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

3

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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 2nd and 3rd tertile of SEnv
33 exposure. In the single pollutant analysis, PM₁₀, NO₂, 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 (SO₂), nitrogen oxides (NO_x), particulate matter (PM₁₀ and PM_{2.5}),

66 and ozone (O₃). 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/km²) 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 NO₂ and PM₁₀ 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 PM₁₀ and NO₂ 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 PM₁₀ and NO₂ 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 PM₁₀ (trend $p=0.022$),
232 and from 1.05 [0.95-1.16] to 1.10 [0.99-1.22] for NO₂ (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 O₃, NO₂ and PM_{2.5}) 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, NO₂, SO₂, 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 PM₁₀ and NO₂ 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 PM₁₀ and NO_x 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 NO₂ exposure in men (RR=1.0084 [1.0035-
277 1.0166] for one NO₂ unit increment) (Barceló et al., 2009). However, the association with NO₂ in
278 women and with PM₁₀ in men or women were not statistically significant. In California, a significant
279 increment in CHD mortality rates in areas exposed to PM_{2.5} 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/m³
281 increase in concentration (Garcia et al., 2016). A significant association between the SO₂ 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 PM₁₀ and PM_{2.5}, 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.* PM₁₀, NO₂, copper, cadmium,
303 nickel, and palladium) may have a common origin in urbanized areas: road traffic emissions. While
304 NO₂ 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 NO₂, 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 NO₂, PM₁₀ and PM_{2.5}.

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.

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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.

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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)

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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

513 **Table captions**

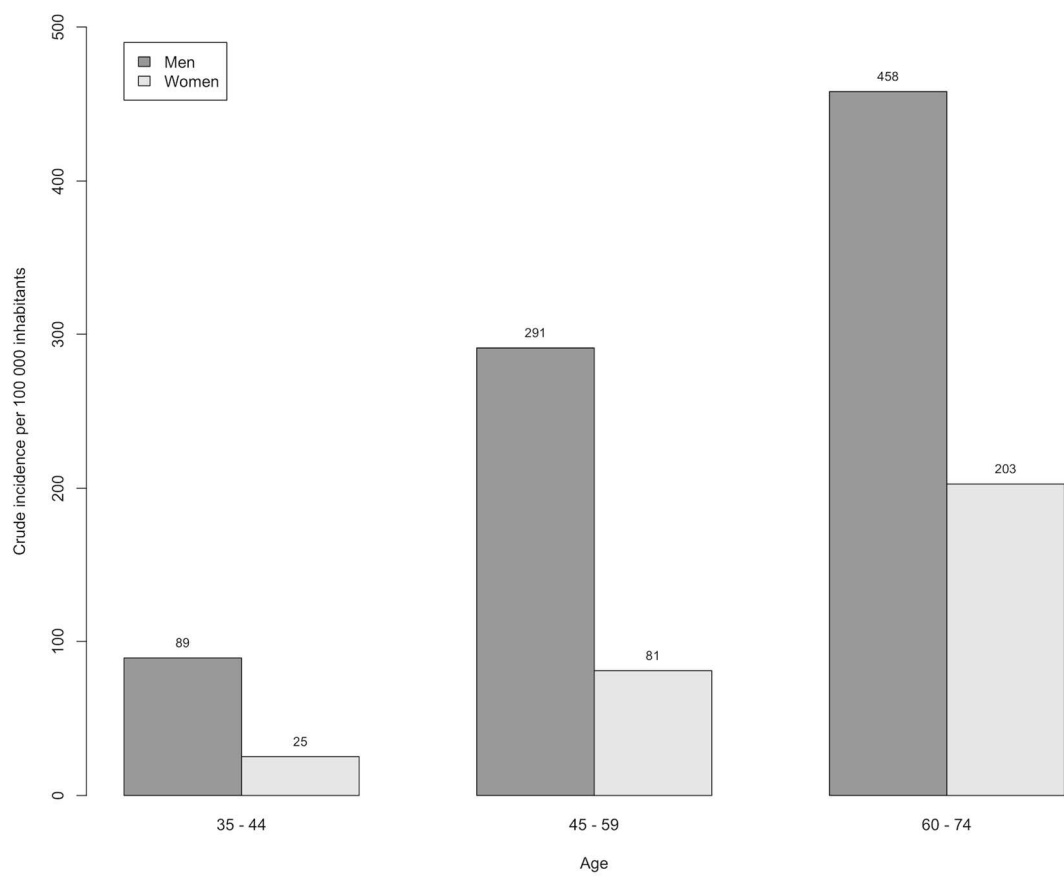
514 **Table 1.** Median [IQR] levels of the 20 environmental indicators (in $\mu\text{g}/\text{m}^3$ for PM_{10} and NO_2 , and
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516 correlation.

