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Does air pollution really impact the onset of spontaneous pneumothorax? A French case-crossover study

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1 **aaTitle page:**

2 **1. Title**

3 Does air pollution really impact the onset of spontaneous pneumothorax? A French case-
4 crossover study

5

6 **2. Name and address of the Corresponding Author**

7 Tania Marx, Emergency Departement, CHU of Besançon, 3 boulevard Fleming, 25030
8 Besançon, France

9 tmarx@chu-besancon.fr

10 tel : +33-381- 66 81 62 / +33-675-95 20 46

11 fax: +33-381-66 89 08

12

13 **3. Authors**

14 Tania Marx^{1,2,6}, Nadine Bernard^{2,3,6}, Anne-Laure Parmentier^{2,4,6}, Marc Puyraveau^{2,4,6},
15 Berenger Martin⁴, Madeleine Gantelet^{4,6}, Jean-Baptiste Pretalli¹, Jean-Charles Dalphin^{2,5,6},
16 Frédéric Mauny^{2,4,6} and Thibaut Desmettre^{1,2,6}.

17

18 **4. Name of department(s) and institution(s)**

19 ¹Emergency Department, CHU de Besançon, 3 boulevard Alexandre Fleming 25030
20 Besançon, France;

21 ²Laboratory Chrono-environnement, UMR 6249 Centre National de la Recherche
22 Scientifique, 16 route de Gray 25000 Besançon, France;

23 ³Laboratory TheMA, UMR 6049 Centre National de la Recherche Scientifique, 16 route de
24 Gray 25000 Besançon, France;

25 ⁴Clinical Methodology Center, CHU de Besançon, 2 place Saint-Jacques 25030 Besançon,
26 France ;

27 ⁵Pneumology Department, CHU de Besançon, 3 boulevard Alexandre Fleming 25030
28 Besançon, France;

29 ⁶Université Bourgogne Franche-Comté, 32 avenue de l'Observatoire 25000 Besançon,
30 France;

31

32 ***5. Declaration of interest***

33 Declarations of interest: none

34

35 **ABSTRACT**

36 **Rationale:** A link is established between air pollution and respiratory diseases. Very few
37 studies evaluated this link with primary spontaneous pneumothorax (PSP). Contrasted
38 results, low statistical power and methodological limits of these studies brought us to
39 evaluate in a more thorough way this link.

40 **Objectives:** (1) to estimate the relation between PSP and air pollutants namely nitrogen
41 dioxide (NO₂), ozone (O₃) and particulate matter with a diameter ≤ 10µm (PM₁₀); (2) to
42 investigate a time lag effect between these pollutants and occurrence of PSP.

43 **Methods :** This study has a case-crossover design. Subjects aged ≥ 18 years admitted from 1st
44 June 2009 to 31st May 2013, in 14 Emergency Departments centers on the French territory.
45 Were excluded: patients with traumatic, secondary, recurrent or history of previous
46 pneumothorax. NO₂, O₃ and PM₁₀ data were collected hourly in monitoring stations. Three
47 exposure assessments were retained: quantitative values, fast increase concentration of air
48 pollutants and peak of pollution. These assessments were calculated for the entire exposure
49 period and for each of the four days of all case and control periods.

50 **Results:** 948 subjects included. Whatever the pollutant considered, no differences were
51 observed between case and control periods, regardless of whether the quantitative values of
52 air pollutants exposure (p>0.09), fast increase concentration (p>0.46) and peak of pollution
53 (p>0.20).

54 **Conclusions:** There is no impact of short-term air pollution exposure and low to moderate
55 level of NO₂, O₃ and PM₁₀ concentration on the onset of PSP. An impact at higher exposure
56 level, and/or a potentiating effect of different meteorological factors remain to be
57 demonstrated.

