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Exposure to multiple air pollutants and the incidence of coronary heart disease: A fine-scale geographic analysis

Florent Occelli a,⁎, Caroline Lanier a, Damien Cuny a, Annabelle Derama a, Julie Dumont b, Philippe Amouyel b, Michèle Montayeb, Luc Dauchet b, Jean Dallongeville b, Michaël Geninc

a Univ. Lille, CHU Lille, Institut Pasteur de Lille, EA 4483 IMPECS (IMpact of Environmental ChemicalS on human health), F-59000 Lille, France
b Univ. Lille, CHU Lille, Institut Pasteur de Lille, Inserm UMR1167 RID-AGE (Risk Factors and Molecular Determinants of Aging-Related Diseases), F-59000 Lille, France
c Univ. Lille, EA 2694 - Santé Publique épidémiologie et qualité des soins, F-59000 Lille, France

HIGHLIGHTS

• A small area level geographic analysis from a coronary heart disease (CHD) registry
• Long-term exposure to heavy metals assessed by lichen biomonitoring
• Proposed a composite air pollution index (SEnv) for multiple exposure
• Found associations between SEnv and CHD incidence
• Exposure to multiple low-dose air pollutants may increase cardiovascular risks

GRAPHICAL ABSTRACT

Abstract

Geographical variations in cardiovascular disease rates have been linked to individual air pollutants. Investigating the relation between cardiovascular disease and exposure to a complex mixture of air pollutants requires holistic approaches. We assessed the relationship between exposure to multiple air pollutants and the incidence of coronary heart disease (CHD) in a general population sample. We collected data in the Lille MONICA registry (2008–2011) on 3268 incident cases (age range: 35–74). Based on 20 indicators, we derived a composite environmental score (SEnv) for cumulative exposure to air pollution. Poisson regression models were used to analyse associations between CHD rates on one hand and SEnv and each single indicator on the other (considered in tertiles, where T3 is the most contaminated). We adjusted models for age, sex, area-level social deprivation, and neighbourhood spatial structure. The incidence of CHD was a spatially heterogeneous (p = 0.006). There was a significant positive association between SEnv and CHD incidence (trend p = 0.0151). The relative risks [95%CI] of CHD were 1.08 [0.98–1.18] and 1.16 [1.04–1.29] for the 2nd and 3rd tertile of SEnv exposure. In the single pollutant analysis, PM10, NO2, cadmium, copper, nickel, and palladium were significantly associated with CHD rates. Multiple air pollution was associated with an increased risk of CHD. Single pollutants reflecting road traffic pollution were the most strongly associated with CHD. Our present results are consistent with the literature data on the impact of road traffic on the CHD risk in urban areas.

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1. Introduction

The World Health Organization has defined coronary heart disease (CHD) as the world’s leading cause of death and disability between 2000 and 2016 (World Health Organization, 2018). In Europe, CHD continues to contribute significantly to mortality (Lelieveld et al., 2019).

A recent systematic review of the literature by Mena et al. (Mena et al., 2018) showed that cardiovascular event rates and risk factor prevalence tend to cluster in specific geographical areas and differ according to the place of residence (e.g. rural vs. urban). In France, there is a clear North to South decreasing geographical gradient in CHD mortality rates (Arveiler et al., 2005) and cardiovascular risk factors prevalence (Wagner et al., 2014). However, much less is known about effects on a smaller geographic scale, such as that of a region or a conurbation, exposed to contrasted environmental factors.

The geographical heterogeneity can be accounted for (at least in part) by disparities in socio-economic factors (such income and educational level, which are associated with inequality in health access) and in health-related behaviours (such as dietary habits, physical activity, and smoking). By using spatial ecological analyses adjusted for the socio-economic level, several research groups have reported associations between air pollution and CHD (Barceló et al., 2009; Bennett et al., 2014; Chen et al., 2015; Dijekema et al., 2016; Garcia et al., 2016; Hu and Rao, 2009; Maheswaran et al., 2005; Pannullo et al., 2016; Pascal et al., 2013) using mortality or hospitalization rates indicators. Much less is known on the effect of environmental factors on CHD incidence rates.