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518 adjusted for FDep.

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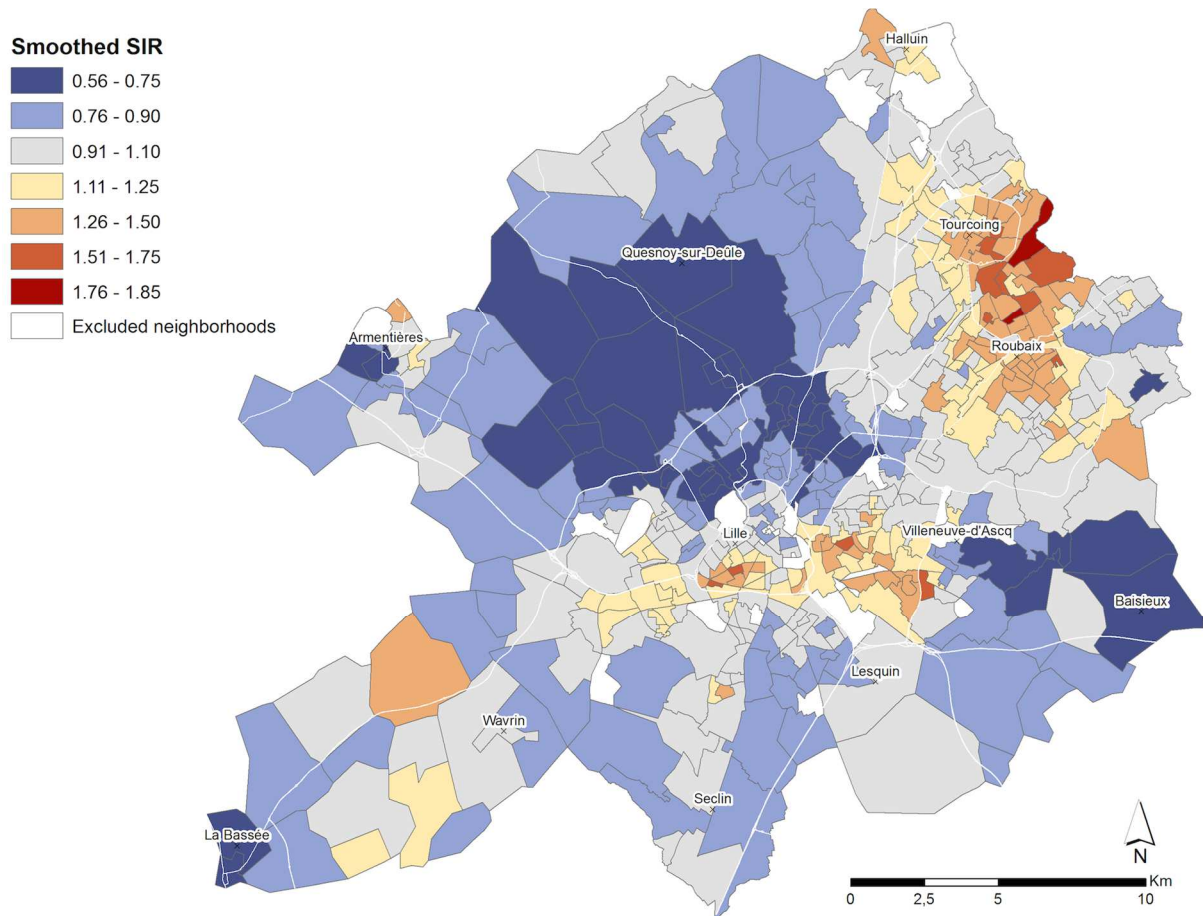
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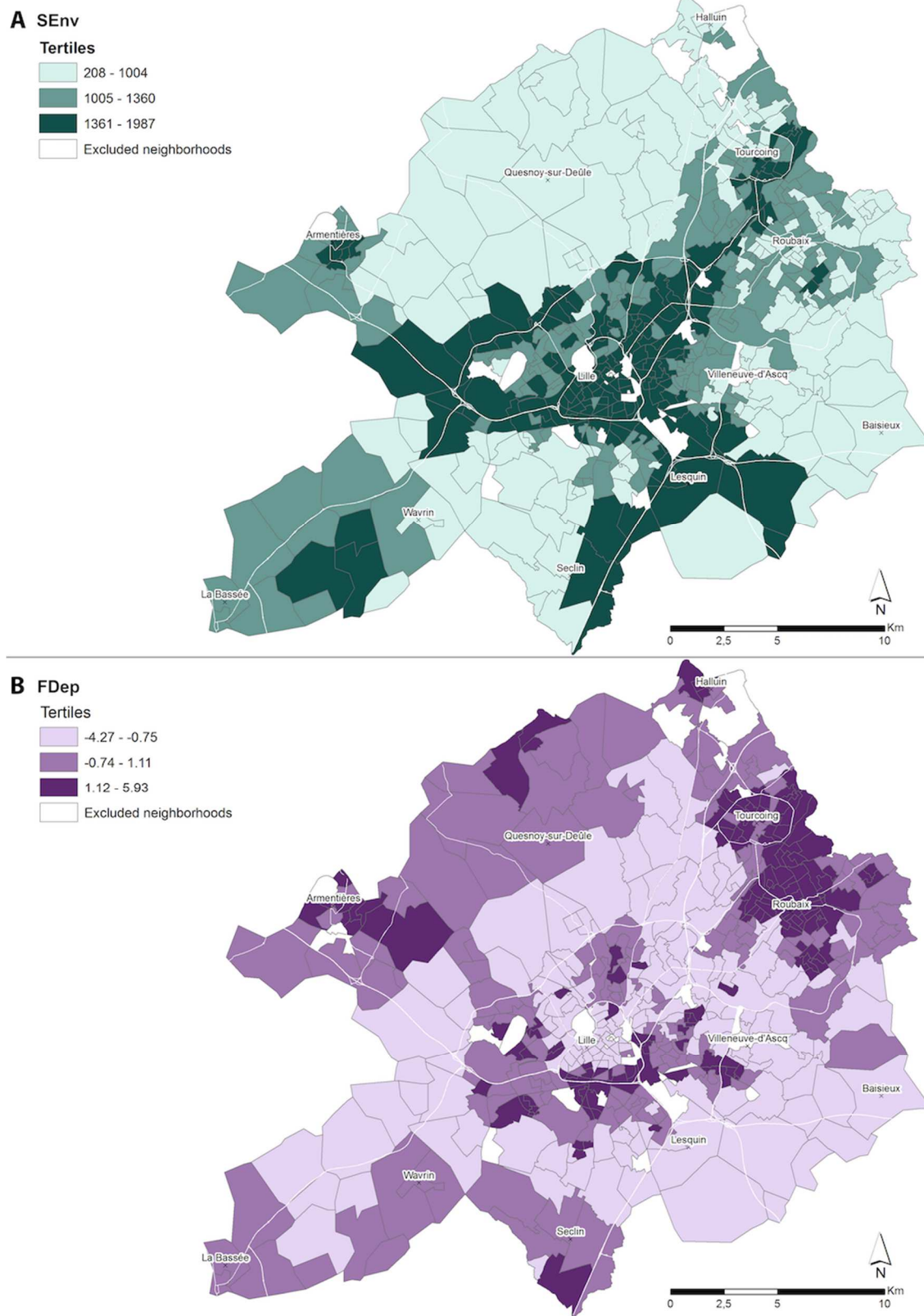