58 **Keywords:** pneumothorax, air pollution, case-crossover study

59 **Highlights:**

- 60 - Mean hourly concentration of NO₂, O₃ and PM₁₀ showed regular and daily variation
- 61 - No impact of short-term air pollution exposure on the onset of spontaneous
- 62 pneumothorax
- 63 - No association between moderate levels of NO₂, O₃ and PM₁₀ and spontaneous
- 64 pneumothorax

65

66 **1. INTRODUCTION**

67 Spontaneous pneumothorax (SP) is defined as the spontaneous presence of air in the pleural
68 spaces. When SP occurs in a healthy lung, it is called primary SP (PSP), otherwise it is termed
69 secondary SP (SSP) when occurring in the context of underlying pulmonary disease. The
70 incidence of PSP is estimated of 7.4-18/100 000 per year among men, and 1.2-6/100 000
71 per year among women (Sahn and Heffner, 2000). Although mortality is low with a rate of
72 1,26 and 0.62/1 000 000 per year for men and women (Gupta et al., 2000), the economic
73 consequences are substantial, with an average hospital stay of seven days (Bobbio et al.,
74 2015). The causal mechanism of SP is thought to involve rupture of the alveolar walls or of
75 sub-pleural structures (bullae and blebs) (Sahn and Heffner, 2000), while some authors have
76 incriminated diffuse increased porosity at the periphery of the lungs (Noppen et al., 2006).
77 Factors that can facilitate or trigger SP remain unknown. It occurs most frequently at rest.
78 Some authors have hypothesized that there is a link between SP and meteorological factors,
79 in view of the occurrence of temporal clusters (Accard et al., 1972). Several studies have
80 investigated the relation between the occurrence of PSP and the atmospheric pressure
81 variation (Alifano et al., 2007), but with contradictory results (Smit et al., 1999; Suarez-
82 Varela et al.,2000). Similarly, temperature increases have been reported to be related to PSP
83 (Obuchi et al., 2011), whereas other authors have failed to find any such association (Celik et
84 al., 2009; Özpolat et al., 2009). Some authors studied then the impact of seasons on the
85 occurrence of SP. The results are again very contrasted (Alifano et al.,2007; Ayed et al., 2006;
86 Zhang et al.,2012). Concerning air pollution, the link with various respiratory disease such as
87 chronic obstructive pulmonary disease (COPD), asthma and lung infection is well established
88 (Arbex et al., 2012; Kelly and Fussell, 2011; Ko and Hui, 2012; Sbihi et al., 2016; To et al.,
89 2016). Conversely, the association between air pollution and PSP has not been widely

90 investigated. Bertolaccini et al. (2011, 2015) suggest a link between nitrogen dioxide (NO₂),
91 ozone (O₃) and the occurrence of PSP. These results were partially confirmed by Abul et al.
92 (2011). Previous studies lacked consensual results and suffered from low statistical power
93 and methodological limits (e.g. single-centre studies). In this context, we sought to
94 investigate the relation between air pollution and PSP. The objectives of the study were: (1)
95 to estimate the relation between PSP and air pollutants namely NO₂, O₃ and particulate
96 matter with a diameter ≤ 10µm (PM₁₀); (2) to investigate a time lag effect between exposure
97 and occurrence of PSP.

98

99

100 **2. METHODS**

101 A time stratified case-crossover design was chosen (Maclure 1991). This study's design,
102 particularly adapted for the researches on air pollution (Bateson and Schwartz, 1999; Janes
103 et al., 2005; Levy et al., 2001; Maclure 1991), concerned 14 Emergency Departements (EDs)
104 centers from middle size cities distributed on the French territory (Figure 1).

105 For each PSP, the period prior to occurrence of the event (case-period) was compared to
106 several other periods at a distance from the PSP (control periods). The date of admission to
107 the EDs was retained as the date of occurrence of PSP (date D). The case-period was defined
108 as the total time during which the subject was exposed to the risk of occurrence of PSP: the
109 four days before admission was retained to define the period (day D-1 to day D-4). The
110 control periods were defined for each subject as the same weekdays as the case period
111 within the same month. The exposure periods were defined by all of case and control
112 periods.

113

114

115

116 **2.1. Study population**

117 Inclusion criteria were: occurrence of PSP between 1st June 2009 to 31st May 2013, age over
118 18 years and provision of written informed consent. Were excluded patients with traumatic,
119 secondary, recurrent or history of previous SP, and not living in the study area or with home
120 address missing. Sex, age, date of admission, home address, smoking status, and history of
121 asthma were collected in the ED medical records. The study was approved by the National
122 authority for the protection of privacy and personal data.