Outdoor air pollution is a complex phenomenon that involves the chronic exposure to many different pollutants (Levy et al., 2014). Hence, environmental pollution must be considered holistically and in the long term. To date, very few studies have assessed the spatialized, cumulative exposure to multiple pollutants (Bennett et al., 2014; Scarborough et al., 2012). In contrast, exposure to conventionally individual air pollutants has been extensively studied – usually by modelling annual mean concentrations of sulphur dioxide (SO2), nitrogen oxides (NOx), particulate matter (PM10 and PM2.5), and ozone (O3). Composite index groups together indicators of the various facets of a multiple exposure to air pollutants (European Commission et al., 2008). In this respect, spatialized composite indices are increasingly acknowledged to be valuable indicators for determining overall air quality (Occelli et al., 2016).

Therefore, the primary objective of the present study was to assess the putative relationship between exposure to multiple environmental pollutants and the incidence of CHD. To this end, we compared the spatial distributions of a composite air pollution index and the CHD rate after adjusting for the level of social deprivation.

2. Methods

We conducted a geographical ecological analysis in northern France, to estimate associations between the incidence rates of CHD from 2008 to 2011, and the long term exposure to multiple air pollutants.

2.1. Geographical area and spatial unit

We studied the Lille urban area (Lille European Metropolis) in northern France, situated at the crossroads between France, the UK, and the Low Countries. This is a densely populated area (mean density: 1821 inhabitants/km2) with high levels of socio-economic heterogeneity. Many sources of air pollutant emissions are present, including road traffic, residential heating, industry, and intensive crop farming.

The spatial unit used for statistical analysis (referred to as a neighbourhood in the present study) typically includes around 2000 inhabitants, and is the unit most commonly used by the French National Institute for Statistics and Economic Studies (INSEE) for the dissemination of administrative information below the municipality level. In our study, 23 of the 496 spatial units in the Lille urban area did not have a residential population and were therefore excluded: hence, 473 neighbourhoods were included in the analysis.

2.2. Incident cases of CHD

The data on CHD were obtained from the French WHO-MONICA population-based CHD registry for the Lille urban area. The methods for the registry have been described elsewhere (Ducimetiere et al., 2011). Briefly, the registry concerns men and women aged 35–74 residing in the corresponding area: there are around 220,000 inhabitants in this age range in the Lille urban area. All fatal and non-fatal CHD events whether hospitalised or not, recorded by public- or private-sector hospitals, emergency departments or at home that occurred in the study area were assessed. Multiple overlapping sources of case-ascertainment were used to document the CHD events. Medical and administrative sources were cross-checked to ensure the inclusion of all information (discharge letters, computer listings covering the diagnosis on hospital discharge, emergency department listings, death certificates, etc.). Cases of acute coronary events were documented on the basis of the clinical history and the hospital records. The clinical diagnoses were obtained from medical records. For each event, the patient’s vital status was recorded. Information on this outcome was obtained directly from the patient’s general practitioner, the city’s registry office, or the national death certificate database. The causes of death were checked in hospital or autopsy records and by interviewing general practitioners. For the present study, we used data from the 2008–2011 period, which represented 5448 cases. As secondary prevention may affect outcome, only incident coronary events were considered here – yielding a total of 3268 cases.

2.3. Ecological variables

2.3.1. Deprivation index (FDep)

The FDep index (Rey et al., 2009) was used to describe the socioeconomic characteristics for each neighbourhood. FDep is a deprivation index reflecting the spatial socioeconomic heterogeneity, validated in the French context. FDep was built from four variables in the INSEE database: the median household income, the percentage of high school graduates in the population aged 15 and over, the percentage of blue-collar workers in the active population, and the unemployment rate. The higher the FDep index, the greater the level of deprivation.

2.3.2. Environmental indicators

A previously described environmental score (SEnv) was considered as a guide to the long-term, overall air quality (Lanier et al., 2019). SEnv was calculated from 20 spatialized environmental indicators, including both physical-chemical and plant biomonitoring measurements:

- the annual mean modelled concentration for NO2 and PM10 in 2009, given a 25 × 25 m grid and an atmospheric dispersion modelling system. Data were obtained from the local approved association for air quality monitoring (Atmo Nord-Pas de Calais, 2015).
- multimetal burdens, evaluated by measuring 16 metal loads having bioaccumulated in the thalli of the foliose lichen Xanthoria parietina over the period 2003–2009 at 120 georeferenced locations, according to French standards (NF X43-904) (Occelli et al., 2016). Lichens are exclusively dependent on the atmosphere for their nourishment, and absorb pollutants in the same way as essential elements (Loppi and Nascimbene, 2010). With an annual growth rate of approximately 1 cm, the harvesting of 6 cm diameter thalli corresponded to approximately 6 years of exposure.
- eutrophication, estimated by the observation of lichen diversity and abundance in 2010 at 73 georeferenced locations, according to French standards (NF EN 16413) (Cuny et al., 2018). This biological measure indicates the ecological responses of epiphytic lichens as...
The 18 biomonitoring indicators (16 metals, eutrophication, and dust) were modelled in a 100 × 100 m grid using spatial kriging method. Lastly, all 20 indicators were aggregated to the neighbourhood level by using a mean value (Occelli et al., 2016).

