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# Long-term exposure to atmospheric metals assessed by mosses and mortality in France

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ABSTRACT

*Background:* Long-term exposure to air pollution affects health, but little is known about exposure to atmospheric metals. Estimating exposure to atmospheric metals across large spatial areas remains challenging. Metal concentrations in mosses could constitute a useful proxy. Here, we linked moss biomonitoring and epidemiological data to investigate the associations between long-term exposure to metals and mortality.

*Methods:* We modelled and mapped 13 atmospheric metals from a 20-year national moss biomonitoring program to derive exposure estimates across France. In the population-based Gazel cohort, we included 11,382 participants from low to intermediate population density areas and assigned modelled metals to their residential addresses. We distinguished between airborne metals that are primarily of natural origin and those primarily of anthropogenic origin. Associations were estimated between exposure to metals and mortality (natural-cause, cardiovascular and respiratory), using Cox models, with confounder adjustment at individual level.

*Findings:* Between 1996 and 2017, there were 1313 deaths in the cohort (including 181 cardiovascular and 33 respiratory). Exposure to the anthropogenic metals was associated with an increased risk of natural-cause mortality (hazard ratio of 1.16 [1.08–1.24] per interquartile range of exposure), while metals from natural sources were not.

*Interpretation:* Some atmospheric anthropogenic metals may be associated with excess mortality – even in areas with relatively low levels of exposure to air pollution. Consistent with the previous literature, our findings support the use of moss biomonitoring as a tool to assess health effects of air pollution exposure at individual level.

## 1. Introduction

It has been estimated that, worldwide, outdoor air pollution caused 4.2 million premature deaths in 2016 alone (WHO, 2018). Evidence has accumulated that particulate matter (PM) and other pollutants increase mortality (Beelen et al., 2015; Dockery et al., 1993; Pope et al., 1995). Advanced modelling approaches enabled assessment of individual-level exposures at residential addresses for pollutants including sulphur dioxide, nitrogen oxides and particulate matter (PM) mass, especially in urban areas (Cohen et al., 2005). Despite attempts to specify PM components (Stanek et al., 2011), it remains unclear which components of PM are responsible for premature deaths.

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PM contains various metals, including some categorized by the International Agency for Research on Cancer as recognized human carcinogens (International Agency for Research on Cancer, 2016). The role of such atmospheric metals in relation to morbidity or mortality is poorly understood. Atmospheric metals come from either natural sources such as windblown soil dust, or from anthropogenic sources of pollution such as road traffic or industry. Studies on health effects of atmospheric metals are few, and they are often limited by the absence of widespread monitoring stations (Kelly and Fussell, 2012; Ostro et al., 2011), or by their focus on small areas near busy roads or industries (Ancona et al., 2015; Bessö et al., 2003). Further, technical and methodological constraints limit long-term measurement of atmospheric metals over large areas. Biomonitoring of moss, however, offers an innovative approach to assess airborne metal levels (Markert et al., 2003). Even though moss-based biomonitoring cannot directly measure the atmospheric concentration of metals, it allows for estimation of relative levels over space and over time (Harmens et al., 2012). Mosses are easy to collect, thereby allowing for large scale sampling surveys. While the idea of using biomonitoring data in epidemiologic studies is not new (Gailey and Lloyd, 1986), it has rarely been applied and only in the context of ecological studies – that is, using fairly crude geographic resolution and lacking individual information on exposure, disease or confounders (Cislaghi and Nimis, 1997; Sarmento et al., 2008; Wolterbeek and Verburg, 2004).

We conducted this analysis partly as a "proof of principle" of using this methodology to derive individual exposures in a cohort study, and partly to elucidate relationships between airborne metals and natural-cause mortality (also referred to as all-cause mortality excluding external causes). We conducted this study in rural France, over a 20-year follow-up period (between 1996 and 2017) in the population-based GAZEL cohort with individual level outcome and covariate information. Exposure was based on moss biomonitoring data in areas of low to intermediate population density from the BRAMM (Moss biomonitoring of atmospheric metals deposition) moss surveys (Lequy et al., 2016), as a proxy for atmospheric metals (Fig. 1).

## 2. Material and methods

### 2.1. Study population

The GAZEL cohort was launched in 1989 among workers of the French utility company for energy production and distribution Electricité de France-Gaz de France (EDF-GDF) (Goldberg et al., 2015). At inception, the cohort included 20,625 participants, men aged 40–50 years and women 35–50 years, distributed all over France. At inclusion, each participant completed a self-administered comprehensive questionnaire and then was followed up annually completing a new self-administered questionnaire. In addition, residential history has been collected and geocoded for each participant since 1989.

In the present study we set the baseline in January 1996, reflecting the first date when biomonitoring-based air pollution data were available. Thus, we considered all the participants with any available lifetime residential addresses since 1996. Since moss biomonitoring data were collected throughout France, mostly in rural areas, the validity of our nation-wide modelling would be greatest in non-urban areas. Consequently, for each participant, we classified her/his residential area's population density into low, intermediate, or high according to Insee (the French national office of statistics) as described in Supplementary Appendix 1. We restricted our study population to participants living only in low to intermediate population density areas (referred to as 'rural' hereafter), during the study period (1996–2017). Any participant who resided in a high population density ('urban') area at least once during follow up was excluded. Further, to limit exposure misclassification, the annual residential history of "rural" participants was used to exclude those living longer than 20% of their follow-up outside of mainland France. Participants who died before 1996 were excluded. The final dataset included 11,382 participants.