123

124 **2.2. Environmental data**

125 Air pollution data were provided by the French Air Quality Monitoring Association (AASQA)
126 Network and the local AASQA for each study area. NO₂, O₃ and PM₁₀ data were collected
127 hourly in each monitoring station. Home address was used to estimate the residential
128 exposure of each subject at the date of PSP. The home address of each subject was
129 geolocated, and the choice of the appropriate monitoring station in relation to each patient
130 address was made by the team of every local AASQA. Since the number of monitoring
131 stations is limited, this choice was optimized taking into account the distance between the
132 patient's home and the station, the geomorphological situation of the subject's residence
133 and the proximity of the major sources of air pollution.

134 Three exposure assessments were retained: quantitative absolute values, fast increase
135 concentration of air pollutants and peak of pollution. To investigate a potential lag effect,
136 these assessments were calculated for the entire exposure period and for each of the four
137 days of all case and control periods: from date D-1 (Lag1) to date D-4 (Lag4).

138 Minimum, maximum, mean and range of absolute quantitative values of the three pollutants
139 were computed.

140 A fast increase of pollutant concentration was defined as a positive difference of
141 concentration occurring in a 3-hour interval, noted Δ_{3h} . For each hour, Δ_{3h} was calculated as
142 the difference between the concentration measured at hour h, minus the concentration
143 measured at hour h-3. A fast increase was retained if a Δ_{3h} exceeded : $40\mu\text{g}/\text{m}^3$ for NO_2 and
144 O_3 , $20\mu\text{g}/\text{m}^3$ for PM_{10} . This threshold value was chosen as the third quartile of distribution
145 of all the Δ_{3h} .

146 According to the European legislation on the air quality (Ministère de l'écologie, de
147 l'énergie, du développement durable et de la mer; 2010), peaks of pollution were defined
148 using the following norms as the cut-off: NO_2 hourly average = $200\mu\text{g}/\text{m}^3$, PM_{10} daily average
149 = $50\mu\text{g}/\text{m}^3$, O_3 8-hour average = $120\mu\text{g}/\text{m}^3$.

150

151 **2.3. Statistical analysis**

152 The number of necessary cases was estimated at 838 (unilateral situation, proportion of
153 exposure among controls = 0.25, odds ratio = 1.25, and statistical power = 80%). The value of
154 the odds ratio was voluntarily maintained at a low value given the environmental nature of
155 the study.

156 The relationship between the case or control status of each period and air pollution
157 exposure was analysed using conditional logistic regression. Considering the number of
158 exposure indices analysed, Benjamini Yekutieli's correction for multiple testing was applied
159 to control the false discovery rate (Benjamini et al., 1995; Benjamini and Yekutieli, 2001;
160 Reiner et al., 2003). Sensitivity analyses were performed to verify that the effect of
161 concentrations of pollutants was not modified by individual factors: age, sex, smoking status,

162 history of asthma and center. The statistical analysis was performed using SAS, version 9.4
163 (SAS Institute Inc., Cary, NC, USA). A p-value <0.05 was considered statistically significant.

164

165

166 **3. RESULTS**

167 **3.1. Participants**

168 Among 1946 eligible patients, 948 were included in this study (Figure 2). The characteristics
169 of the population are shown in Table 1.

170 Mean age was 30.8 (standard deviation 13.2) years. The male/female ratio was 3.6. Current
171 smoker accounted for 71.5%. Only 6.4% declared a history of asthma. The percent of PSP
172 observed was the same whatever the season considered.

173

174 **3.2. Air pollution exposure**

175 Not surprisingly, the mean hourly concentration of NO₂, O₃ and PM₁₀ showed regular and
176 daily variation (Figure 3). No significant association between exposure to air pollutants
177 (treated as quantitative) and the occurrence of PSP was observed in Table 2 (all OR ranged
178 between 0.99 and 1.01, and all multiple testing with Benjamini Yekutieli corrected P_{Corr}
179 values > 0.09).

180 The proportion of periods where at least one fast increase in pollutant concentration was
181 observed is presented in Figure 4. No differences were observed between case and control
182 periods (all P_{Corr.} values > 0.46) (Table 3). At least one fast increase in NO₂, O₃ and PM₁₀ was
183 observed in respectively 14%, 20% and 13% of both case and control periods on each Lag.
184 Over the whole period, at least one fast increase in pollutant concentrations was observed in
185 40% of both case and control periods, whatever the pollutant considered, while at least one

186 peak of pollution of NO₂ was observed in less than 1% of both case and control periods.
187 Exposure to at least one peak of O₃ and PM₁₀ values for case and control periods were
188 respectively 9.99% versus 9.59% and 8.33% versus 9.15% (Figure 5). No significant
189 differences were observed between cases and controls periods, whatever the pollutant
190 considered, and regardless of whether the whole period or the Lags were considered (all
191 P_{Corr.} values > 0.20) (Table 4).