To calculate SEnv, neighbourhoods were ranked (from 1 to 473) according to the value of each indicator. For a given geographical unit, the SEnv was obtained by summing the ranks of each of its environmental indicators. The higher the SEnv, the greater the level of air pollution.

2.4. Statistical analyses

2.4.1. Standardized incidence ratios (SIRs)

The spatial distribution of CHD was assessed by computing SIRs for each spatial unit. The SIR is defined as the ratio between the observed number of CHD cases and the expected number after indirect standardization for age and gender (i.e. well-known confounding factors in CHD incidence) (Rothman et al., 2008).

2.4.2. Evaluation of spatial heterogeneity and spatial autocorrelation

The presence or absence of spatial variations in CHD incidence from one spatial unit to another was probed using the Pothoff-Whittinghill test (Pothoff and Whittinghill, 1966). The presence or absence of spatial autocorrelations among the spatial units was quantified using Moran's index (Moran, 1948) where a value > 0 indicates the presence of autocorrelation and probed using Moran's test (Cliff et al., 1981).

2.4.3. Smoothed SIRs and ecological regression

Given that the SIRs were unstable (due to low frequencies and spatial autocorrelation), the ratios were smoothed using the Bayesian Poisson regression model developed by Besag et al. (Besag et al., 1991). Associations between the age- and gender-standardized incidence of CHD and ecological variables (considered in tertiles) were assessed using an extension of the previous model, namely ecological regression (i.e. the inclusion of ecological covariates as fixed effects). For each covariate, the relative risk (RR) of CHD incidence and its 95% confidence interval (BCI) were computed. For each categorical variable, the relative risk (RR) of CHD incidence and its 95% Bayesian credibility interval (BCI) were computed. For each ecological covariate, a trend test was performed. The different models were fitted using an integrated nested Laplace approximation (Blangiardo and Cameletti, 2015). Details about the previous Bayesian statistical model are provided as supplementary material.

2.4.4. Software

All statistical analyses were carried out using R software (version 3.4.3; packages: DCluster, R-INLA). The threshold for statistical significance was set to p=0.05. Maps were produced using ArcGIS software (version 10.5; ESRI; http://www.esri.com).

3. Results

3.1. Crude incidence of CHD

For the present study, we used data from the 2008–2011 period, which represented 5448 coronary events. As secondary prevention outcomes may be affected by secondary prevention, only incident events were considered in the present study. Between 2008 and 2011, 3268 incident coronary events (2333 (71.4%) in men and 935 (28.6%) in women) were recorded in the Lille urban area. The crude annual CHD incidence rate was 176 per 100,000 inhabitants for both sexes, 264 per 100,000 for men, and 96 per 100,000 for women. The crude CHD incidence rate increased with age (Fig. 1).

3.2. Geographical variation in the incidence of CHD

We observed significant spatial heterogeneity in the CHD incidence rates (p=0.006 in a Pothoff-Whittinghill test), together with evidence of spatial autocorrelation between the different spatial units (Moran I statistics = 0.20; p=0.001). The age- and gender-smoothed SIRs [95% BCI] ranged from 0.56 [0.37–0.80] to 1.85 [1.29–2.56]. There were three hot spots of increased CHD incidence rates (SIR=1.5) in the north-east of the area and in the southern and south-eastern suburbs of the main city (Lille), and three cold spots (SIR=0.75) in the north-west, southwest and southeast (corresponding to more rural neighbourhoods). These data revealed clear geographic heterogeneity in the CHD incidence rates (Fig. 2).

3.3. Geographical variations in air pollution

In the study area, SEnv ranged from 208 to 1987, with a median [IQR] value of 1153 [941;1465] (Fig. 3A). Hot spots of pollution were found along the main roads (white lines on the map) in both urban and rural areas. Hot spots of high pollution tend to overlap with high CHD incidence rates. Several neighbourhoods with medium incidence rates (i.e. in the south or in the west of Lille) also overlapped with high-pollution areas. Conversely, low pollution areas tend to overlap with low CHD incidence spatial units – most of which were located in rural neighbourhoods.