Vital status data were collected from the EDF-GDF company until March 2017. Because of the low-turnover rate and excellent retirement benefits in this company, the company records represent a reliable source of information on vital status of current and past employees (Goldberg et al., 2001). Causes of death were recorded by the French national cause-of-death registry and coded using the international classification of diseases (ICD: ninth revision ICD-9 until 1998, and tenth revision ICD-10 thereafter). Natural-cause mortality was analysed after discarding participants who died from accidental or violent deaths

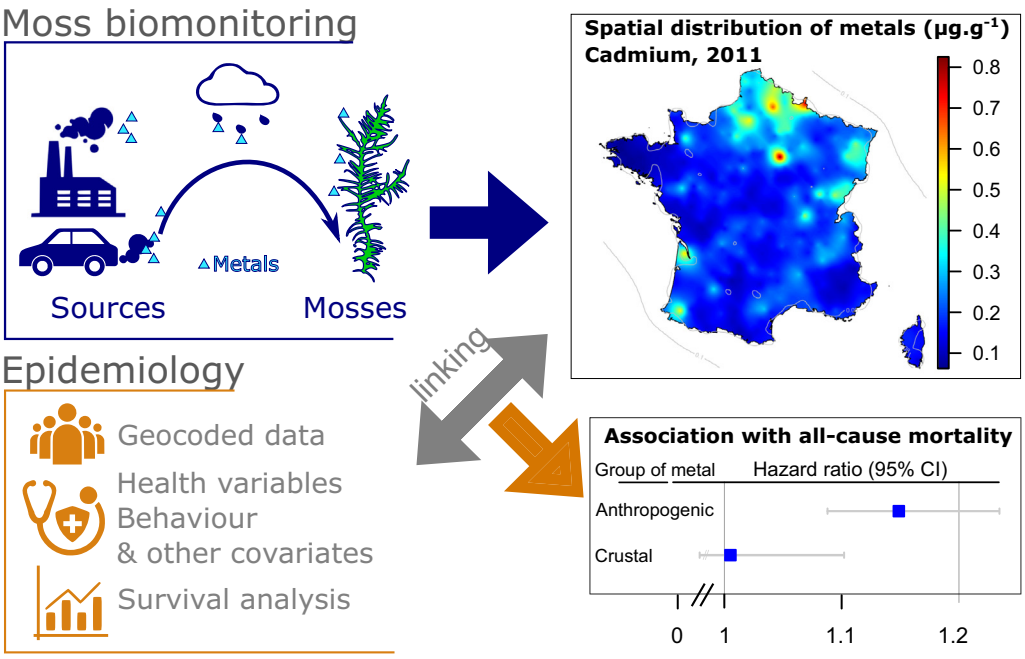


**Fig. 1.** General principle of linking moss-biomonitoring and epidemiological methods to explore associations between exposure to metals and natural-cause mortality in France. Metals emitted by sources are transported in the atmosphere and deposited on mosses. Moss surveys involve sampling mosses, recording the location of each collection site, and analysing their metal content in the laboratory. Four moss biomonitoring surveys were conducted between 1996 and 2011. Together with the metal concentrations and geographical coordinates of the sample, geostatistical methods can be used to model and map the spatial distribution of each metal for each survey over France (e.g. cadmium in 2011). Metal concentrations are then extracted on the basis of geocodes for the home address of the Gazel cohort's participants, and grouped by principal component analysis. Survival analysis is used to estimate the association between an increase in exposure and mortality, expressed as hazard ratios.

(Supplementary Appendix 2). Until March 2017, 1313 participants had died from natural-cause death. Due to a lag between the census of mortality and the extraction of the cause of mortality, we obtained the specific causes of mortality until December 2014; this included 181 cases of cardiovascular deaths and 33 cases of respiratory deaths.

### 2.2. Exposure to atmospheric metals

In France, moss biomonitoring of atmospheric metals is conducted by the French National Museum of Natural History, which manages the BRAMM program. The BRAMM database includes four surveys (1996, 2000, 2006, and 2011) during which 13 metals were measured: Aluminium (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). The objective of this programme is to monitor background atmospheric metal levels, mainly in forest sites and away from major industrial, urban, and traffic sources. Details on the sampling protocol in the field, preparation in laboratory, and analytical procedure of the BRAMM program are available elsewhere (Lequy et al., 2016). Briefly, at each survey, mosses were collected at approximately 500 sampling sites in mainland France (Supplementary Fig. 1). Within one week, moss samples were shipped to the laboratory where they were cleaned before drying and grinding. Finally, moss samples were analysed for their complete metals content after dissolution in nitric acid. Sampling period and analytical techniques varied between surveys (Supplementary Appendix 3). Analytical uncertainty was assessed with respect to moss standards, which enabled us to apply a correction factor to all our data (Lequy et al., 2016). 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. Although duration of retention of metals in moss has not been definitively established, it is generally believed that mosses integrate metals over approximately up to three years (Markert et al., 2003). This study followed the guidelines from the ICP-Vegetation (https://icpvegetation.ceh.ac.uk/get-involved/manuals/moss-survey).