192 Sensitivity analyses performed on different patient subgroups (age, sex, smoking status,
193 history of asthma and center) yielded similar results (data not shown).

194

195

196 **4. DISCUSSION**

197 No association between the occurrence of PSP and environmental exposure to low to
198 moderate levels of NO₂, O₃ and PM₁₀ was observed in this study, whatever considering
199 quantitative absolute values, fast increases in concentrations of air pollutants and pollution
200 peaks. Furthermore, no lag effect was identified.

201 The strength of our study resides in several different points. Firstly, to the best of our
202 knowledge, our study includes the largest sample size to date in studies analyzing the link
203 between the occurrence of PSP and air pollution. Very few studies have been published on
204 this particular topic up to now, with fewer than 500 and 79 subjects included respectively in
205 the studies of Bertolaccini et al. (2011, 2015) and Abul et al. (2011).

206 Secondly, we were particular meticulous with the process used to identified patients and to
207 collect data. All patients with a diagnosis of pneumothorax (International Classification of
208 Diseases (ICD) 10th revision code = J93) during the study period were retrospectively
209 identified by medical informatics queries of the emergency unit databases in the

210 participating centers. The diagnosis of PSP (ICD code J93.11) or SSP (ICD code J93.12) was
211 checked by research assistants in the medical files of the EDs admissions database.
212 Demographic characteristics of the study subjects were similar to those of the large
213 descriptive study of Bobbio et al. (2015).

214 Thirdly, air pollution exposure was assessed using measurements provided by the French
215 National AASQA Network, which is accredited by the French Ministry for the Environment
216 and whose quality is guaranteed by ISO/TC146 standard for air quality. Every patient's home
217 was situated at a median distance of station of 6.76 km (first quartile 1.89 ; third quartile
218 25.16). Air pollution assessment was based on a reproducible process, especially among
219 cases and controls and across the study centers. The assessments of air pollution levels
220 focused on residential exposure; and not professional exposure, or exposure during
221 transportation or travel. Indeed, PSP most frequently occurs at home and at rest, so
222 restricting the assessment of exposure to the patient's residential address likely did not
223 introduce any substantial bias into the results.

224 The multicentre approach used in our study made it possible to include subjects from
225 various urban and periurban areas distributed nationwide. Thus, the patients in our study
226 were not all subject to the same pollution profile, conversely to the situations reported in
227 some other studies (Abul et al., 2011; Bertolaccini et al., 2011, 2015).

228 A further key point of this study is the time stratified case-crossover design. It is specifically
229 adapted to the analysis of relationships between the acute occurrence of disease and
230 environmental exposure in case of short-term temporal variations (Bateson and Schwartz,
231 1999; Janes et al., 2005). The case-crossover design could be considered as a variant of the
232 matched case-control design: each case becomes its own control (Maclure, 1991), and
233 matching occurred on characteristic of each subject, regardless of whether these

234 characteristics are known or unknown. This design has previously been used to analyze the
235 relationship between respiratory diseases such as COPD, asthma and air pollution, with
236 convincing results (Kwon et al., 2016; Medina-Ramón et al., 2006; Yamazaki et al., 2015), but
237 has never yet been applied to the study of PSP.

238 Lastly, the design of this study and the sensitivity analysis by subgroup including the major
239 risk factors made it possible to explore potential interactions and confusion effects; the
240 probability of type I error due to multiple testing was minimized by applying the appropriate
241 corrective measures to the analysis.

242

243 No significant association between concentrations of NO₂, O₃ or PM₁₀ and the occurrence of
244 PSP was identified in this study. Indeed, to assess the statistical power of this study, the odds
245 ratios that could be appropriately identified from a statistical point of view were calculated *a*
246 *posteriori*, taking into account the study size and the proportion of controls effectively
247 exposed to air pollution. The smallest odds ratios which could be declared significant for a
248 fast increase of pollutant concentration or a peak of pollution would be respectively 1.13
249 and 1.22, which indicate a high statistical power. These results plead in favor of the absence
250 of any relation between the occurrence of PSP and air pollution in the context of this study.

