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1 **Exposure to multiple air pollutants and the incidence of coronary**  
2 **heart disease: a fine-scale geographic analysis**

3

4 Florent Occelli<sup>1</sup>, Caroline Lanier<sup>1</sup>, Damien Cuny<sup>1</sup>, Annabelle Deram<sup>1</sup>, Julie Dumont<sup>2</sup>, Philippe  
5 Amouyel<sup>2</sup>, Michèle Montaye<sup>2</sup>, Luc Dauchet<sup>2</sup>, Jean Dallongeville<sup>2</sup>, Michaël Genin<sup>3</sup>

6

7 <sup>1</sup> Univ. Lille, CHU Lille, Institut Pasteur de Lille, EA 4483 IMPECS (IMPact of Environmental  
8 ChemicalS on human health), F-59000 Lille, France

9 <sup>2</sup> Univ. Lille, CHU Lille, Institut Pasteur de Lille, Inserm UMR1167 RID-AGE (Risk Factors and  
10 Molecular Determinants of Aging-Related Diseases), F-59000 Lille, France

11 <sup>3</sup> Univ. Lille, EA 2694 - Santé Publique épidémiologie et qualité des soins, F-59000 Lille, France

12

13 **Corresponding author**

14 Florent Occelli

15 ORCID: 0000-0001-7478-7000

16 florent.occelli@univ-lille.fr

17 Laboratoire des Sciences Végétales et Fongiques – Faculté de Pharmacie

18 3 rue du Pr Laguesse BP83, 59006 Lille cedex

19

## 20 **Abstract**

21 Geographical variations in cardiovascular disease rates have been linked to individual air pollutants.  
22 Investigating the relation between cardiovascular disease and exposure to a complex mixture of air  
23 pollutants requires holistic approaches. We assessed the relationship between exposure to multiple air  
24 pollutants and the incidence of coronary heart disease (CHD) in a general population sample. We  
25 collected data in the Lille MONICA registry (2008-2011) on 3,268 incident cases (age range: 35-74).  
26 Based on 20 indicators, we derived a composite environmental score (SEnv) for cumulative exposure  
27 to air pollution. Poisson regression models were used to analyse associations between CHD rates on  
28 one hand and SEnv and each single indicator on the other (considered in tertiles, where T3 is the most  
29 contaminated). We adjusted models for age, sex, area-level social deprivation, and neighbourhood  
30 spatial structure. The incidence of CHD was a spatially heterogeneous ( $p=0.006$ ). There was a  
31 significant positive association between SEnv and CHD incidence (trend  $p=0.0151$ ). The relative risks  
32 [95%CI] of CHD were 1.08 [0.98-1.18] and 1.16 [1.04-1.29] for the 2<sup>nd</sup> and 3<sup>rd</sup> tertile of SEnv  
33 exposure. In the single pollutant analysis, PM<sub>10</sub>, NO<sub>2</sub>, cadmium, copper, nickel, and palladium were  
34 significantly associated with CHD rates. Multiple air pollution was associated with an increased risk  
35 of CHD. Single pollutants reflecting road traffic pollution were the most strongly associated with  
36 CHD. Our present results are consistent with the literature data on the impact of road traffic on the  
37 CHD risk in urban areas.

38

39 **Keywords:** Cardiovascular disease, heavy metal, traffic pollution, composite index, multiple exposure

40

## 41        **1. Introduction**

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

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

52        The geographical heterogeneity can be accounted for (at least in part) by disparities in socio-economic  
53        factors (such income and educational level, which are associated with inequality in health access) and  
54        in health-related behaviours (such as dietary habits, physical activity, and smoking). By using spatial  
55        ecological analyses adjusted for the socio-economic level, several research groups have reported  
56        associations between air pollution and CHD (Barceló et al., 2009; Bennett et al., 2014; Chen et al.,  
57        2015; Dijkema et al., 2016; Garcia et al., 2016; Hu and Rao, 2009; Maheswaran et al., 2005; Pannullo  
58        et al., 2016; Pascal et al., 2013) using mortality or hospitalization rates indicators. Much less is known  
59        on the effect of environmental factors on CHD incidence rates.

60        Outdoor air pollution is a complex phenomenon that involves the chronic exposure to many different  
61        pollutants (Levy et al., 2014). Hence, environmental pollution must be considered holistically and in  
62        the long term. To date, very few studies have assessed the spatialized, cumulative exposure to multiple  
63        pollutants (Bennett et al., 2014; Scarborough et al., 2012). In contrast, exposure to conventionally  
64        individual air pollutants has been intensively studied – usually by modelling annual mean  
65        concentrations of sulphur dioxide (SO<sub>2</sub>), nitrogen oxides (NO<sub>x</sub>), particulate matter (PM<sub>10</sub> and PM<sub>2.5</sub>),

66 and ozone (O<sub>3</sub>). Composite index groups together indicators of the various facets of a multiple  
67 exposure to air pollutants (European Commission et al., 2008). In this respect, spatialized composite  
68 indices are increasingly acknowledged to be valuable indicators for determining overall air quality  
69 (Occelli et al., 2016).

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

74

## 75 **2. Methods**

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

78

### 79 **2.1. Geographical area and spatial unit**

80 We studied the Lille urban area (Lille European Metropolis) in northern France, situated at the  
81 crossroads between France, the UK, and the Low Countries. This is a densely populated area (mean  
82 density: 1,821 inhabitants/km<sup>2</sup>) with high levels of socio-economic heterogeneity. Many sources of air  
83 pollutant emissions are present, including road traffic, residential heating, industry, and intensive crop  
84 farming.

85 The spatial unit used for statistical analysis (referred to as a neighbourhood in the present study)  
86 typically includes around 2,000 inhabitants, and is the unit most commonly used by the French  
87 National Institute for Statistics and Economic Studies (INSEE) for the dissemination of administrative  
88 information below the municipality level. In our study, 23 of the 496 spatial units in the Lille urban

89 area did not have a residential population and were therefore excluded: hence, 473 neighbourhoods  
90 were included in the analysis.

91

## 92 **2.2. Incident cases of CHD**

93 The data on CHD were obtained from the French WHO-MONICA population-based CHD registry for  
94 the Lille urban area. The methods for the registry have been described elsewhere (Ducimetiere , P et  
95 al., 2011). Briefly, the registry concerns men and women aged 35-74 residing in the corresponding  
96 area: there are around 220,000 inhabitants in this age range in the Lille urban area. All fatal and non-  
97 fatal CHD events whether hospitalised or not, recorded by public- or private-sector hospitals,  
98 emergency departments or at home that occurred in the study area were assessed. Multiple overlapping  
99 sources of case-ascertainment were used to document the CHD events. Medical and administrative  
100 sources were cross-checked to ensure the inclusion of all information (discharge letters, computer  
101 listings covering the diagnosis on hospital discharge, emergency department listings, death  
102 certificates, *etc.*). Cases of acute coronary events were documented on the basis of the clinical history  
103 and the hospital records. The clinical diagnoses were obtained from medical records. For each event,  
104 the patient's vital status was recorded. Information on this outcome was obtained directly from the  
105 patient's general practitioner, the city's registry office, or the national death certificate database. The  
106 causes of death were checked in hospital or autopsy records and by interviewing general practitioners.  
107 For the present study, we used data from the 2008-2011 period, which represented 5,448 cases. As  
108 secondary prevention may affect outcome, only incident coronary events were considered here -  
109 yielding a total of 3,268 cases.