Based on the geographic coordinates and the measured values of metal concentrations at each sampling site, we performed ordinary kriging to interpolate and map (at 2-km resolution) individual metal concentrations over France for each survey year. The kriging models used in this study are shown in Supplementary Fig. 2, and information on the statistical validity of kriging is available in Supplementary Table 1. Briefly, to test the robustness of our kriging models, we developed five hold out validation (HOV) models (Wang et al., 2013), each built on randomly selected 80% of the sampling sites and validated using the remaining 20%. 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; Vienneau et al., 2013). The kriging interpolation was performed using R software version 3.3.2 (R Core Team, 2015), and the package GSTAT (Pebesma, 2004).

To each participant and each residential address at the year of an available moss-biomonitoring survey (1996, 2001, 2006, and 2011), we assigned atmospheric metals exposure based on the krigged map of the corresponding year (see details in the statistical analyses section). We imputed the exposure to arsenic in 2000. Details on the management of the residential addresses are available in Supplementary Appendix 4.

### 2.3. Defining exposure variables for analysis

Because of the high correlations among some of the estimated metal exposures and to avoid unrealistic attempts to tease out the different effects of individual metals, we adopted a strategy of aggregating the 13 metals into a smaller number of sets of metals for analysis. To test the implementation of and the findings from different aggregation approaches, we used two separate strategies: a) a priori grouping of metals, and b) data-based grouping of metals.

#### 2.3.1. A priori subsets

All the metals that we studied are present in the Earth's crust (Nriagu, 1989). Some are main components thereof, such as Al, Fe, or Ca. Others, such as Cd and Pb, are present only in traces. A consensus emerged in environmental sciences to classify airborne elements according to their main source. In general, atmospheric Pb and Cd are considered to be mainly of anthropogenic origin while atmospheric Al, Fe, and Ca, are considered to be mainly of natural origin. Further, in France it was found that, as measured in moss, Cd, Cu, Hg, Pb, and Zn, were mainly of anthropogenic origins, whereas Al, As, Cr, Fe, Ni, and V were mainly of natural origins (Gombert et al., 2004; Meyer et al., 2015). To create synthetic exposure variables corresponding to those two subsets of metals, and since concentrations in moss varied tremendously among the individual metals, we used the rank of exposure level among the individuals, for each metal, and averaged the ranks across the individual metals in each subset (anthropogenic or natural).

#### 2.3.2. Data-driven subsets

We used Principal Component Analysis (PCA) to define a small number of composite variables that capture the essential underlying groupings of highly correlated variables among the individual atmospheric metals as measured in moss and assessed at each person's address (Jackson, 2003). Due to eliminating Hg from this analysis because of missing values in the first BRAMM survey, the PCA was conducted on 12 atmospheric metals after log-transforming time-varying single metals. The PCA was performed using R software and the package ade4 (Chessel et al., 2004; Dray et al., 2007).

The PCA on the overall exposure yielded three principal components (Fig. 2): 1. mainly Fe, Cr, V, and Al (50% of variance explained; all are abundant metal of earth's crust – we called this the crustal metal-component), 2. mainly Cd, Zn, and Pb (22% of variance explained; these metals are mostly anthropogenic – we called this the anthropogenic metal-component), and 3. mainly Na (8% of variance explained; Na being mainly a marine element, we called this the marine metal-component).

### 2.4. Covariates

Covariates used in these analyses were collected from the baseline and the follow-up questionnaires. The following data were used as individual potential confounders in the main or sensitivity analyses (see the statistical analyses section below). For non-time-varying variables, we included the information collected at baseline (1996) or, if unavailable, at the nearest available year: sex, occupation class (blue collar-workers, administrative clerks, foremen/supervisors, and executives), alcohol intake (alcohol consumption was assessed in 1989 and subjects classified according to the weekly intake of alcohol beverages as abstinent, light drinker, moderate drinker, heavy drinker), marital status (single, married or equivalent, separated, divorced, or widowed), and level of education (Low: primary and middle school diploma, Intermediate: professional certification, and High: high school diploma, university, or advanced technical certification). We included the following variables as time-varying: smoking status parametrized as the number of pack-years accumulated since the baseline information in 1996, 2000, 2006 and 2011 (non-smokers: zero pack-years), and body mass index (BMI). Associations between these variables and natural-cause, cardiovascular and respiratory mortality are shown in Supplementary Table 5.

We selected additional variables for our sensitivity analyses or to investigate effect modification.

Because we hypothesize most metals are included in airborne particles, we conducted a sensitivity analysis in which we included exposure to $PM_{2.5}$ as a potentially confounding covariate and to disentangle the effects of PM components from those of PM mass. Exposure