251

252 Two points merit discussion in this regard, namely the level of exposure and the
253 consideration of factors other than air pollution, such as meteorological data.

254 The level of exposure of the subjects in our study to air pollution is lower than that reported
255 by Abul et al. (2011) in their study of PSP, and lower than in other studies of respiratory
256 diseases (Abbey et al., 1998; Kwon et al. 2016; Medina-Ramón et al, 2006; To et al., 2016).

257 These studies mainly focused on pollution exposure in big cities, whereas the cities included

258 in our study were medium-sized, i.e. 100 000 to 500 000 inhabitants, where exposure is low
259 to moderate. It is clearly plausible that exposure to air pollution is considerably higher in big
260 cities given the more numerous sources of primary pollutants, which could in turn impact on
261 the occurrence of PSP.

262 Abul et al. (2011) demonstrated a link between the increase of O₃ and the occurrence of PSP,
263 while Bertolaccini et al. (2011, 2015) reported contrasting results from two studies. In the
264 first of these two studies (Bertolaccini et al., 2011), the occurrence of PSP was significantly
265 triggered by higher values of NO₂, lower values of O₃ and less dispersed temperature and
266 wind speed. In his second study Bertolaccini et al. (2015) confirmed that PSP was
267 significantly more likely to occur on warm windy days with high atmospheric pressure and
268 high mean NO₂ concentration. This discrepancy in their results may be explained by the
269 inclusion of factors other than air pollution in the analysis. Indeed, climate parameters were
270 included in the air pollution analysis in the study by Bertolaccini et al. (2011, 2015), but not
271 in the study by Abul et al. (2011) or in our own study.

272 The pathophysiology of PSP is actually better understood. The concept of PSP associated
273 with a localised rupture of a bleb, or a bulla has been discussed (Tschopp and Marquette,
274 2017). The occurrence of PSP could be the result of a diffuse histopathological change in the
275 lung parenchyma under the visceral pleura. Some authors identified diffuse increased
276 porosity at the periphery of both lungs (Noppen et al., 2006). This could lend credence to the
277 hypothesis of an impact of air pollution on the onset of PSP.

278 Concerning O₃ in particular, it's recognized that megacities emit higher levels of O₃
279 precursors and particulate matter, and these are crucial to local and regional air quality.
280 Megacities can be warmer than the surrounding rural environments by up to several
281 degrees. Ozone concentration increase almost linearly with the ambient temperatures

282 (Baklanov et al., 2016), and with greater sun exposure. The potential of air pollution to affect
283 PSP is therefore a particularly major challenge in megacities, particularly those that are
284 located at latitudes that enjoy extensive sunshine.

285

286

287 **5. CONCLUSIONS**

288 In conclusion, in this large sample of patient, our results are in favour of a lack of connection
289 between PSP and short-term air pollution exposure and low to moderate level of NO₂, O₃
290 and PM10 concentration. Conversely, an impact at higher exposure level, and/or a
291 potentiating effect of different meteorological factors remain to be demonstrated.

292

293

294

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302

303 **COMPETING INTERESTS**

304 The authors declare they have no actual or potential competing financial and non financial
305 interest in relation to this work

306

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309

310

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400 **TABLES**

401

402 Table 1. Baseline characteristics of study population

N = 948	Mean (SD) or N (%)
Age (years)	30.8 (13.2)
Sex*	
Males	739 (78.12)
Females	207 (21.88)
History of asthma	61 (6.44)
Smoking status†	
Current	519 (71.49)
Never	168 (23.14)
Former	39 (5.37)
Season	
Spring	229 (24.16)
Summer	230 (24.26)
Autumn	253 (26.69)
Winter	236 (24.89)

403 *Missing values N = 2

404 †Missing values N =222

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411 Table 2. Association between maximum, minimum, mean and range of pollutants over the
 412 exposure period, and occurrence of primary spontaneous pneumothorax