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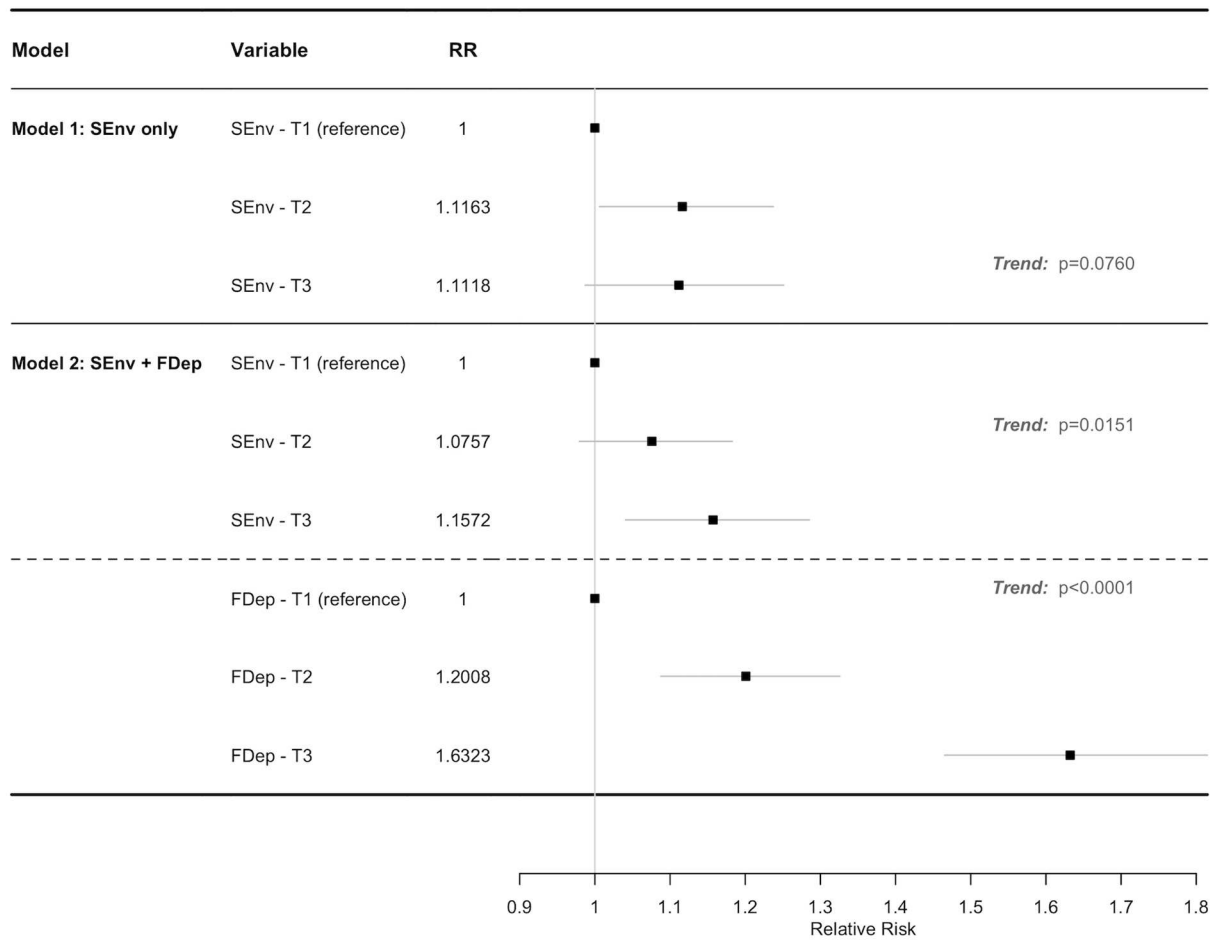
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 537 $\mu\text{g}/\text{g}$ for metals and dust) by SEnv tertile (T1, T2 and T3), and Spearman's coefficient for the
 538 correlation.