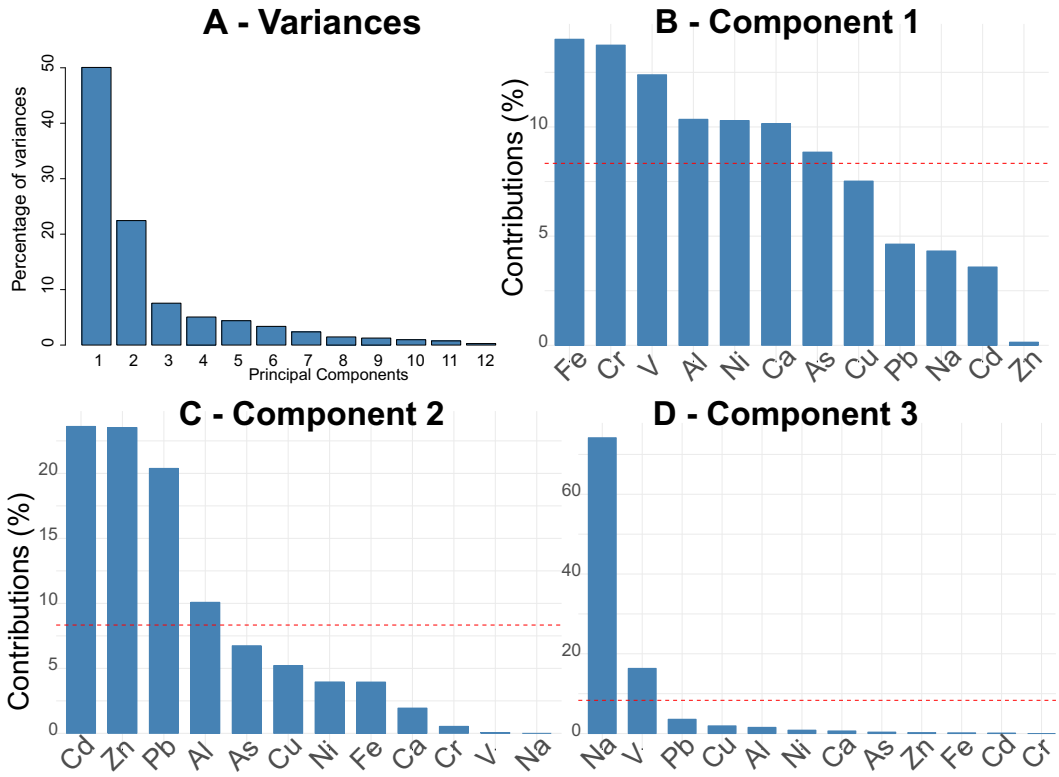


**Fig. 2.** Results yielded by the Principal Component Analysis (PCA) conducted on the cumulative averages of metals over the follow-up (except mercury). Percentage of variance explained by each component (A), and relative contribution of each metal to the three first components (B, C, and D). The red line corresponds to the expected value if the contributions of all metals were uniform. (For interpretation of the references to colour in this figure legend, the reader is referred to the web version of this article.)

to $PM_{2.5}$ was assessed for each participant and each available address in 1996, 2001, 2006, and 2011 using the 2010 European wide land use regression models developed by Vienneau et al. (2013). We further extrapolated these concentrations over the 1990–2015 period using the method developed in the ELAPSE project (de Hoogh et al., 2018). We applied back-extrapolation at regional level (i.e. European Classification of Territorial Units for Statistics; NUTS1, $n = 8$) using dispersion model estimates to derive exposures for other years. As such, we estimated $PM_{2.5}$ exposures for all addresses and all participants in 2010, and extrapolated to 1996, 2000, 2006, and 2011.

Distance to major roads (data from the National Institute of Geographic and Forest Information) for each individual was computed as the average distance from the home address for each year of the BRAMM surveys. We also attributed a population density indicator (low or intermediate) and an indicator for NUTS1 region to account for potential regional differences in France. Finally, we used the French deprivation index value calculated in 2009 (Rey et al., 2009) to capture each participant's socioeconomic environment as a non-time-varying covariable, and we used tobacco status (current or non-smoker) as a time-varying covariable.

### 2.5. Statistical analyses

As main outcome, we chose natural-cause mortality. We also conducted analyses for respiratory (excluding lung cancer) and cardiovascular mortality (Supplementary Appendix 2). To account for the variation of atmospheric metals exposure and other covariates over time, we used the extended Cox model with follow-up time as timescale.

For each metal and total PM2.5, we separately calculated cumulative means for each participant over the follow-up. We then used these cumulative means to derive the two subsets of metal exposure according to our two aggregation strategies as described above.

For our main analysis, we used the following set of Cox models for each exposure variable: (i) a crude model including only age and sex, and (ii) an adjusted model including the set of potential confounders (age, sex, occupational status, marital status, cumulative amount smoked (time-varying), alcohol intake, and BMI (time-varying)). To account for missing values and maximize statistical power, we transformed numerical variables containing missing data into categorical variables including a specific class for missings (BMI: underweight < 20, normal 20–25, overweight 25–30, obese 30–35, extremely obese > 35; deprivation index in tertiles).

We introduced continuous variables (exposure to atmospheric metals and to $PM_{2.5}$, and cumulative pack-years) as spline functions with 3 degrees of freedom to take into account potential non-linear relationship with mortality. No major deviations from linearity were detected. Therefore all air pollutant exposures these were included as linear variables in all Cox models.

We checked the proportional hazard assumption using Schoenfeld residuals and observed no significant deviation.

We present the associations between exposure and natural-cause, cardiovascular and respiratory mortality as hazard ratios (HR) and their 95% confidence interval (CI). All HRs represent the increase in risk corresponding to an increase in exposure from the 25th to the 75th percentile. Results presented individually for each metal-component are yielded from single-pollutant models (i.e. not adjusted for other metals).

Given that metals are components of $PM_{2.5}$, we conducted a sensitivity analysis for natural-cause mortality in a two-pollutant model, in which we adjusted for time-varying $PM_{2.5}$ exposure and for the French deprivation index (included as a strata variable to satisfy the proportional hazard assumption). We observed a significant deviation from linearity for $PM_{2.5}$ exposure, which we included as tertiles to best match

our observations. We conducted another sensitivity analysis by adjusting our main model further for tobacco status (to further control for tobacco use in addition to pack-years), for the level of education, and by including a frailty function to add a random effect for the regions (NUTS1 described above) to take into account the geographical hierarchy of our data.