110

## 111 **2.3. Ecological variables**

112 ***Deprivation index (FDep)***. The FDep index (Rey et al., 2009) was used to describe the socioeconomic  
113 characteristics for each neighbourhood. FDep is a deprivation index reflecting the spatial

114 socioeconomic heterogeneity, validated in the French context. FDep was built from four variables in  
115 the INSEE database: the median household income, the percentage of high school graduates in the  
116 population aged 15 and over, the percentage of blue-collar workers in the active population, and the  
117 unemployment rate. The higher the FDep index, the greater the level of deprivation.

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

- 122 - the annual mean modelled concentration for NO<sub>2</sub> and PM<sub>10</sub> in 2009, given a 25 x 25m grid  
123 and an atmospheric dispersion modelling system. Data were obtained from the local approved  
124 association for air quality monitoring (Atmo Nord-Pas de Calais, 2015).
- 125 - multimetal burdens, evaluated by measuring 16 metal loads having bioaccumulated in  
126 the thalli of the foliose lichen *Xanthoria parietina* over the period 2003-2009 at 120  
127 georeferenced locations, according to French standards (NF X43-904) (Occelli et al., 2016).  
128 Lichens are exclusively dependent on the atmosphere for their nourishment, and absorb  
129 pollutants in the same way as essential elements (Loppi and Nascimbene, 2010). With an  
130 annual growth rate of approximately 1 cm, the harvesting of 6 cm diameter thalli corresponded  
131 to approximately 6 years of exposure.
- 132 - eutrophication, estimated by the observation of lichen diversity and abundance in 2010 at 73  
133 georeferenced locations, according to French standards (NF EN 16413) (Cuny et al., 2018).  
134 This biological measure indicates the ecological responses of epiphytic lichens  
135 as integrators of environmental conditions (air quality, climate, etc.) over a ten-year period. A  
136 high eutrophic ratio can be considered to indicate a significant nitrogenous influence on the  
137 lichenic flora.
- 138 - dust deposition, quantified by measuring the accumulation of total dust on poplar leaves in  
139 2013 at 73 georeferenced locations, according to French standards (NF X43-905).

140 The 18 biomonitoring indicators (16 metals, eutrophication, and dust) were modelled in a 100 x 100 m  
141 grid using spatial kriging method. Lastly, all 20 indicators were aggregated to the neighbourhood level  
142 by using a mean value (Occelli et al., 2016).

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

146

## 147 **2.4. Statistical analyses**

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

152 ***Evaluation of spatial heterogeneity and spatial autocorrelation.*** The presence or absence of spatial  
153 variations in CHD incidence from one spatial unit to another was probed using the Pothoff-  
154 Whittinghill test (Pothoff and Whittinghill, 1966). The presence or absence of spatial autocorrelations  
155 among the spatial units was quantified using Moran's index (Moran, 1948) (where a value greater than  
156 0 indicates the presence of autocorrelation) and probed using Moran's test (Cliff et al., 1981).

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



165 Cameletti, 2015). Details about the previous Bayesian statistical model are provided as supplementary  
166 material.

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

170

171

## 172 **3. Results**

### 173 **3.1. Crude incidence of CHD**

174 For the present study, we used data from the 2008-2011 period, which represented 5,448 coronary  
175 events. As secondary prevention outcomes may be affected by secondary prevention, only incident  
176 events were considered in the present study. Between 2008 and 2011, 3,268 incident coronary events  
177 (2,333 (71.4%) in men and 935 (28.6%) in women) were recorded in the Lille urban area. The crude  
178 annual CHD incidence rate was 176 per 100,000 inhabitants for both sexes, 264 per 100,000 for men,  
179 and 96 per 100,000 for women. The crude CHD incidence rate increased with age (Figure 1).

180

### 181 **3.2. Geographical variation in the incidence of CHD**

182 We observed significant spatial heterogeneity in the CHD incidence rates ( $p=0.006$  in a Potthoff-  
183 Whittinghill test), together with evidence of spatial autocorrelation between the different spatial units  
184 (Moran I statistics = 0.20;  $p=0.001$ ). The age-and-gender-smoothed SIRs [95%BCI] ranged from 0.56  
185 [0.37-0.80] to 1.85 [1.29-2.56]. There were three hot spots of increased CHD incidence rates  
186 ( $SIR > 1.5$ ) in the north-east of the area and in the southern and south-eastern suburbs of the main city  
187 (Lille), and three cold spots ( $SIR < 0.75$ ) in the northwest, southwest and southeast (corresponding to

188 more rural neighbourhoods). These data revealed clear geographic heterogeneity in the CHD incidence  
189 rates (Figure 2).

190

### 191 **3.3. Geographical variations in air pollution**

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

198 The median [IQR] levels of 20 environmental indicators by SEnv tertile, and Spearman's coefficient  
199 (SC) for the correlation are shown in Table 1. The values of these indicators did not vary greatly over  
200 the study area. Most values were higher in T3 than T1. The PM<sub>10</sub> and NO<sub>2</sub> concentrations were  
201 strongly correlated with SEnv (SC>0.8; p<0.001). Medium and weak correlations were observed for  
202 total dust and eutrophication (SC: 0.40; p<0.001, and 0.13; p<0.01, respectively). The metals most  
203 strongly correlated with SEnv (p<0.001) were lead (SC: 0.50), copper (SC: 0.47), antimony (SC:  
204 0.42), zinc (SC: 0.42), palladium (SC: 0.37), chromium (SC: 0.33), and cadmium (SC: 0.32). Arsenic  
205 and cobalt were not significantly correlated with SEnv, whereas beryllium and titanium were  
206 negatively correlated with SEnv.

207

### 208 **3.4. Geographical variations in social deprivation**

209 In the Lille urban area, the FDep index ranged from -4.27 to 5.93, with a median [IQR] of 0.14 [-  
210 1.2;1.63] (Figure 3B). High deprivation areas overlapped with hot spots of CHD incidence rates in the  
211 northeast, and in the south-eastern suburbs of Lille. Cold spots of CHD incidence were characterized

212 by both low and medium levels of deprivation. The association between FDep and SEnv was not  
213 significant (SC: -0.07;  $p=0.15$ ).

214

### 215 **3.5. Association with air pollution**

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

221 In an ecological regression analysis (Figure 4, Model 1), there was a borderline association between  
222 SEnv and the CHD incidence rate (trend  $p=0.08$ ). Compared with T1 of SEnv, the RR [95%BCI] CHD  
223 was 1.12 [1.01-1.24] for T2 and 1.11 [0.99-1.25] for T3. After adjustment for the FDep index (Figure  
224 4, Model 2), there was a significant association (trend  $p=0.0151$ ) between SEnv and the CHD  
225 incidence rate (RR was 1.08 [0.98-1.18] for T2 and 1.16 [1.04-1.29] for T3). Furthermore, FDep was  
226 associated with the CHD incidence rate (trend  $p<0.0001$ ). Compared with the T1 of FDep, the RR of  
227 CHD was 1.20 [1.09-1.33] for T2 and 1.63 [1.47-1.82] for T3.