The median [IQR] levels of 20 environmental indicators by SEnv tertile, and Spearman’s coefficient (SC) for the correlation are shown in Table 1. The values of these indicators did not vary greatly over the study area. Most values were higher in T3 than T1. The PM10 and NO2 concentrations were strongly correlated with SEnv (SC > 0.8; p<0.001). Medium and weak correlations were observed for total dust and eutrophication (SC: 0.40; p<0.001, and 0.13; p<0.01, respectively).

The metals most strongly correlated with SEnv (p<0.001) were lead (SC: 0.50), copper (SC: 0.47), antimony (SC: 0.42), zinc (SC: 0.42), palladium (SC: 0.37), chromium (SC: 0.33), and cadmium (SC: 0.32). Arsenic and cobalt were not significantly correlated with SEnv, whereas beryllium and titanium were negatively correlated with SEnv.

3.4. Geographical variations in social deprivation

In the Lille urban area, the FDep index ranged from −4.27 to 5.93, with a median [IQR] of 0.14 [−1.2;1.63] (Fig. 3B). High deprivation areas overlapped with hot spots of CHD incidence rates in the northeast, and in the south-eastern suburbs of Lille. Cold spots of CHD incidence were characterized by both low and medium levels of deprivation. The association between FDep and SEnv was not significant (SC: −0.07; p=0.15).

3.5. Association with air pollution

Higher incidence rates of CHD might be associated with FDep and SEnv (Figs. 2 and 3). The hot spots of incidence rates observed in the Lille urban area differed with regard to some of their characteristics. The north-eastern area was characterized by the highest deprivation levels and medium levels of exposure to air pollution. In contrast, populations living in the south-eastern suburbs of Lille were exposed to high levels of air pollution but were less deprived.

In an ecological regression analysis (Fig. 4, Model 1), there was a borderline association between SEnv and the CHD incidence rate (trend p=0.08). Compared with T1 of SEnv, the RR [95%BCI] CHD was 1.12 [1.01–1.24] for T2 and 1.11 [0.99–1.25] for T3. After adjustment for the FDep index (Fig. 4, Model 2), there was a significant association (trend
Fig. 1. Crude mean incidence of CHD by age class and by sex (2008–2011).

Fig. 2. Smoothed age- and-gender-standardized incidence ratios for CHD (2008–2011).
between SEnv and the CHD incidence rate (RR was 1.08 [0.98–1.18] for T2 and 1.16 [1.04–1.29] for T3). Furthermore, FDep was associated with the CHD incidence rate (trend \( p=0.0001 \)). Compared with the T1 of FDep, the RR of CHD was 1.20 [1.09–1.33] for T2 and 1.63 [1.47–1.82] for T3.

The association between each environmental indicator and the CHD incidence rate was evaluated in an ecological regression analysis after adjustment for FDep (Table 2). There were significant associations between the CHD incidence rate on one hand and both PM\(_{10}\) and NO\(_2\) on the other. Compared with T1, the RR ranged from 1.06 [0.97–1.17] to 1.11 [1.00–1.23] for T2 and T3 for PM\(_{10}\) (trend \( p=0.022 \)) and from 1.05 [0.95–1.16] to 1.10 [0.99–1.22] for NO\(_2\) (trend \( p=0.036 \)).

Regarding the metals, significant associations were observed for copper (1.08 [0.98–1.20] for T2 and 1.17 [1.05–1.31] for T3; trend \( p=0.003 \)), cadmium (1.09 [0.99–1.20] for T2 and 1.14 [1.01–1.28] for T3; trend \( p=0.009 \)), palladium (1.11 [0.99–1.24] for T2 and 1.13 [1.00–1.29] for T3; trend \( p=0.032 \)), and nickel (1.09 [0.98–1.21] for T2 and 1.11 [1.00–1.23] for T3; trend \( p=0.033 \)). We did not observe a significant association between CHD and the 12 other heavy metals, dust, or eutrophication. It should be noted that after Bonferroni’s correction for multiple comparisons, none of these associations were significant.

4. Discussion

The present results highlighted a strong spatial heterogeneity of CHD incidence in the Lille urban area. After adjustment for the neighbourhoods’ socioeconomic level, this heterogeneity was associated with multiple air pollution indicators. These data suggest that air pollution may increase the risk of CHD.