We tested potential effect modification by running the adjusted Cox model on population subsets for natural-cause mortality. Analyses of risks due to metal exposure were stratified on the following covariates: sex, as females have been reported – even if not consistently – more susceptible to air pollution effects (Clougherty, 2010); smoking status (never-smoker with zero pack-years, versus ever-smoker); population density (low versus intermediate); and distance to major roads (< 1000 m and > 1000 m). We then formally tested for interactions.

All statistical analyses were performed using R software version 3.3.2 and the package SURVIVAL (Therneau, 2015; Therneau and Grambsch, 2000).

## 3. Results

### 3.1. Study population

Table 1 shows baseline characteristics of the study subjects, stratifying on vital status at the end of follow-up. The population is mainly male and non-smoker and evenly split between low and intermediate population density. There were 34.7% ever-smokers and 43.8% moderate to heavy drinkers.

### 3.2. Exposure assessment

Estimated exposure to atmospheric metals at the residential addresses of GAZEL participants ranged between medians of $78.10^{-3}\,\mu g{\cdot}g^{-1}$ of dry weight of moss for Hg and $4700\,\mu g{\cdot}g^{-1}$ of dry weight of moss for Ca (Table 2). The exposure ranges for each metal are similar to the ranges of concentrations in mosses of our modelled maps (Supplementary Fig. 1). We also found higher exposures for participants living in intermediate than in low population density areas, and exposure to traffic-related metals (such as Pb) decreased with increasing distance to major roads. For each metal, estimates from successive surveys correlated well, with a median spearman correlation of 0.76 [IQR: 0.65–0.81] for the participants who did not move or did not leave the NUTS1 region they inhabited in 1996.

When pooling all BRAMM surveys, Al, As, Cd, Cr, Hg, Pb, and V in mosses correlated with $PM_{2.5}$, with Spearman correlation coefficients ranging from 0.32 (As) to 0.65 (Pb). For the remaining elements, we computed correlation coefficients by survey: for Ca, Cu, Fe, Ni, and Zn, we found correlation coefficients larger than 0.3 at least during one survey. However, we found Na always correlated negatively with $PM_{2.5}$ with values ranging from $-0.10$ to $-0.42$.

**Table 1**
Baseline characteristics of the study population, for all and by vital status.

| | | Median (IQR) or N (%) | | |
|---|---|---|---|---|
| | | All | Alive | Dead |
| Variable | n | 11,382 | 10,069 | 1313 |
| Age | | 50.5 [48.5, 53.5] | 50.5 [48.5, 53.5] | 52.0 [49.5, 54.5] |
| Sex | Female | 2484 (21.8) | 2326 (23.1) | 158 (12.0) |
| | Male | 8898 (79.2) | 7734 (76.9) | 1155 (88.0) |
| Smoking status | Neversmoker | 7406 (65.1) | 6810 (67.6) | 596 (45.4) |
| | Smoker | 3421 (30.1) | 2775 (27.6) | 646 (49.2) |
| | Former smoker | 526 (4.6) | 461 (4.6) | 65 (5.0) |
| | Missing | 29 (0.3) | 23 (0.2) | 6 (0.5) |
| Pack-years among ever smokers | | 19.0 [9.0, 29.8] | 17.3 [8.2, 27.6] | 27.5 [17.0, 37.6] |
| Alcohol intake* | None | 306 (2.7) | 259 (2.6) | 47 (3.6) |
| | Low | 6089 (53.5) | 5540 (55.0) | 549 (41.8) |
| | Medium | 2832 (24.9) | 2414 (24.0) | 418 (31.8) |
| | High | 2153 (18.9) | 1855 (18.4) | 298 (22.7) |
| | Missing | 2 (0.0) | 1 (0.0) | 1 (0.1) |
| Level of education | Low | 780 (6.9) | 657 (6.5) | 123 (9.4) |
| | Intermediate | 8233 (72.3) | 7292 (72.4) | 941 (71.7) |
| | High | 2117 (18.6) | 1898 (18.8) | 219 (16.7) |
| | Missing | 252 (2.2) | 222 (2.2) | 30 (2.3) |
| Occupational level | Blue-collar worker | 3903 (34.3) | 3349 (33.3) | 554 (42.2) |
| | Admininstrative clerk | 2396 (21.1) | 2137 (21.2) | 259 (19.7) |
| | Foreman or supervisor | 3263 (28.7) | 2931 (29.1) | 332 (25.3) |
| | Executive | 1809 (15.9) | 1642 (16.3) | 167 (12.7) |
| | Missing | 11 (0.1) | 10 (0.1) | 1 (0.1) |
| Family status | Single | 280 (2.5) | 245 (2.4) | 35 (2.7) |
| | Married or equivalent | 10,625 (93.3) | 9424 (93.6) | 1201 (91.5) |
| | Separated or widow | 463 (4.1) | 390 (3.9) | 73 (5.6) |
| | Missing | 14 (0.1) | 10 (0.1) | 4 (0.3) |
| BMI | < 20 | 337 (3.0) | 290 (2.9) | 47 (3.6) |
| | 20–25 | 4392 (38.6) | 3950 (39.2) | 442 (33.7) |
| | 25–30 | 5038 (44.3) | 4488 (44.6) | 550 (41.9) |
| | 30–35 | 971 (8.5) | 835 (8.3) | 136 (10.4) |
| | < 35 | 127 (1.1) | 105 (1.0) | 22 (1.7) |
| | Missing | 517 (4.5) | 401 (4.0) | 116 (8.8) |
| Population density of area of residence | Low | 5111 (44.9) | 4477 (45.5) | 634 (48.3) |
| | Intermediate | 6271 (55.1) | 5592 (55.5) | 679 (51.7) |
| Distance to major roads | 0–1000 m | 5943 (52.2) | 5271 (52.3) | 672 (51.2) |
| | > 1000 m | 5439 (47.8) | 4798 (47.7) | 641 (48.8) |

IQR: interquartile range; BMI: body mass index; *: Value taken in 1989.