228 The association between each environmental indicator and the CHD incidence rate was evaluated in an  
229 ecological regression analysis after adjustment for FDep (Table 2). There were significant associations  
230 between the CHD incidence rate on one hand and both PM<sub>10</sub> and NO<sub>2</sub> on the other. Compared with  
231 T1, the RR ranged from 1.06 [0.97-1.17] to 1.11 [1.00-1.23] for T2 and T3 for PM<sub>10</sub> (trend  $p=0.022$ ),  
232 and from 1.05 [0.95-1.16] to 1.10 [0.99-1.22] for NO<sub>2</sub> (trend  $p=0.036$ ). Regarding the metals,  
233 significant associations were observed for copper (1.08 [0.98-1.20] for T2 and 1.17 [1.05-1.31] for T3;  
234 trend  $p=0.003$ ), cadmium (1.09 [0.99-1.20] for T2 and 1.14 [1.01-1.28] for T3; trend  $p=0.009$ ),  
235 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-  
236 1.21] for T2 and 1.11 [1.00-1.23] for T3; trend  $p=0.033$ ). We did not observe a significant association

237 between CHD and the 12 other heavy metals, dust, or eutrophication. It should be noted that after  
238 Bonferroni's correction for multiple comparisons, none of these associations were significant.

239

## 240 **4. Discussion**

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

244

### 245 **4.1. Multiple pollutant analysis, using a composite index**

246 Long-term exposure to mixtures of low-dose air pollutants have harmful effects on health (Bopp et al.,  
247 2018). However, these effects may be difficult to assess when considering conventional single-  
248 pollutant exposure because of a lack of statistical sensitivity and the multifactorial aetiology of chronic  
249 diseases.

250 Multiple exposure is rarely assessed in environmental health studies (Levy et al., 2014). Earlier reports  
251 in China have shown a positive association between the Air Pollution Index (API) and mortality rates  
252 (Li et al., 2015) or severe acute respiratory syndrome (Cui et al., 2003). However, the API does not  
253 really consider the cumulative exposure but only the effect of peak exposure to different pollutants  
254 (Thach et al., 2018). In Canada, the Air Quality Health Index (summing up the estimated health risks  
255 associated with O<sub>3</sub>, NO<sub>2</sub> and PM<sub>2.5</sub>) has been used to assess the impact of air quality on  
256 hospitalizations for asthma (To et al., 2013).

257 In contrast, very few studies have assessed the cumulative effect of several pollutants on  
258 cardiovascular disease. Bennett's application of the Air Quality Indicator (which sums the emissions  
259 of benzene, NO<sub>2</sub>, SO<sub>2</sub>, and particulates) for small areas revealed a significant positive association with  
260 heart failure morbidity and mortality across the county of Warwickshire, UK (Bennett et al., 2014).

261 Using the same indicator, Scarborough *et al.* found a small association with coronary heart mortality  
262 rates after adjustment for confounding variables among UK wards (Scarborough et al., 2012). In the  
263 present study, we calculated a composite index that provides an overall picture of air pollution. This  
264 makes it easier to integrate the complex nature of an environmental mixture into an ecological study.  
265 We found a 16% rise in the risk of incident CHD for the third tertile of SEnv, suggesting that a set of  
266 several pollutants have a cumulative impact on CHD. Taken as a whole, these data suggest that  
267 cumulative exposure to multiple low-dose air pollutants may generate cardiovascular complications.

268

#### 269 **4.2. Single-pollutant analysis**

270 In addition to the overall effect of air pollution, we found an approximately 10% rise in the risk of  
271 incident CHD for the third tertiles of PM<sub>10</sub> and NO<sub>2</sub> exposure. In agreement with these results, earlier  
272 studies have reported associations between monitored air pollutants and CHD hospitalizations and  
273 mortality rates. In the UK, Maheswaran *et al.* reported on significant elevated CHD mortality risks in  
274 the highest quintile of PM<sub>10</sub> and NO<sub>x</sub> annual concentration exposures (1.17 [1.06-1.29] and 1.08 [0.96-  
275 1.20], respectively) (Maheswaran et al., 2005). Similarly, a study in Barcelona reported a significant  
276 association between CHD mortality and high levels of NO<sub>2</sub> exposure in men (RR=1.0084 [1.0035-  
277 1.0166] for one NO<sub>2</sub> unit increment) (Barceló et al., 2009). However, the association with NO<sub>2</sub> in  
278 women and with PM<sub>10</sub> in men or women were not statistically significant. In California, a significant  
279 increment in CHD mortality rates in areas exposed to PM<sub>2.5</sub> was reported, whatever the spatial  
280 exposure model used; the RR ranged from 1.20 [1.17-1.23] to 1.28 [1.25-1.32] for each 10 µg/m<sup>3</sup>  
281 increase in concentration (Garcia et al., 2016). A significant association between the SO<sub>2</sub> concentration  
282 and the myocardial infarction hospitalization rate was found in southern France (Pascal et al., 2013).  
283 Compared with the reference concentration, the RRs were 1.13 [0.94-1.37] and 1.26 [1.02-1.57] for  
284 medium and high concentrations in men, respectively, and 1.38 [1.04-1.83] and 1.54 [1.14-2.10] in  
285 women, respectively. Together with these literature data, our present results suggest that some  
286 components of air pollution may increase the risk of CHD.

287 To the best of our knowledge, the association between exposure to metal loads and CHD has not  
288 previously been assessed in an ecological study. In general, the epidemiologic literature has focused  
289 on the concentrations of PM<sub>10</sub> and PM<sub>2.5</sub>, rather than the chemical composition of these particulates. In  
290 a systematic review of environmental metals and CVD, Nigra *et al.* highlighted the need to understand  
291 the role of metals (including exposure to metal mixtures) in the development of cardiovascular disease  
292 (Nigra et al., 2016). In the present study, we found a 17% rise in CHD incidence risk for the T3 of  
293 copper, a 14% rise for cadmium, a 13% rise for palladium and an 11% rise for nickel. Mechanistically,  
294 the elevated CHD risk might be due to the known adverse effects on intracellular and extracellular  
295 structures of an imbalance in the production and detoxification of reactive oxygen species. These  
296 consequences include greater lipid peroxidation, cell membrane damage, DNA damage, and oxidation  
297 of amino acids in proteins, and therefore change in these components' conformation and function.  
298 Oxidative modifications are considered to be early events in cardiovascular system dysfunction  
299 (Solenkova et al., 2014).

300

### 301 **4.3. The influence of road traffic**

302 The individual indicators associated with CHD incidence rates (*i.e.* PM<sub>10</sub>, NO<sub>2</sub>, copper, cadmium,  
303 nickel, and palladium) may have a common origin in urbanized areas: road traffic emissions. While  
304 NO<sub>2</sub> is primarily released into the air by the combustion engines of motor vehicles, metals can account  
305 for a large proportion of PMs in urban areas because particulate emissions near roads are also due to  
306 the wear of brakes, tires, other vehicle components and the road surface, as well as exhaust emissions  
307 (Jandacka et al., 2017). In the present study, these indicators were strongly correlated with SEnv, the  
308 highest values of which were observed close to main roads. We hypothesize that SEnv reflects a major  
309 influence of road traffic in the Lille urban area, a major agglomeration located at the crossroads of  
310 several European freight routes. These large flows of heavy goods vehicles are combined with large

311 numbers of cars, as people commute to work. Thus, road traffic is likely to make the most important  
312 contribution to people's exposure in such urbanized area.