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 [2.89;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;3.25]	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**

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

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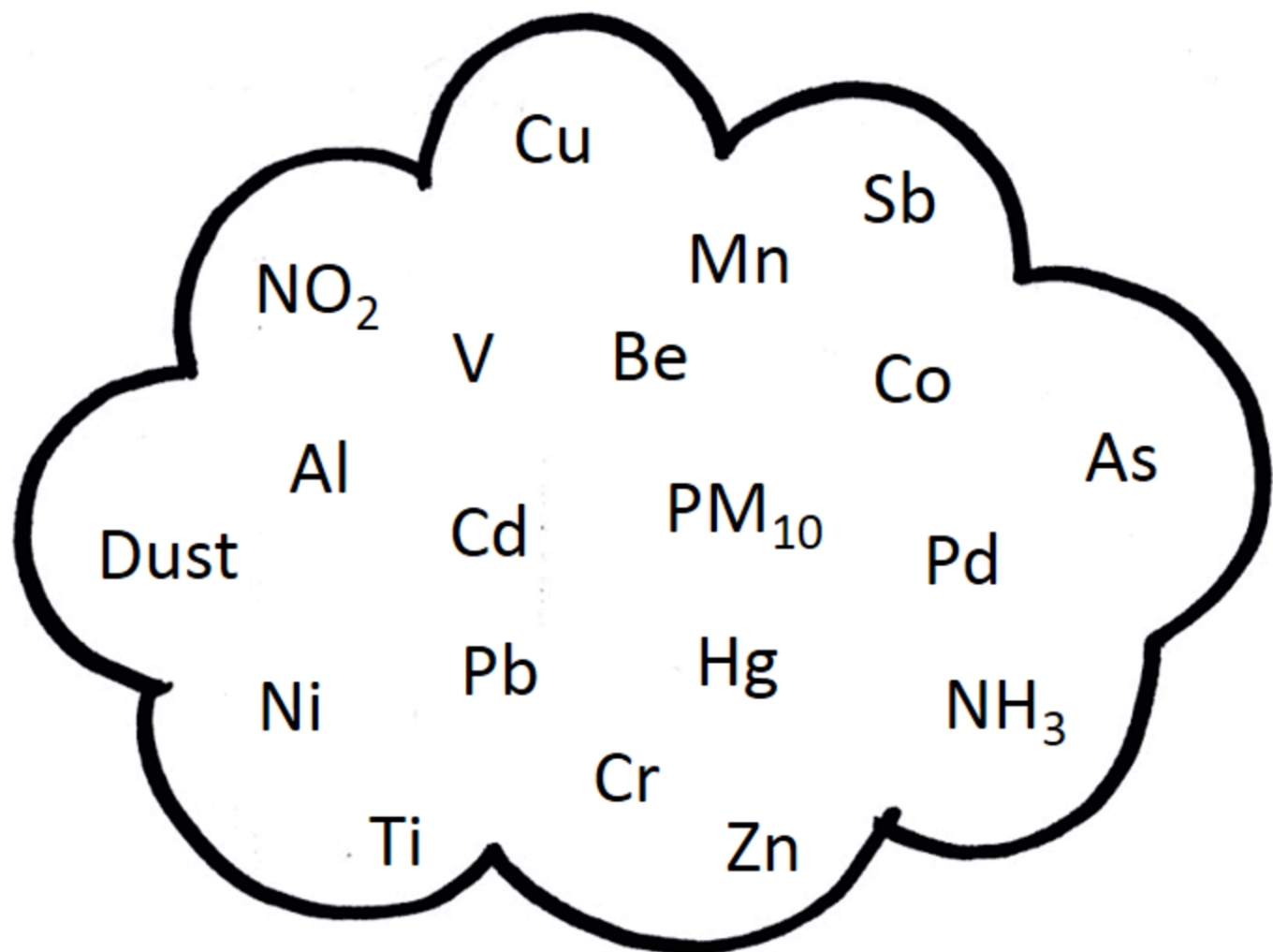
540