**Table 2**
Atmospheric metals exposure for each year of BRAMM survey (median and interquartile range). $N = 43,899$.

| Metal | Unit | 1996 | 2000 | 2006 | 2011 |
|---|---|---|---|---|---|
| Al | $\mu g \cdot g^{-1}$ | 825 [704, 1084] | 806 [557, 1163] | 1253 [709, 2110] | 504 [431, 708] |
| Ca | | 4428 [3481, 5256] | 4878 [4050, 6251] | 4443 [3557, 5712] | 5189 [4414, 6023] |
| Cr | | 2 [2, 3] | 2 [2, 3] | 3 [2, 4] | 2 [1, 2] |
| Cu | | 6 [5, 7] | 6 [5, 8] | 6 [5, 7] | 7 [6, 8] |
| Fe | | 738 [581, 890] | 740 [560, 966] | 923 [539, 1616] | 545 [409, 745] |
| Na | | 233 [197, 308] | 150 [111, 212] | 133 [93, 215] | 92 [64, 161] |
| Ni | | 3 [2, 3] | 2 [2, 3] | 3 [2, 4] | 3 [2, 3] |
| Pb | | 11 [8, 16] | 7 [5, 8] | 5 [4, 7] | 4 [3, 5] |
| V | | 3 [2, 4] | 3 [2, 4] | 3 [2, 4] | 1 [1, 2] |
| Zn | | 36 [32, 41] | 48 [38, 63] | 33 [29, 39] | 35 [30, 41] |
| As | $ng \cdot g^{-1}$ | 419 [337, 536] | 480 [335, 694] | 538 [310, 870] | 257 [191, 363] |
| Cd | | 243 [191, 301] | 201 [168, 237] | 146 [117, 175] | 186 [151, 243] |
| Hg | | – | 75 [69, 86] | 87 [77, 100] | 70 [63, 78] |

### 3.3. Natural-cause mortality

Between baseline and March 2017, 1313 participants had died from natural causes. In adjusted models, we found increased risks of natural-cause mortality for overall exposure to the a priori anthropogenic group, and the PCA anthropogenic and marine metal-components with fully adjusted HR of 1.17 (CI 1.08–1.27), 1.16 (CI 1.08–1.24), and 1.30 (CI 1.19–1.41), respectively. We found no evidence linking the a priori natural group or the PCA crustal-component to natural-cause mortality. These results remained unchanged in our sensitivity analyses, when we adjusted (i) for smoking status, education, and included a frailty function for the NUTS1 region, or (ii) for $PM_{2.5}$ exposure and deprivation index (Supplementary Table 4).

We found similar results with single metals, with associations between natural-cause mortality and most metals we considered mainly from anthropogenic origin: Cd, Hg, Pb, and Zn, but not with Cu or with metals we considered mainly from natural origin (Supplementary Table 3).

When we stratified our analyses for specific population subgroups, hazard ratios for metal exposure tended to be higher among females, among non-smokers, among participants living in low population density areas, and among those living < 1000 m to major roads (Fig. 3 and Supplementary Fig. 3). Yet we found no significant interaction between exposure to metals and any of these variables; for example, interaction tests between the a priori anthropogenic group and sex or distance to the road yielded *p*-values of 0.19 and 0.16, respectively, while we found p-values of 0.40 and 0.76 for ever- versus never smoker and for population density, respectively.

### 3.4. Cardiovascular and respiratory mortality

Among 1015 cases of death with a known cause of death until 2014, we registered 181 cases of cardiovascular deaths and 33 cases of respiratory deaths. We found associations between the PCA anthropogenic and marine metal-components and both cardiovascular and respiratory mortality (Table 3) with adjusted HRs ranging between 1.23 (CI: 1.02–1.47) and 1.91 (CI: 1.18–3.09); we found an association with the a priori anthropogenic group and respiratory mortality with an adjusted HR of 1. 91 (CI: 1.13–3.25). We found no association with the a priori natural group and the PCA crustal metal-component. We also found significantly positive associations between Cd, Pb and both cardiovascular and respiratory mortality (Supplementary Table 3)

The analyses of cardiovascular and respiratory diseases were based on small numbers and led to imprecise estimates of hazard ratios.