313

#### 314 **4.4. Strengths and limitations**

315 The present analysis was based on data on 3,268 incident cases of CHD recorded over a 4-year period  
316 in a general population CHD registry. Our results demonstrate the utility of these monitoring tools  
317 from an environmental health perspective. The study area is a densely populated metropolis with both  
318 urban and rural neighbourhoods, and a complex mixture of low-level air pollutants. The healthcare  
319 supply is dense, and so lack of access is unlikely to have an effect on the incidence of CHD. We used  
320 recently develop, validated statistical methods in spatial epidemiology. Our approach to air pollution is  
321 novel because we used data from lichen and plant biomonitoring, and a composite pollution index.  
322 Environmental biomonitoring might be able to track cumulative exposure over several years, and thus  
323 reflect the overall effects of environmental contamination. Consistent with other authors, our findings  
324 support the use of environmental biomonitoring as a tool to assess health effects of air pollution  
325 (Lequy et al., 2019). The exposure assessed by this approach can therefore be considered to have  
326 occurred before the observed health events.

327 Caution must be taken when building composite indices (Burgass et al., 2017). The environmental  
328 score calculated in this study considers cumulative exposure to 20 atmospheric pollutants, including  
329 NO<sub>2</sub>, particles, and heavy metals. These data came from different sources, and were provided in  
330 various formats and units and on various spatiotemporal scales. However, the methodology used to  
331 design our score helps to ensure interoperability. Although standard Principal Component Analysis  
332 (PCA) is a robust statistical methodology to derive composite index from multivariate data, this leads  
333 a risk of overrepresentation of some pollutants compared to others. As we do not know which  
334 potential toxic effects each individual pollutant has on CHD, we favored rank normalization and  
335 unweighted aggregation for an explorative research. Through the sum of ranks, territories that  
336 accumulate high levels of contamination for all pollutants are identified as hot spots. This method

337 guarantees the equal weighting of each variable in the overall score, regardless of the data distribution  
338 and variance. Furthermore, this method may not capture the spatial structure of each individual  
339 pollutant, and spatial autocorrelation. Geographically weighted PCA or PCA with spatial  
340 autocorrelation appears to be useful statistical techniques for these purposes (Demšar et al., 2013), but  
341 these consequently involve a weighted aggregation.

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

348

## 349 **5. Conclusion**

350 In a fine-scale geographic analysis, we observed an association between exposure to multiple  
351 environmental pollutants (as assessed with a composite air pollution index) and CHD incidence,  
352 independently of social deprivation status. Our results are consistent with an influence of road traffic  
353 on the cardiovascular risk in urban areas. Populations living in neighbourhoods close to high-traffic  
354 roads are more exposed to multiple air pollutants, and have a greater risk of developing cardiovascular  
355 complications. These risks appear to be related to metal pollutants as well as to more commonly  
356 studied pollutants like NO<sub>2</sub>, PM<sub>10</sub> and PM<sub>2.5</sub>.

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

360 Future studies should consider not only exposure to multiple air pollutants but also exposure to other  
361 burdens, such as noise, urban heat, and soil pollution. The living environment might also be a source



362 of health benefits (Bixby et al., 2015). Thus, future studies on environmental amenities or ecosystem  
363 services might provide a better understanding of the factors underlying the observed spatial variability  
364 in the CHD risk.

365

366

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370

### 371 **Competing Interests**

372 The authors declare that they have no known competing financial interests or personal relationships  
373 that could have appeared to influence the work reported in this paper.

374

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505 **Figure captions**

506 **Figure 1.** Crude mean incidence of CHD by age class and by sex (2008-2011)

507 **Figure 2.** Smoothed age- and-gender-standardized incidence ratios for CHD (2008-2011)

508 **Figure 3.** The spatial distributions of SEnv (A) and FDep (B) in the area covered by the MONICA  
509 registry.

510 **Figure 4.** The relative risk [95%BCI] of CHD by SEnv tertile (Model 1) and by SEnv and FDep  
511 tertiles (Model 2), in a Bayesian ecological regression.

512

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514 **Table 1.** Median [IQR] levels of the 20 environmental indicators (in  $\mu\text{g}/\text{m}^3$  for  $\text{PM}_{10}$  and  $\text{NO}_2$ , and  
515  $\mu\text{g}/\text{g}$  for metals and dust) by SEnv tertile (T1, T2 and T3), and Spearman's coefficient for the  
516 correlation.

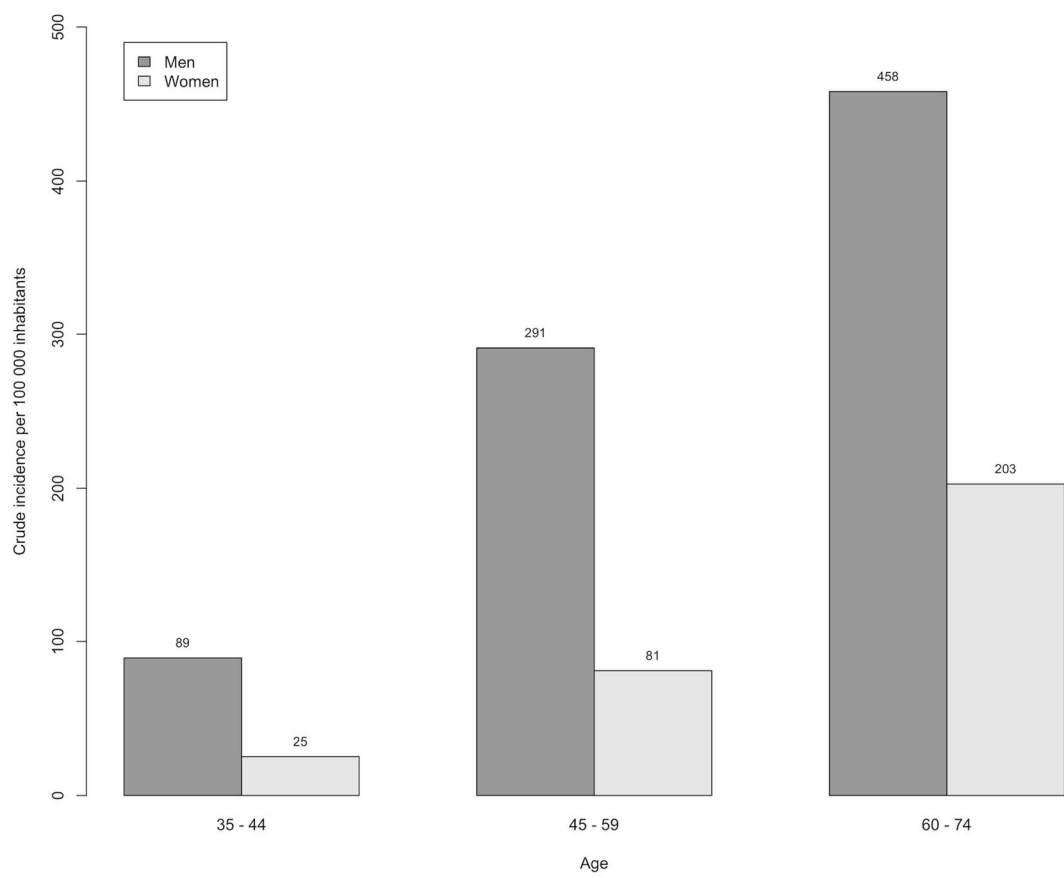
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518 adjusted for FDep.