541 **Table 2.** The relative risk [95%BCI] of CHD by tertiles of the 20 individual environmental indicators,
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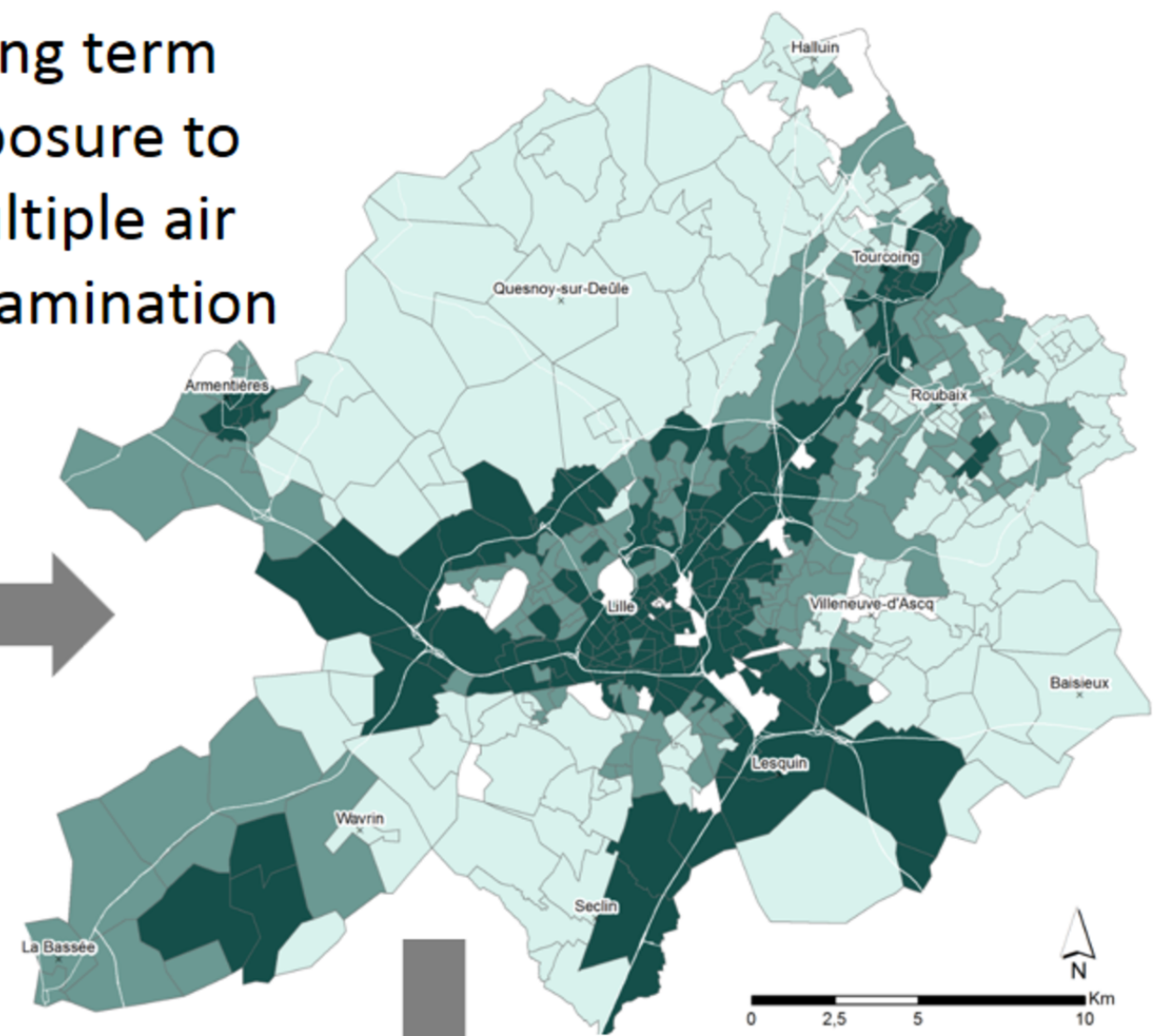
Environmental indicators		RR	95%BCI	Trend (p)
PM ₁₀	<i>T1-reference</i>	1.00		
	<i>T2</i>	1.06	[0.97-1.17]	0.022
	<i>T3</i>	1.11	[1.00-1.23]	
NO ₂	<i>T1-reference</i>	1.00		
	<i>T2</i>	1.05	[0.95-1.16]	0.036
	<i>T3</i>	1.10	[0.99-1.22]	
Aluminium	<i>T1-reference</i>	1.00		
	<i>T2</i>	1.01	[0.91-1.12]	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]	0.009
	<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]	0.003
	<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]	0.033
	<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]	0.032
	<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]	