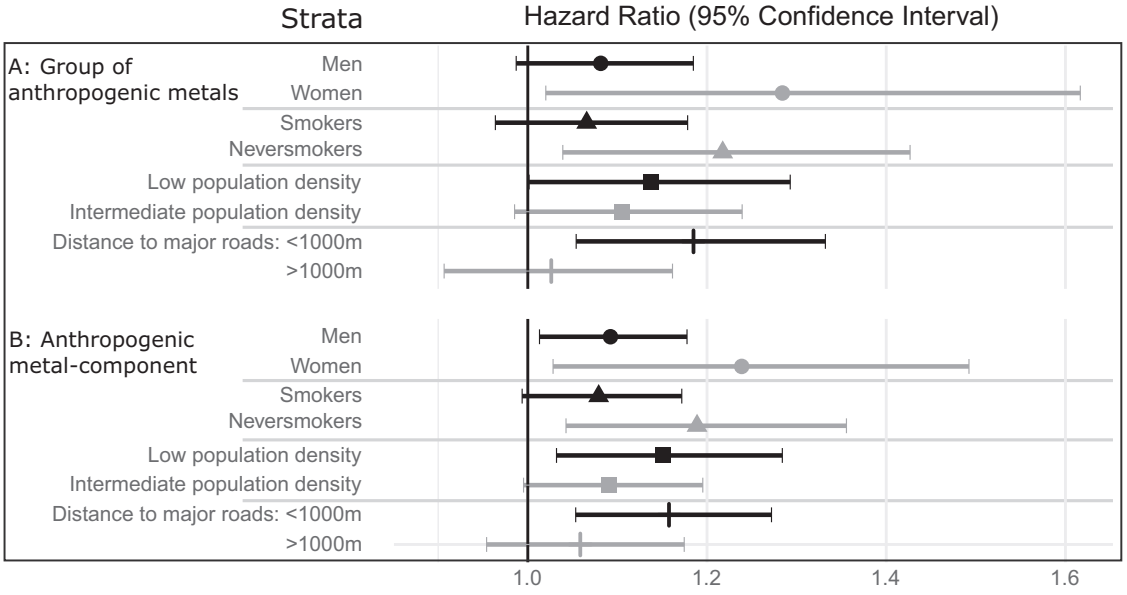


**Fig. 3.** Associations between exposure to the (A) a priori group of anthropogenic metals and the (B) PCA anthropogenic metal-component and natural-cause mortality, within selected sub-strata of the study population; using the extended Cox model with follow-up as time axis, and with time-varying exposure to atmospheric metals, adjusted for sex, age (time-varying), pack-years (time-varying), alcohol intake, occupational status, marital status, and body mass index (time-varying). Hazard ratios and 95% CI expressed per an interquartile range increase of exposure. The rest of our findings are given in the Supplementary Fig. 3.

**Table 3**
Associations between exposure to atmospheric metals and natural-cause, cardiovascular, and respiratory mortality (Hazard ratios and 95% Confidence Interval). Hazard ratios correspond to the increased risk of mortality for an interquartile range increase of exposure to atmospheric metals.

| Variable | | Natural-cause mortality | | Cardiovascular mortality | | Respiratory mortality | |
|---|---|---|---|---|---|---|---|
| | | Hazard Ratio | 95% CI | Hazard Ratio | 95% CI | Hazard Ratio | 95% CI |
| A priori groups | GA | **1.17** | **1.08–1.27** | 1.20 | 0.95–1.50 | **1.91** | **1.13–3.25** |
| | GN | 1.04 | 0.95–1.13 | 1.04 | 0.83–1.31 | 0.93 | 0.54–1.61 |
| PCA components | Crustal | 1.03 | 0.95–1.11 | 1.00 | 0.81–1.23 | 1.01 | 0.61–1.65 |
| | Anthropogenic | **1.16** | **1.08–1.24** | **1.23** | **1.02–1.47** | **1.84** | **1.23–2.76** |
| | Marine | **1.30** | **1.19–1.41** | **1.54** | **1.23–1.91** | **1.91** | **1.18–3.09** |

Extended Cox model with follow-up as time axis, and with time-varying exposure to atmospheric metal-components, adjusted for sex, age (time-varying), pack-years (time-varying), alcohol intake, socioeconomic status, marital status, and body mass index (time-varying). Bold values represent statistically significant ($p < 0.05$) hazard ratios. GA and GN stand for anthropogenic and natural groups, respectively. N = 43,899 for 11,382 participants.

## 4. Discussion

To our knowledge, this is the first study conducted in a cohort that investigates the links between long-term exposure to atmospheric metals assessed by moss biomonitoring and risk of death. We focussed on low population density areas of France because the exposure estimates were likely more valid for rural than for urban areas. Our results are based on 11,382 participants distributed over mainland France, with large spatial heterogeneity for most metals. Such exposure assessment, away from major cities, industries, and highways, focus on levels of exposure that are likely lower than those of participants directly exposed to urban, traffic or industrial pollution, and that are rarely investigated. Yet, our exposure assessment was coherent: participants in higher population density areas or closer to main roads had higher exposures, even though we worked only with rural participants. Thus, we found exposure contrast for participants residing all over France, while using data coming from mosses collected in forest or very rural sampling sites. Since GAZEL's participants were more exposed to PM in urban than in rural areas (Bentayeb et al., 2014), and atmospheric metals are components of PM, we can hypothesize that GAZEL's urban participants (whom we excluded in this study) were probably much more exposed to atmospheric metals, and therefore may experience more adverse health effects from such pollutants – even if decreasing levels does not necessarily imply decreasing health effects. Besides, now that air pollution levels (such as $PM_{10}$ or nitrogen oxides) have decreased in many places, especially in Europe (Guerreiro et al., 2014), it is important to determine the effects of relatively low air pollution levels on population health. Indeed, the current air pollution levels do not allow establishing a threshold below which no harm is observed.