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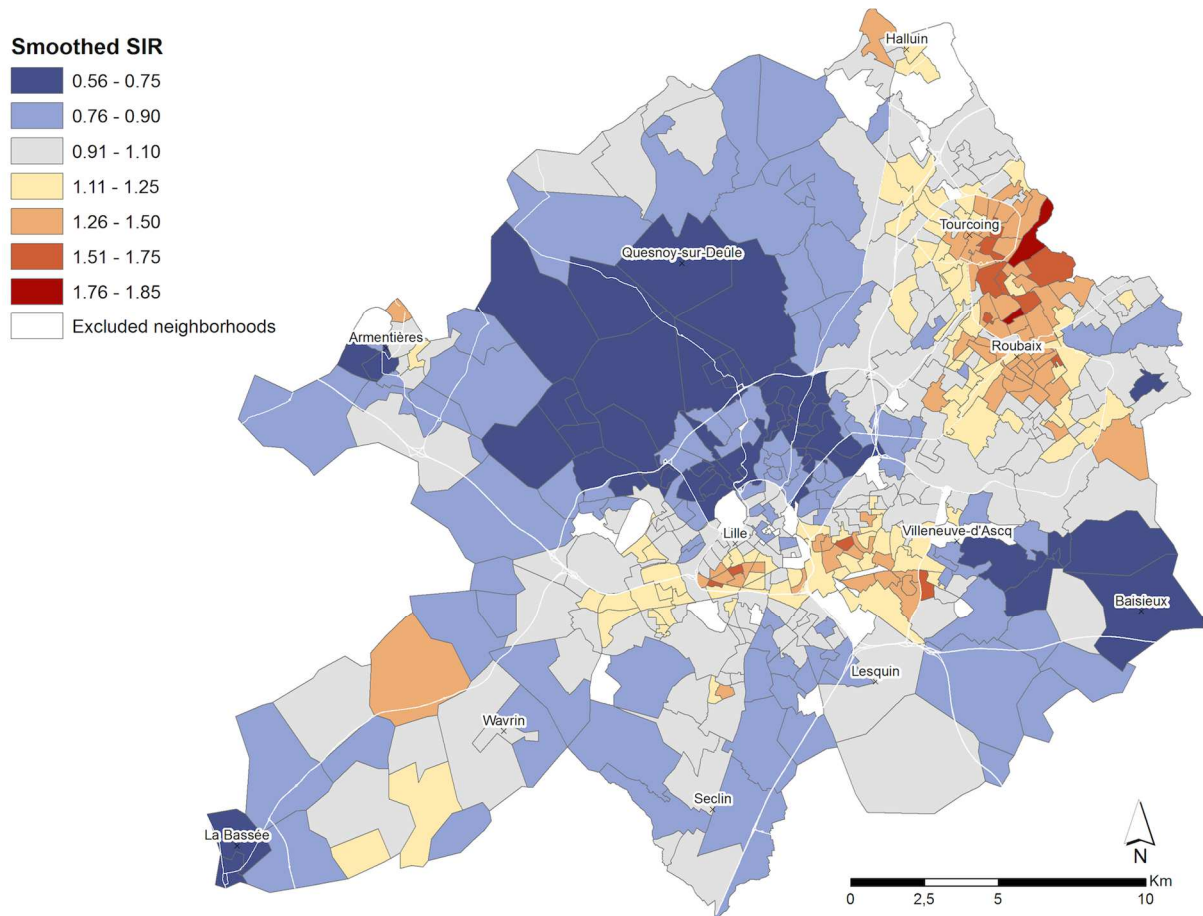
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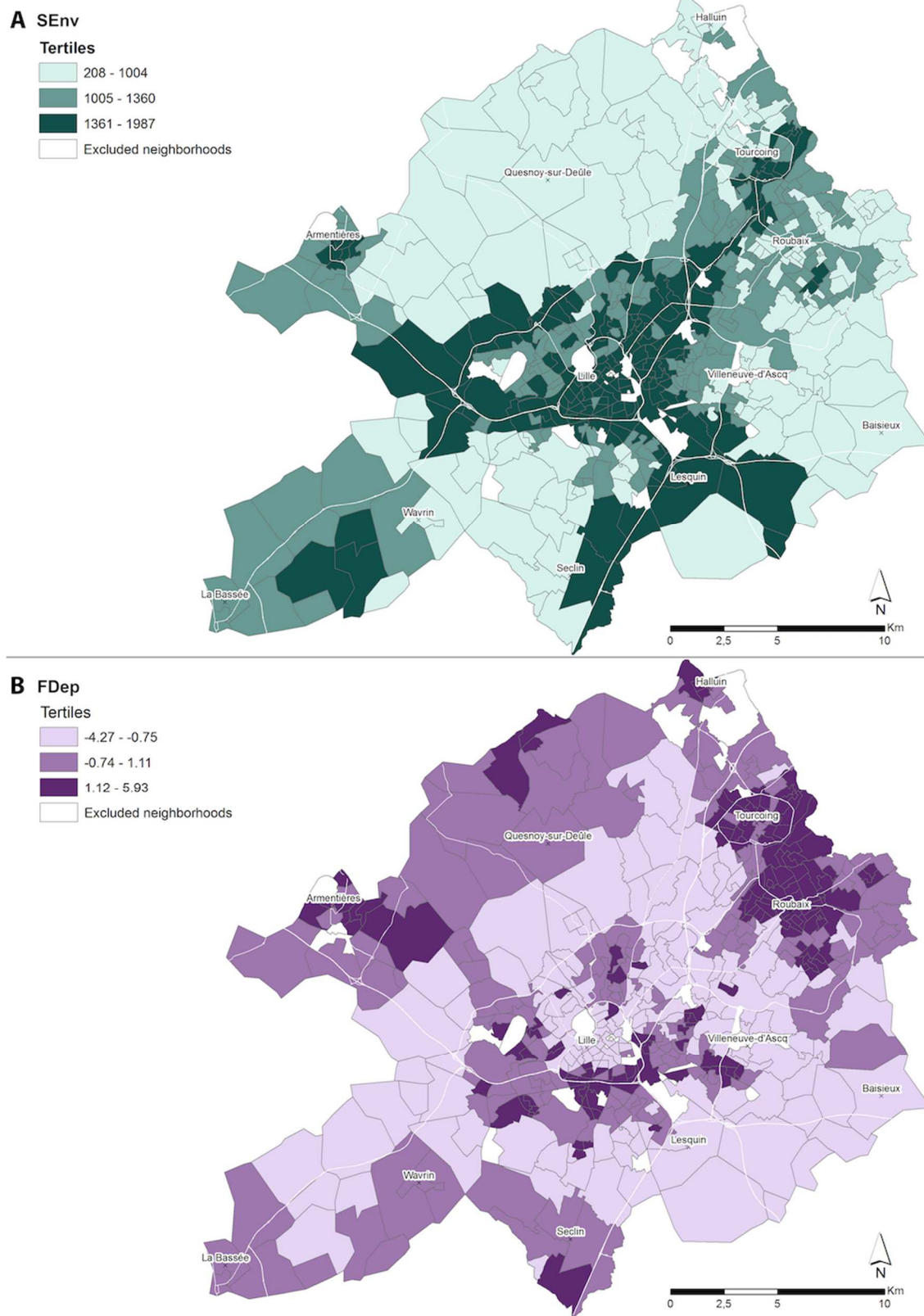