4.1. Multiple pollutant analysis, using a composite index

Long-term exposure to mixtures of low-dose air pollutants have harmful effects on health (Bopp et al., 2018). However, these effects may be difficult to assess when considering conventional single-
Table 1
Median [IQR] levels of the 20 environmental indicators (in μg/m³ for PM₁₀ and NO₂, and μg/g for metals and dust) by SEnv tertile (T1, T2 and T3), and Spearman’s coefficient for the correlation.

| Environmental indicator | All [n = 473] | T1 [208–1010] [n = 158] | T2 [1010–1360] [n = 158] | T3 [1360–1987] [n = 157] | Spearman coefficient |
|--------------------------|---------------|--------------------------|--------------------------|--------------------------|---------------------|
| PM₁₀                    | 33.3 [32.0;35.4] | 31.1 [29.8;32.3] | 33.3 [32.6;34.0] | 36.3 [34.5;40.3] | 0.84***             |
| NO₂                     | 33.5 [30.5;37.3] | 28.7 [25.9;31.1] | 33.5 [31.9;34.7] | 39.0 [35.5;44.1] | 0.83***             |
| Aluminium               | 1001 [901;1176] | 970 [848;1277] | 976 [874;1094] | 1083 [991;1185] | 0.20***             |
| Arsenic                 | 1.09 [0.97;1.19] | 1.07 [0.96;1.19] | 1.10 [0.94;1.19] | 1.09 [0.99;1.18] | 0.04                |
| Beryllium               | 0.24 [0.23;0.25] | 0.24 [0.23;0.26] | 0.24 [0.22;0.25] | 0.24 [0.22;0.24] | -0.31***            |
| Cadmium                 | 0.66 [0.47;0.84] | 0.56 [0.42;0.74] | 0.65 [0.47;0.81] | 0.77 [0.60;0.93] | 0.32***             |
| Cobalt                  | 0.67 [0.57;0.76] | 0.66 [0.54;0.76] | 0.67 [0.57;0.75] | 0.67 [0.59;0.76] | 0.07                |
| Chromium                | 4.35 [3.63;4.96] | 3.97 [3.89;4.76] | 4.23 [3.66;4.88] | 4.69 [4.21;5.12] | 0.33***             |
| Copper                  | 19.2 [15.2;27.5] | 16.1 [11.8;19.7] | 19.4 [16.0;25.1] | 26.0 [18.2;36.3] | 0.47***             |
| Mercury                 | 0.13 [0.10;0.14] | 0.11 [0.10;0.14] | 0.12 [0.10;0.14] | 0.14 [0.12;0.15] | 0.30                |
| Manganese               | 47.3 [42.4;53.1] | 44.8 [39.1;52.9] | 47.6 [43.0;53.2] | 47.9 [44.7;53.0] | 0.17***             |
| Nickel                  | 2.86 [2.52;3.18] | 2.72 [2.26;3.03] | 2.94 [2.56;3.23] | 2.92 [2.66;3.26] | 0.22***             |
| Lead                    | 28.5 [19.7;45.7] | 22.6 [15.5;29.6] | 28.1 [19.8;39.4] | 46.3 [27.2;53.6] | 0.50***             |
| Palladium               | 20.1 [17.0;24.5] | 17.8 [16.0;21.2] | 19.3 [16.7;23.9] | 22.9 [19.4;27.0] | 0.37***             |
| Antimony                | 1.97 [1.52;2.37] | 1.69 [1.25;2.06] | 1.95 [1.59;2.16] | 2.31 [1.95;2.55] | 0.42***             |
| Titanium                | 15.6 [13.9;16.7] | 16.3 [14.3;17.3] | 15.6 [14.2;16.8] | 15.0 [13.8;15.9] | -0.23***            |
| Vanadium                | 3.61 [3.28;3.98] | 3.57 [3.00;3.96] | 3.64 [3.29;4.02] | 3.61 [3.38;3.95] | 0.11                |
| Zinc                    | 113 [95.9;131] | 102 [78.2;121] | 110 [96.9;125] | 126 [108;139] | 0.42***             |
| Dust                    | 1973 [1847;2084] | 1895 [1803;1992] | 1978 [1843;2085] | 2041 [1951;2133] | 0.40***             |
| Eutrophication          | 5.72 [5.63;5.85] | 5.69 [5.62;5.83] | 5.73 [5.63;5.86] | 5.75 [5.65;5.84] | 0.13***             |

* p<0.05.
** p<0.01.
*** p<0.001.

