalent Cr compounds as carcinogens, but we could not distinguish chemical forms of Cr in our dataset. Similarly for Ni, only Ni compounds was classified group 1 carcinogen (IARC 2012), but not Ni metal, classified 2B, i.e. "possibly carcinogenic". Statistical power was low for most specific site cancers, and the all-site combined cancer outcome provided adequate statistical power though it lacks precision to mechanisms and etiology. The study population consisted of workers from a national company with healthcare specificities, most likely with a healthy worker effect; for these reasons, we cannot generalize our findings to other populations. Finally, this observational study cannot establish causality.

6.6. Implications

Despite its limitations, the BRAMM moss biomonitoring data allowed us to assess exposures to background levels of airborne metals in rural areas, or in areas with moderate population density. In these areas, Gazel participants were exposed to lower levels of $PM_{2.5}$ than in large cities (Lequy et al., 2022b), with a likely different composition including metallic compounds. We can hypothesize that, during the follow-up, Gazel urban participants were exposed to much higher levels of airborne metals. This was demonstrated in a previous study in two major French cities Paris and Lyon, based on a dedicated urban moss collection (Lequy et al., 2022a), although another moss species was used in these urban areas – in addition, such recent maps could not be used in the present study. Even when focusing on rural and semiurban population, we estimated mostly positive associations with risk of cancer, although statistical power limited analyses except those pertaining to all-site cancer. Therefore, this study adds to the literature showing that even rural populations can be affected by air pollution. Further, that low levels of air pollution affect health is consistent with the recent updates of the World Health Organization guidelines for air pollution (WHO, 2021). Mosses could help identify sources of diffuse pollution, or emerging pollutants such as platinoids (Zechmeister et al. 2015) and therefore be of public health importance. We showed significantly positive correlations with LUR-estimated levels of $PM_{2.5}$ among the Gazel participants: more cross-comparison between classic and innovative exposure assessments should mutually help increase their quality.

7. Conclusion

We estimated mostly positive associations between anthropogenic airborne metals, as tracers of metal-emitting sources, and risk of cancer in a study population including only semi-urban and rural dwellers, exposed to relatively low levels of air pollution. The associations with Cr or "crustal" and "marine" PCA components, which do not seem traffic-related, suggest that some yet-to-be-identified sources or co-occurring components of air pollution may help explain the carcinogenicity of air pollution. The single-metal and PCA approaches are complementary. More research on airborne metals, their sources, co-occurring air pollutants, and their relationships with $PM_{2.5}$ should help refine our findings and understand their role in air pollution adverse effects and carcinogenicity.

CRediT authorship contribution statement

Emeline Lequy: Conceptualization, Data curation, Methodology, Formal analysis, Writing – original draft, Writing – review & editing. **Sébastien Leblond:** Resources, Methodology, Writing – review & editing. **Jack Siemiatycki:** Conceptualization, Writing – review & editing. **Caroline Meyer:** Methodology, Writing – review & editing. **Danielle Vienneau:** Resources, Writing – review & editing. **Kees de Hoogh:** Resources, Writing – review & editing. **Marie Zins:** Conceptualization, Funding acquisition, Writing – review & editing. **Marcel Goldberg:** Conceptualization, Funding acquisition, Writing – review & editing. **Bénédicte Jacquemin:** Conceptualization, Funding acquisition, Supervision, 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.

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Appendix A. Supplementary material

Supplementary data to this article can be found online at https://doi.org/10.1016/j.envint.2023.107999.

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