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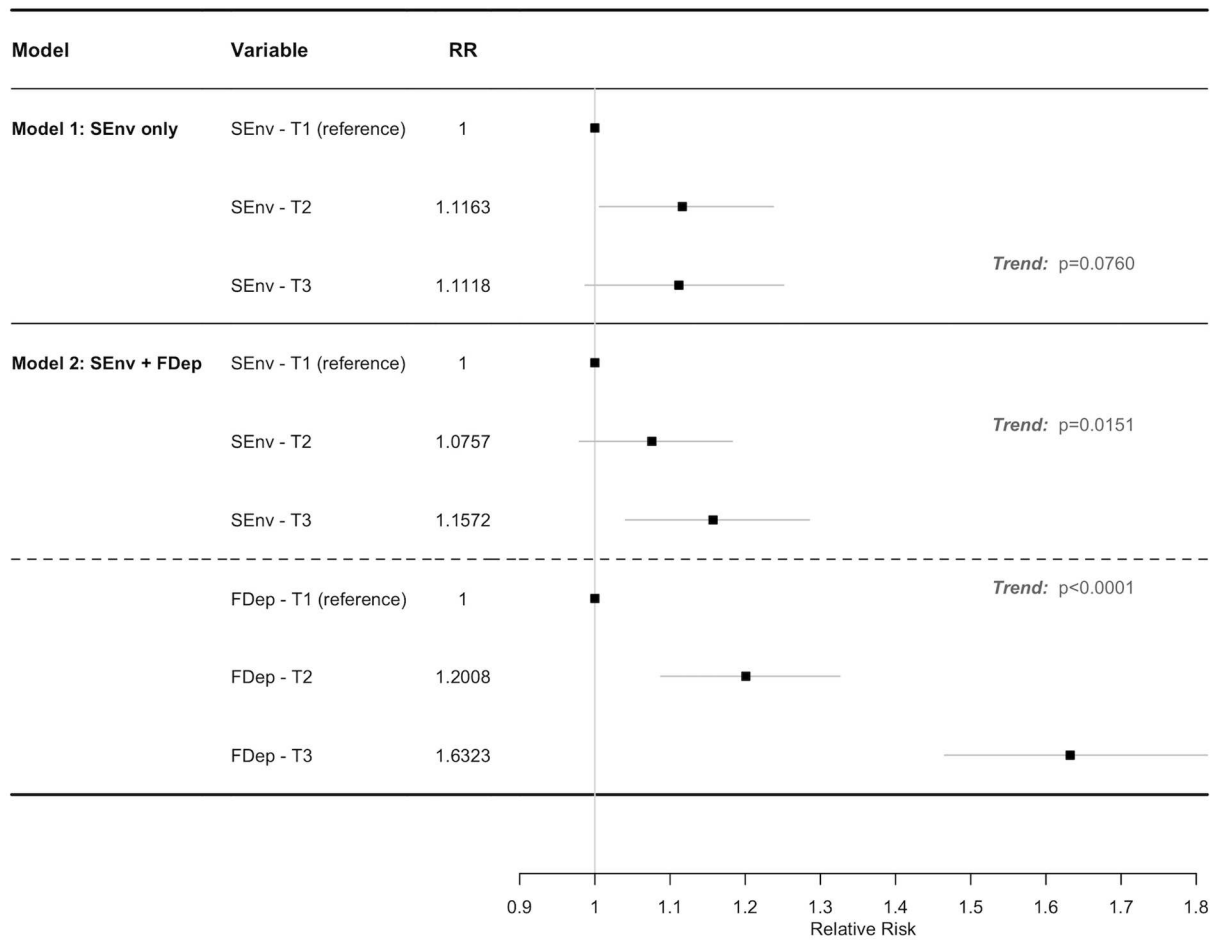
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538 correlation.

<b>Environmental indicator</b>	<b>All</b> n=473	<b>T1 [208-1010]</b> n=158	<b>T2 [1010-1360]</b> n=158	<b>T3 [1360-1987]</b> n=157	<b>Spearman coefficient</b>
<b>PM<sub>10</sub></b>	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***
<b>NO<sub>2</sub></b>	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***
<b>Aluminium</b>	1001 [901;1176]	970 [848;1277]	976 [874;1094]	1083 [991;1185]	0.20***
<b>Arsenic</b>	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
<b>Beryllium</b>	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***
<b>Cadmium</b>	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***
<b>Cobalt</b>	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
<b>Chromium</b>	4.35 [3.63;4.96]	3.97 [2.89;4.76]	4.23 [3.66;4.88]	4.69 [4.21;5.12]	0.33***
<b>Copper</b>	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***
<b>Mercury</b>	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***
<b>Manganese</b>	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***
<b>Nickel</b>	2.86 [2.52;3.18]	2.72 [2.26;3.03]	2.94 [2.56;3.23]	2.92 [2.66;3.25]	0.22***
<b>Lead</b>	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***
<b>Palladium</b>	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***
<b>Antimony</b>	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***
<b>Titanium</b>	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***
<b>Vanadium</b>	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*
<b>Zinc</b>	113 [95.9;131]	102 [78.2;121]	110 [96.9;125]	126 [108;139]	0.42***
<b>Dust</b>	1973 [1847;2084]	1895 [1803;1992]	1978 [1843;2085]	2041 [1951;2133]	0.40***
<b>Eutrophication</b>	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**