Fig. 4. The relative risk [95%BCI] of CHD by SEnv tertile (Model 1) and by SEnv and FDep tertiles (Model 2), in a Bayesian ecological regression.
pollutant exposure because of a lack of statistical sensitivity and the multifactorial aetiology of chronic diseases.

Multiple exposure is rarely assessed in environmental health studies (Levy et al., 2014). Earlier reports in China have shown a positive association between the Air Pollution Index (API) and mortality rates (Li et al., 2015) or severe acute respiratory syndrome (Cui et al., 2003). However, the API does not really consider the cumulative exposure but only the effect of peak exposure to different pollutants (Thach et al., 2018). In Canada, the Air Quality Health Index (summing up the estimated health risks associated with O₃, NO₂ and PM₂.₅) has been used to assess the impact of air quality on hospitalizations for asthma (To et al., 2013).

In contrast, very few studies have assessed the cumulative effect of several pollutants on cardiovascular disease. Bennett’s application of the Air Quality Indicator (which sums the emissions of benzene, NO₂, SO₂, and particulates) for small areas revealed a significant positive association with heart failure morbidity and mortality across the county of Warwickshire, UK (Bennett et al., 2014). Using the same indicator, Sorensen et al. found a small association with coronary heart mortality rates after adjustment for confounding variables among UK wards (Scarbrough et al., 2012). In the present study, we calculated a composite index that provides an overall picture of air pollution. This makes it easier to integrate the complex nature of an environmental mixture into an ecological study. We found a 16% rise in the risk of incident CHD for the third tertile of SEnv, suggesting that a set of several pollutants have a cumulative impact on CHD. Taken as a whole, these data suggest that cumulative exposure to multiple low-dose air pollutants may generate cardiovascular complications.

### 4.2. Single-pollutant analysis

In addition to the overall effect of air pollution, we found an approximately 10% rise in the risk of incident CHD for the third tertiles of PM₁₀ and NO₂ exposure. In agreement with these results, earlier studies have reported associations between monitored air pollutants and CHD hospitalizations and mortality rates. In the UK, Maheswaran et al. reported on significant elevated CHD mortality risks in the highest quintile of PM₁₀ and NOₓ annual concentration exposures (1.17 [1.06–1.29] and 1.08 [0.96–1.20], respectively) (Maheswaran et al., 2005). Similarly, a study in Barcelona reported a significant association between CHD mortality and high levels of NO₂ exposure in men (RR = 1.0848 [1.0035–1.1066] for one NO₂ unit increment) (Barceló et al., 2009). However, the association with NO₂ in women and with PM₁₀ in men or women was not statistically significant. In California, a significant increment in CHD mortality rates in areas exposed to PM₂.₅ was reported, whatever the spatial exposure model used; the RR ranged from 1.20 [1.17–1.23] to 1.28 [1.25–1.32] for each 10 μg/m³ increase in concentration (Garcia et al., 2016). A significant association between the SO₂ concentration and the myocardial infarction hospitalization rate was found in southern France (Pascal et al., 2013). Compared with the reference concentration, the RR were 1.13 [0.94–1.37] and 1.26 [1.02–1.57] for medium and high concentrations in men, respectively, and 1.38 [1.04–1.83] and 1.54 [1.14–2.10] in women, respectively. Together with these literature data, our present results suggest that some components of air pollution may increase the risk of CHD.

To the best of our knowledge, the association between exposure to metal loads and CHD has not previously been assessed in an ecological study. In general, the epidemiologic literature has focused on the concentrations of PM₁₀ and PM₂.₅, rather than the chemical composition of these particulates. In a systematic review of environmental metals and CVD, Nigra et al. highlighted the need to understand the role of metals (including exposure to metal mixtures) in the development of cardiovascular disease (Nigra et al., 2016). In the present study, we found a 17% rise in CHD incidence risk for the T3 of copper, a 13% rise for palladium and an 11% rise for nickel. Mechanistically, the elevated CHD risk might be due to the known adverse effects on intracellular and extracellular structures of an imbalance in the production and detoxification of reactive oxygen species. These consequences include greater lipid peroxidation, cell membrane damage, DNA damage, and oxidation of amino acids in proteins, and therefore change in these components’ conformation and function. Oxidative modifications are considered to be early events in cardiovascular system dysfunction (Solenskova et al., 2014).