A major strength of this study is that we used a large population-based cohort: we included a detailed set of individual-level covariates, and we assessed exposure to atmospheric metals at the home address and also accounted for address history. Our biomonitoring data allowed for interpolation by kriging over a 2-km grid, providing a unique dataset of exposure to atmospheric metals for a 15-year long follow-up. Complementing previous studies at ecological level (Sarmento et al., 2008; Wolterbeek and Verburg, 2004), our individual-level study supports the idea that mosses are a credible tool to assess exposure of the general population to air pollution.

Our results are based on a very innovative method exploiting moss-biomonitoring, making it possible to distinguish between crustal, anthropogenic, or marine sources of pollution. As such, moss-biomonitoring can prove very complementary to conventional techniques that identify toxic components in PM - which remains challenging especially when assessing long-term exposure (Kelly and Fussell, 2012). Only few studies specified metallic components from PM, for short-term exposure (Stanek et al., 2011), and for long-term exposure (Beelen et al., 2015; Ostro et al., 2011; Valdés et al., 2012), with limited or inconsistent evidence of associations between PM components and mortality. After adjustment for modelled $PM_{2.5}$, our results did not substantially change for natural-cause mortality; this suggests atmospheric metals may be key components involved in mortality having independent effects from total $PM_{2.5}$ mass. Such results agree with previous studies showing associations between long term exposure to metal-rich $PM_{2.5}$ and mortality (Beelen et al., 2015; Ostro et al., 2011; Valdés et al., 2012).

Although not always statistically significant, we found consistently greater associations with cardiovascular and respiratory mortality than with natural-cause mortality. This association patterns has also been found for total PM mass (Adar et al., 2014; Carey et al., 2013; Kim et al., 2017; Pun et al., 2017). Our results, however, were based on small numbers and led to imprecise estimates of hazard ratios: they must be taken interpreted with caution, and could as well be due to chance. These small numbers are consistent with the relatively low cardiovascular mortality generally observed in France. Another potential issue is the recruitment method of the GAZEL cohort, which included workers from a then public company, which may represent healthier participants than the general population (Goldberg et al., 2001).

Although we detected no clear effect modification in our stratified analyses, and found no significant interaction, we found consistently greater associations for women than for men – favouring the hypothesis that women are more susceptible to air pollution effects (Clougherty, 2010). We found slightly lesser associations for ever-smokers than for never-smokers; this is consistent with Puett et al. (2008), who observed that the HR between $PM_{10}$ exposure and all-cause mortality was stronger among non-smokers. On the contrary, small synergistic joint effects were observed with $PM_{2.5}$ exposure and smoking (Lepeule et al., 2012; Turner et al., 2017). These inconsistent findings with PM reveal the complexity in disentangling effects of air pollution and smoking. To our knowledge, no other study investigated interactions between metal components of PM and smoking. Beyond potential explanations such as findings due to chance, this result suggests shared mechanisms between atmospheric and tobacco-related metals that would need further research. The greater associations observed at shorter distance to major roads would indicate an effect of traffic-related metals on mortality.

Our study has some limitations. First, depending on calendar year, between 15 and 43% of our study population were geo-located at the centre of their town, which may not reflect exposure at their actual home address. Second, some questions remain unanswered about the moss-based biomonitoring data, eg. about exactly how much, and under what chemical form ($PM_{10}$, $PM_{2.5}$, other form) atmospheric metals are captured by and measured in mosses, the ability of kriging to estimate air pollutant metals across rural France; most of these are currently being investigated (Boquete et al., 2015, 2011). These questions should not greatly affect our results, as we used moss biomonitoring to derive exposure contrasts relatively in space and time.

In conclusion, in this innovative study, we show that linking moss biomonitoring data to a cohort study allows assessing exposure to air pollution from crustal, anthropogenic or marine sources. We found consistent exposure variability in our study population and our associations with mortality are consistent with the literature, as we

expected anthropogenic pollution to be associated with excess mortality. This supports our use of moss biomonitoring data as an epidemiological tool at individual level and paves the way for research on other health outcomes. Further research needs to be conducted to better identify the sources marked by metal concentrations in mosses and their relation with particles, and to clarify the mechanisms by which atmospheric metals may affect human health (Campen et al., 2002; Carter et al., 1997; Ghio et al., 2012; Prahalad et al., 2001; Quay et al., 1998; Tao et al., 2003). Our findings suggest that even relatively low levels of exposure to atmospheric metals (or to air pollution from sources of which metals are markers), such as those found in the French countryside, may be associated with excess mortality.

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The study funder did not contribute to the study design and had no role in data collection, data analysis, data interpretation, or writing of this manuscript. The corresponding author had full access to all the data used in this study and had final responsibility for the decision to submit for publication.

## Contributors

EL, JS, MG, MZ and BJ contributed to the study design. EL and SZ prepared and cleaned the epidemiological data. EL, SL, and CM contributed to the exposure assessment by moss biomonitoring, while DV and KdH contributed to assess the exposure to $PM_{2.5}$. JS, MG, MZ and BJ provided scientific input in the statistical methods and interpretation of the results. EL, JS, MG, MZ and BJ contributed to the data analyses. EL took the lead in drafting the manuscript. All authors contributed to interpretation of data, provided critical revisions to the manuscript, and approved the final draft.

## Declaration of Competing Interest

We declare no competing interest.

## Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.envint.2019.05.004.

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