\* $p < 0.05$ ; \*\* $p < 0.01$ ; \*\*\* $p < 0.001$

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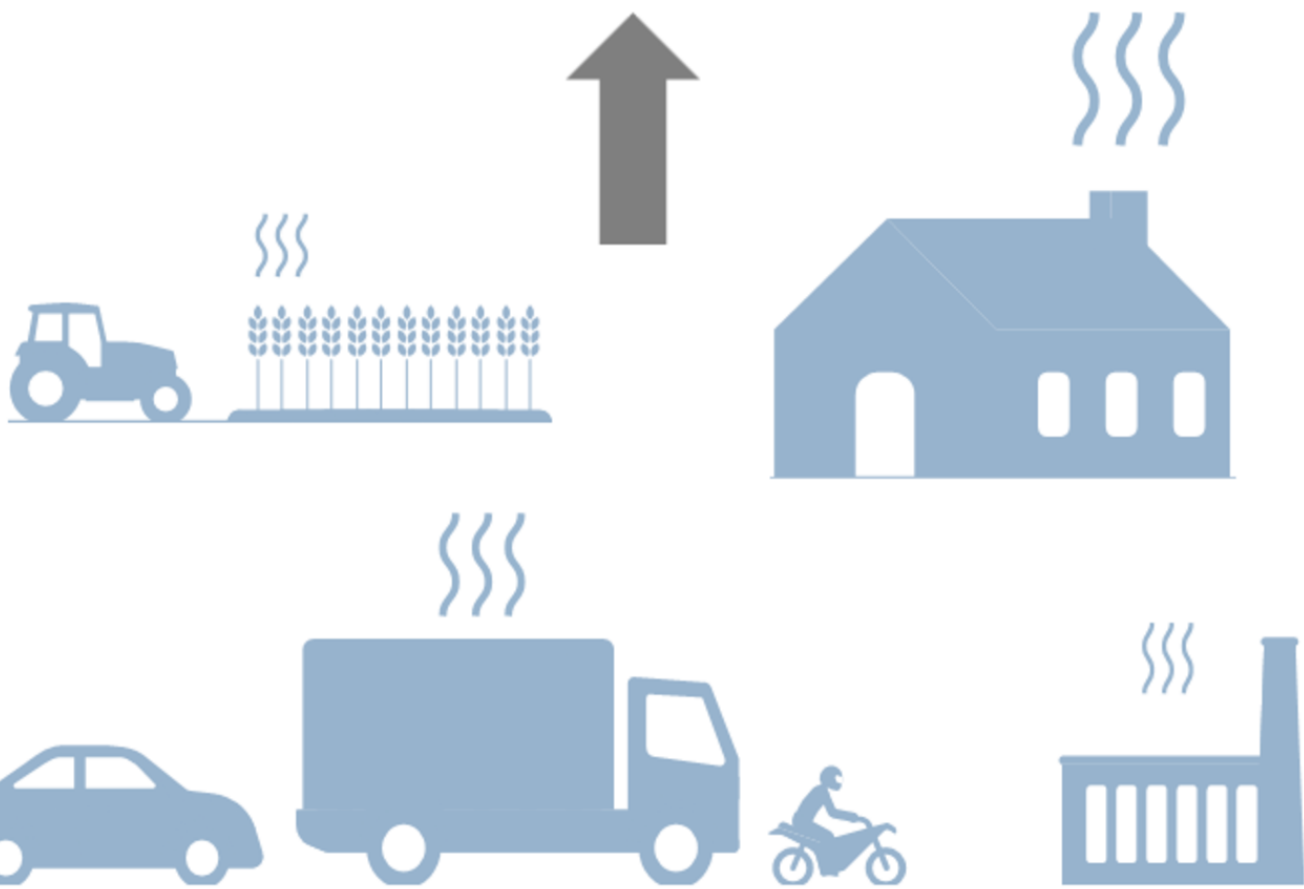
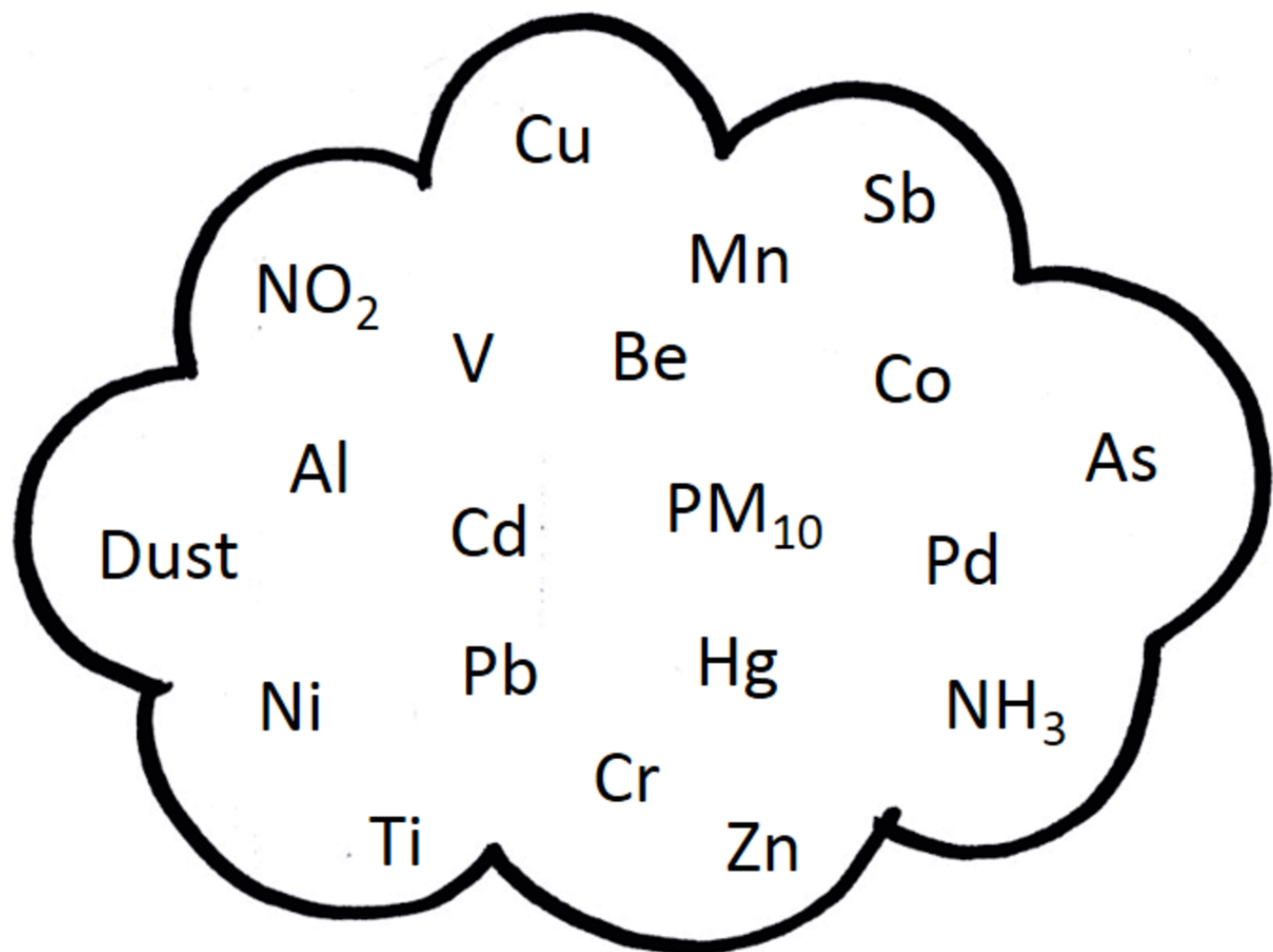
541 **Table 2.** The relative risk [95%BCI] of CHD by tertiles of the 20 individual environmental indicators,  
 542 adjusted for FDep.