### Table 2

| Environmental indicators | RR   | 95% BCI   | Trend (p) |
|--------------------------|------|----------|-----------|
| PM₁₀                     | T1-reference | 1.00 | [0.97–1.17] | 0.022 |
|                         | T2   | 1.06     | [1.00–1.23] | |
|                         | T3   | 1.11     | [0.99–1.22] | |
| NO₂                     | T1-reference | 1.00 | [0.91–1.12] | 0.036 |
|                         | T2   | 1.05     | [0.95–1.16] | |
|                         | T3   | 1.10     | [0.99–1.22] | |
| Aluminium                | T1-reference | 1.00 | [0.89–1.12] | 0.572 |
|                         | T2   | 1.01     | [0.91–1.12] | |
|                         | T3   | 1.00     | [0.89–1.12] | |
| Arsenic                 | T1-reference | 1.00 | [0.89–1.10] | 0.618 |
|                         | T2   | 0.99     | [0.89–1.10] | |
|                         | T3   | 0.99     | [0.89–1.10] | |
| Beryllium               | T1-reference | 1.00 | [0.85–1.07] | 0.969 |
|                         | T2   | 0.95     | [0.80–1.01] | |
|                         | T3   | 0.90     | [0.80–1.01] | |
| Cadmium                | T1-reference | 1.00 | [0.99–1.20] | 0.009 |
|                         | T2   | 1.09     | [1.01–1.28] | |
|                         | T3   | 1.14     | [1.01–1.28] | |
| Cobalt                  | T1-reference | 1.00 | [0.86–1.05] | 0.537 |
|                         | T2   | 0.95     | [0.90–1.10] | |
|                         | T3   | 1.00     | [0.90–1.10] | |
| Chromium               | T1-reference | 1.00 | [0.92–1.13] | 0.673 |
|                         | T2   | 1.02     | [0.89–1.09] | |
|                         | T3   | 0.98     | [0.89–1.09] | |
| Copper                 | T1-reference | 1.00 | [0.98–1.20] | 0.003 |
|                         | T2   | 1.08     | [1.05–1.31] | |
|                         | T3   | 0.99     | [0.87–1.07] | |
| Mercury               | T1-reference | 1.00 | [0.95–1.17] | 0.213 |
|                         | T2   | 0.96     | [0.94–1.15] | |
|                         | T3   | 1.04     | [0.94–1.15] | |
| Manganese             | T1-reference | 1.00 | [0.98–1.21] | 0.033 |
|                         | T2   | 1.09     | [1.00–1.23] | |
|                         | T3   | 1.11     | [1.00–1.23] | |
| Nickel                | T1-reference | 1.00 | [0.99–1.24] | 0.060 |
|                         | T2   | 1.09     | [0.97–1.24] | |
|                         | T3   | 1.10     | [0.97–1.24] | |
| Lead                  | T1-reference | 1.00 | [0.99–1.24] | 0.032 |
|                         | T2   | 1.09     | [1.00–1.29] | |
|                         | T3   | 1.11     | [1.00–1.29] | |
| Palladium             | T1-reference | 1.00 | [0.99–1.24] | 0.162 |
|                         | T2   | 1.11     | [1.05–1.29] | |
|                         | T3   | 1.13     | [1.04–1.19] | |
| Antimony              | T1-reference | 1.00 | [0.97–1.22] | 0.317 |
|                         | T2   | 0.99     | [0.92–1.18] | |
|                         | T3   | 1.04     | [0.92–1.18] | |
| Titanium              | T1-reference | 1.00 | [0.98–1.19] | 0.160 |
|                         | T2   | 0.98     | [0.95–1.17] | |
|                         | T3   | 0.96     | [0.95–1.17] | |
| Vanadium              | T1-reference | 1.00 | [0.97–1.17] | 0.156 |
|                         | T2   | 1.07     | [0.97–1.17] | |
|                         | T3   | 1.06     | [0.95–1.18] | |
| Zinc                 | T1-reference | 1.00 | [0.97–1.18] | 0.592 |
|                         | T2   | 1.07     | [0.97–1.18] | |
|                         | T3   | 1.06     | [0.95–1.18] | |
| Dust                  | T1-reference | 1.00 | [0.87–1.06] | 0.808 |
|                         | T2   | 0.96     | [0.88–1.10] | |
|                         | T3   | 0.99     | [0.88–1.10] | |
| Eutrophication         | T1-reference | 1.00 | [0.87–1.07] | 0.808 |
4.3. The influence of road traffic