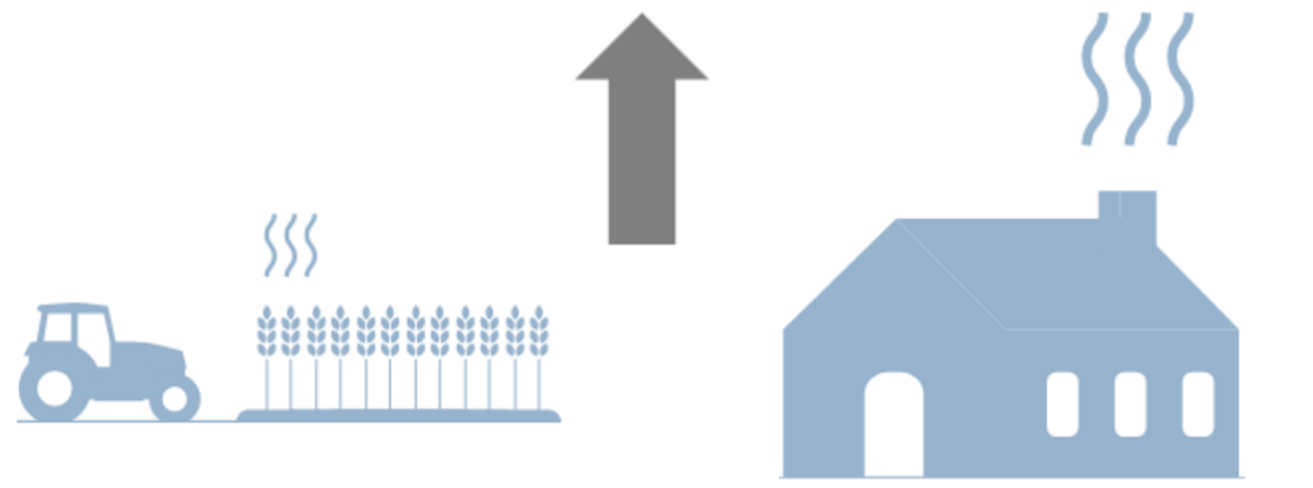
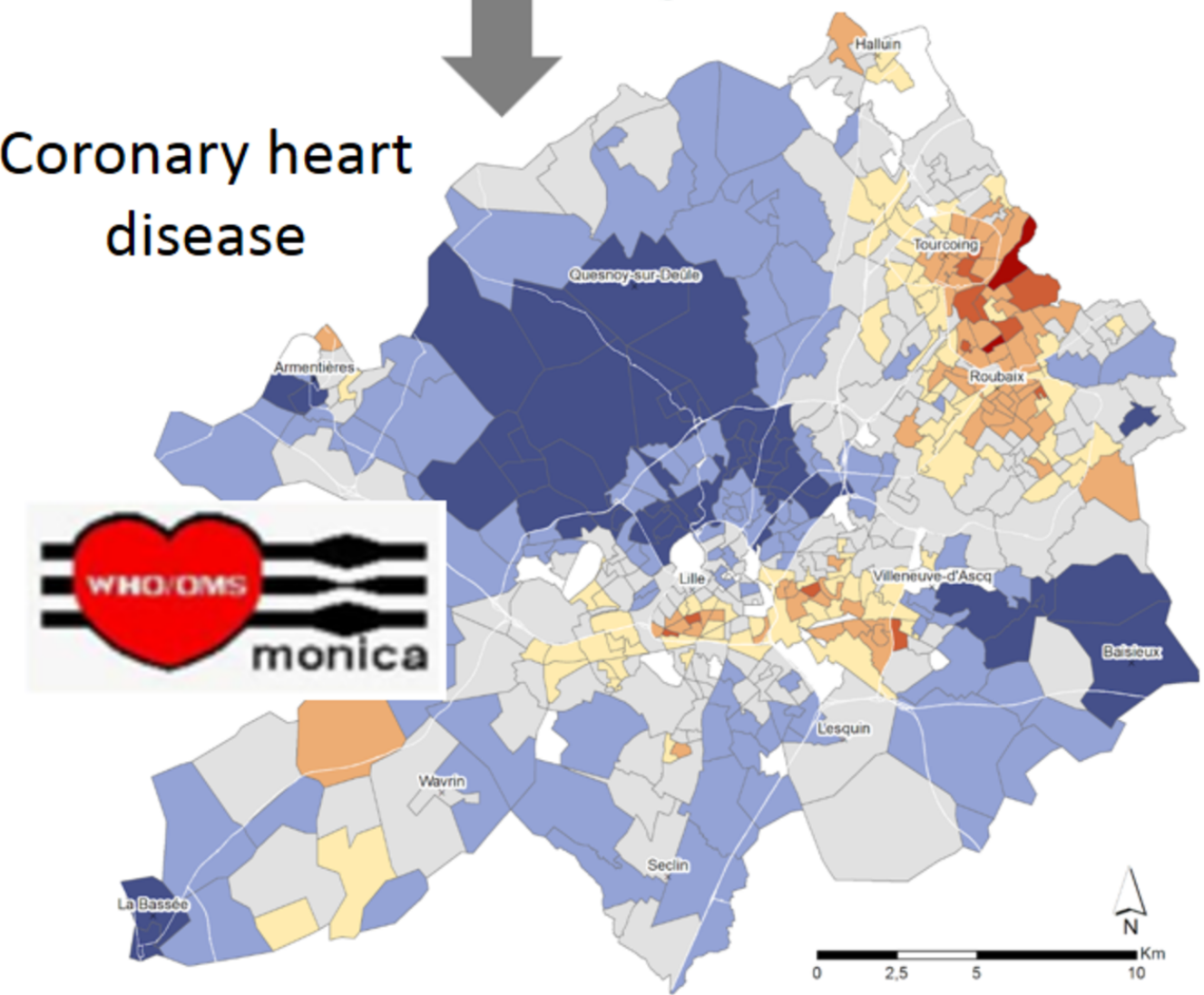
543



Long term exposure to multiple air contamination



Coronary heart disease



Air emissions in European agglomerations