<b>Environmental indicators</b>		<b>RR</b>	<b>95%BCI</b>	<b>Trend (p)</b>
PM <sub>10</sub>	<i>T1-reference</i>	1.00		
	<i>T2</i>	1.06	[0.97-1.17]	<b>0.022</b>
	<i>T3</i>	1.11	[1.00-1.23]	
NO <sub>2</sub>	<i>T1-reference</i>	1.00		
	<i>T2</i>	1.05	[0.95-1.16]	<b>0.036</b>
	<i>T3</i>	1.10	[0.99-1.22]	
Aluminium	<i>T1-reference</i>	1.00		
	<i>T2</i>	1.01	[0.91-1.12]	0.572
	<i>T3</i>	1.00	[0.89-1.12]	
Arsenic	<i>T1-reference</i>	1.00		
	<i>T2</i>	0.99	[0.89-1.09]	0.618
	<i>T3</i>	0.99	[0.89-1.10]	
Beryllium	<i>T1-reference</i>	1.00		
	<i>T2</i>	0.95	[0.85-1.07]	0.969
	<i>T3</i>	0.90	[0.80-1.01]	
Cadmium	<i>T1-reference</i>	1.00		
	<i>T2</i>	1.09	[0.99-1.20]	<b>0.009</b>
	<i>T3</i>	1.14	[1.01-1.28]	
Cobalt	<i>T1-reference</i>	1.00		
	<i>T2</i>	0.95	[0.86-1.05]	0.537
	<i>T3</i>	1.00	[0.90-1.10]	
Chromium	<i>T1-reference</i>	1.00		
	<i>T2</i>	1.02	[0.92-1.13]	0.673
	<i>T3</i>	0.98	[0.89-1.09]	
Copper	<i>T1-reference</i>	1.00		
	<i>T2</i>	1.08	[0.98-1.20]	<b>0.003</b>
	<i>T3</i>	1.17	[1.05-1.31]	
Mercury	<i>T1-reference</i>	1.00		
	<i>T2</i>	0.97	[0.87-1.07]	0.630
	<i>T3</i>	0.99	[0.89-1.10]	
Manganese	<i>T1-reference</i>	1.00		
	<i>T2</i>	1.06	[0.95-1.17]	0.213
	<i>T3</i>	1.04	[0.94-1.15]	
Nickel	<i>T1-reference</i>	1.00		
	<i>T2</i>	1.09	[0.98-1.21]	<b>0.033</b>
	<i>T3</i>	1.11	[1.00-10.23]	
Lead	<i>T1-reference</i>	1.00		
	<i>T2</i>	1.09	[0.99-1.20]	0.060
	<i>T3</i>	1.10	[0.97-1.24]	
Palladium	<i>T1-reference</i>	1.00		
	<i>T2</i>	1.11	[0.99-1.24]	<b>0.032</b>
	<i>T3</i>	1.13	[1.00-1.29]	
Antimony	<i>T1-reference</i>	1.00		
	<i>T2</i>	1.16	[1.05-1.29]	0.162
	<i>T3</i>	1.06	[0.94-1.19]	
Titanium	<i>T1-reference</i>	1.00		
	<i>T2</i>	1.09	[0.97-1.22]	0.317
	<i>T3</i>	1.04	[0.92-1.18]	
Vanadium	<i>T1-reference</i>	1.00		
	<i>T2</i>	0.98	[0.88-1.09]	0.160

	<i>T3</i>	1.06	[0.95-1.17]	
Zinc	<i>T1-reference</i>	1.00		
	<i>T2</i>	1.07	[0.97-1.17]	0.156
	<i>T3</i>	1.06	[0.95-1.18]	
Dust	<i>T1-reference</i>	1.00		
	<i>T2</i>	0.96	[0.87-1.06]	0.592
	<i>T3</i>	0.99	[0.88-1.10]	
Eutrophication	<i>T1-reference</i>	1.00		
	<i>T2</i>	1.03	[0.93-1.15]	0.808
	<i>T3</i>	0.95	[0.85-1.07]	

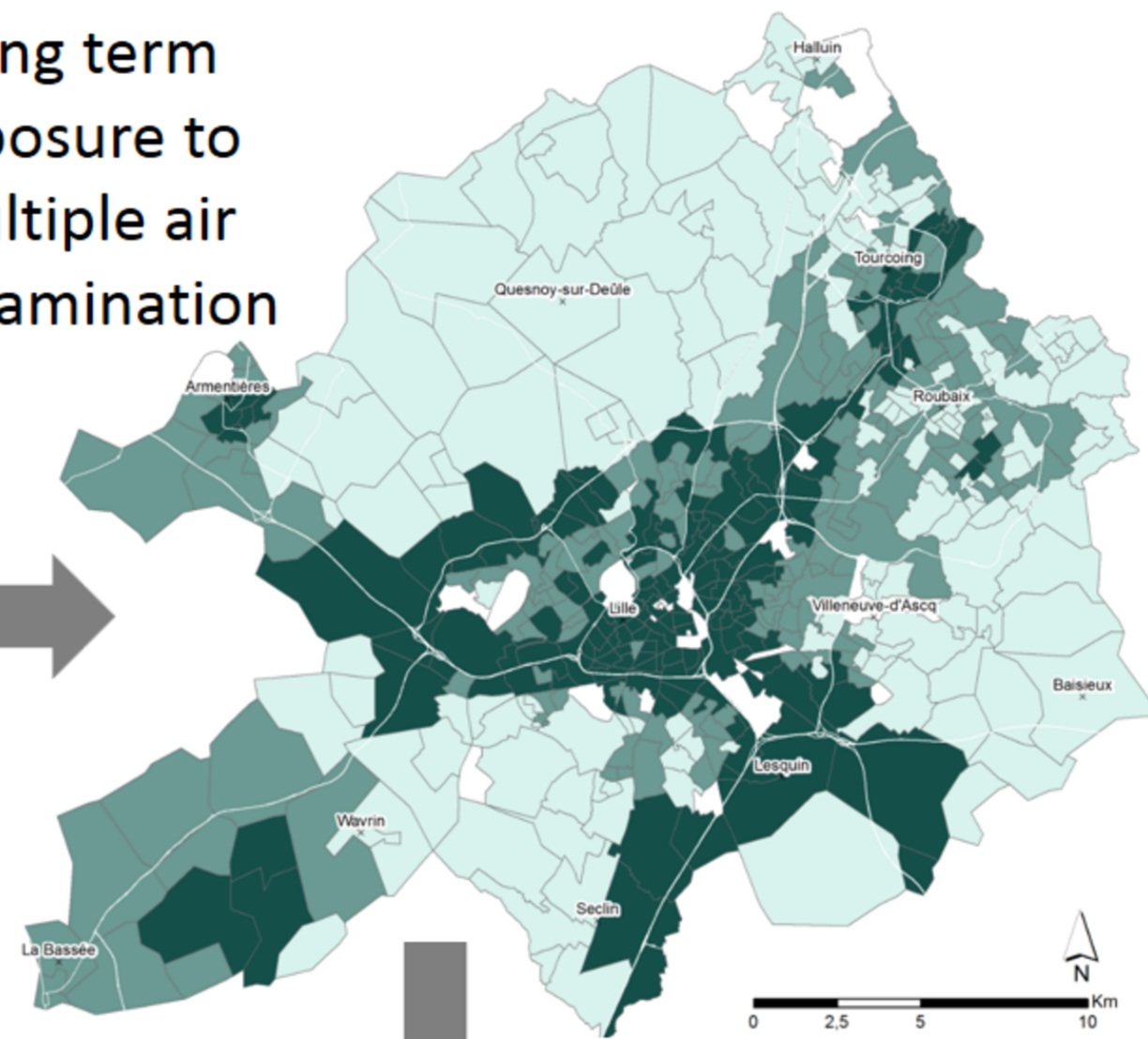
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Air emissions in European agglomerations

Long term exposure to multiple air contamination



Coronary heart disease