The individual indicators associated with CHD incidence rates (i.e. PM_{10}, NO_{2}, copper, cadmium, nickel, and palladium) may have a common origin in urbanized areas: road traffic emissions. While NO_{2} is primarily released into the air by the combustion engines of motor vehicles, metals can account for a large proportion of PMs in urban areas because particulate emissions near roads are also due to the wear of brakes, tires, other vehicle components and the road surface, as well as exhaust emissions (Jandacka et al., 2017). In the present study, these indicators were strongly correlated with SEnv, the highest values of which were observed close to main roads. We hypothesize that SEnv reflects a major influence of road traffic in the Lille urban area, a major agglomeration located at the crossroads of several European freight routes. These large flows of heavy goods vehicles are combined with large numbers of cars, as people commute to work. Thus, road traffic is likely to make the most important contribution to people's exposure in such urbanized areas.

4.4. Strengths and limitations

The present analysis was based on data on 3268 incident cases of CHD recorded over a 4-year period in a general population CHD registry. Our results demonstrate the utility of these monitoring tools from an environmental health perspective. The study area is a densely populated metropolis with both urban and rural neighbourhoods, and a complex mixture of low- and high-level air pollutants. The healthcare supply is dense, and so lack of access is unlikely to have an effect on the incidence of CHD. We used recently developed, validated statistical methods in spatial epidemiology. Our approach to air pollution is novel because we used data from lichen and plant biomonitoring, and a composite pollution index. Environmental biomonitoring might be able to track cumulative exposure over several years, and thus reflect the overall effects of environmental contamination. Consistent with other authors, our findings support the use of environmental biomonitoring as a tool to assess health effects of air pollution (Lequy et al., 2019). The exposure assessed by this approach can therefore be considered to have occurred before the observed health events.

Caution must be taken when building composite indices (Burgess et al., 2017). The environmental score calculated in this study considers cumulative exposure to 20 atmospheric pollutants, including NO_{2}, particles, and heavy metals. These data came from different sources, and were provided in various formats and units and on various spatiotemporal scales. However, the methodology used to design our score helps to ensure interoperability. Although standard Principal Component Analysis (PCA) is a robust statistical methodology to derive composite index from multivariate data, this leads a risk of overrepresentation of some pollutants compared to others. As we do not know which potential toxic effects each individual pollutant has on CHD, we favored rank normalization and unweighted aggregation for an exploratory research. Through the sum of ranks, territories that accumulate high levels of contamination for all pollutants are identified as hot spots. This method guarantees the equal weighting of each variable in the overall score, regardless of the data distribution and variance. Furthermore, this method may not capture the spatial structure of each individual pollutant, and spatial autocorrelation. Geographically weighted PCA or PCA with spatial autocorrelation appears to be useful statistical techniques for these purposes (Demsar et al., 2013), but these consequently involve a weighted aggregation.

We could not take account of certain individual risk factors for CHD, such as smoking or diet. However, these factors were indirectly involved by the FDep index (Kleinschmidt et al., 1995). We did not have data on the incident cases' workplaces, which prevented us from assessing their exposure to air pollution during the day. According, our consideration that patients were exposed only at their place of residence constitutes a potential source of ecological bias. Although we considered chronic exposure at a high level of spatial resolution, our present results should be interpreted accordingly.

5. Conclusion

In a fine-scale geographic analysis, we observed an association between exposure to multiple environmental pollutants (as assessed with a composite air pollution index) and CHD incidence, independently of social deprivation status. Our results are consistent with an influence of road traffic on the cardiovascular risk in urban areas. Populations living in neighbourhoods close to high-traffic roads are more exposed to multiple air pollutants, and have a greater risk of developing cardiovascular complications. These risks appear to be related to metal pollutants as well as to more commonly studied pollutants like NO_{2}, PM_{10} and PM_{2.5}.

As air pollution and its impacts are major public health issues in Europe, our results emphasize the likely importance of urban emission reduction measures in general and road traffic reduction measures in particular.

Future studies should consider not only exposure to multiple air pollutants but also exposure to other burdens, such as noise, urban heat, and soil pollution. The living environment might also be a source of health benefits (Bixby et al., 2015). Thus, future studies on environmental amenities or ecosystem services might provide a better understanding of the factors underlying the observed spatial variability in the CHD risk.

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.

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Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.scitotenv.2020.136608.

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