Variables	NO ₂			O ₃			PM ₁₀		
	OR	<i>P</i>	<i>P</i> _{cor}	OR	<i>P</i>	<i>P</i> _{cor}	OR	<i>P</i>	<i>P</i> _{cor}
	(95% CI)*	Value†	Value‡	(95% CI)	Value	Value	(95% CI)	Value	Value
Maximum									
Lag 1	1.00	0.97	1.00	1.00	0.07	0.12	1.00	0.34	0.90
	(1.00-1.00)			(1.00-1.01)			(1.00-1.00)		
Lag 2	1.00	0.64	1.00	1.00	0.04	0.09	1.00	0.95	0.99
	(0.99-1.00)			(1.00-1.01)			(1.00-1.00)		
Lag 3	1.00	0.76	1.00	1.00	0.23	0.23	1.00	0.33	0.90
	(1.00-1.00)			(1.00-1.01)			(0.99-1.00)		
Lag 4	1.00	0.56	1.00	1.00	0.28	0.28	1.00	0.90	0.99
	(0.99-1.00)			(1.00-1.01)			(1.00-1.01)		
Exposure period	1.00	0.53	1.00	1.00	0.16	0.21	1.00	0.55	0.90
	(0.99-1.00)			(1.00-1.01)			(1.00-1.00)		
Minimum									
Lag 1	1.00	0.82	1.00	1.00	0.20	0.23	1.01	0.20	0.90
	(0.99-1.01)			(1.00-1.01)			(1.00-1.02)		
Lag 2	1.00	0.60	1.00	1.00	0.30	0.30	1.00	0.91	0.99
	(0.98-1.01)			(1.00-1.01)			(0.99-1.01)		
Lag 3	1.00	0.84	1.00	1.01	0.03	0.09	1.00	0.99	0.99
	(0.99-1.01)			(1.00-1.01)			(0.99-1.01)		
Lag 4	0.99	0.28	1.00	1.00	0.50	0.50	1.00	0.50	0.90
	(0.98-1.01)			(1.00-1.01)			(0.99-1.01)		
Exposure period	0.99	0.62	1.00	1.01	0.01	0.09	1.00	0.62	0.93
	(0.97-1.02)			(1.00-1.02)			(0.98-1.01)		

(Table 2 continued)

Mean									
Lag 1	1.00	0.61	1.00	1.00	0.22	0.23	1.01	0.13	0.90
	(0.99-1.01)			(1.00-1.01)			(1.00-1.01)		
Lag 2	1.00	0.67	1.00	1.00	0.11	0.15	1.00	0.95	0.99
	(0.99-1.01)			(1.00-1.01)			(0.99-1.01)		
Lag 3	1.00	0.81	1.00	1.00	0.08	0.13	1.00	0.51	0.90
	(0.99-1.01)			(1.00-1.01)			(0.99-1.01)		
Lag 4	0.99	0.12	1.00	1.00	0.27	0.27	1.00	0.56	0.90
	(0.99-1.00)			(1.00-1.01)			(0.99-1.01)		
Exposure period	1.00	0.95	1.00	1.01	0.03	0.09	1.00	0.93	0.99
	(0.99-1.01)			(1.00-1.01)			(0.99-1.01)		
Range									
Lag 1	1.00	0.90	1.00	1.00	0.45	0.45	1.00	0.66	0.94
	(1.00-1.00)			(1.00-1.01)			(1.00-1.01)		
Lag 2	1.00	0.75	1.00	1.00	0.24	0.24	1.00	0.98	0.99
	(0.99-1.00)			(1.00-1.01)			(0.99-1.01)		
Lag 3	1.00	0.69	1.00	1.00	0.69	0.69	1.00	0.21	0.90
	(0.99-1.00)			(1.00-1.00)			(0.99-1.00)		
Lag 4	1.00	0.78	1.00	1.00	0.62	0.62	1.00	0.57	0.90
	(0.99-1.00)			(1.00-1.00)			(1.00-1.01)		
Exposure period	1.00	0.59	1.00	1.00	0.90	0.90	1.00	0.45	0.90
	(0.99-1.00)			(1.00-1.00)			(1.00-1.00)		

413 *Definition of abbreviations: CI = confidence interval*

414 *Confidence interval without correction in multiple comparison procedure.

415 † For conditionnal logistic regression.

416 ‡ Corrected P Value with Benjamini Yekutieli's method.

417

418

419 Table 3. Association between exposure to at least one fast increase concentration of
 420 pollutants over time windows of three hours, and the occurrence of primary spontaneous
 421 pneumothorax, during the exposure period.

Variables	OR (95% CI)*	P value†	P _{cor} value‡
NO ₂ (concentration of 40µg/m ³)			
Lag 1	1.00 (0.79 - 1.26)	1.00	1.00
Lag 2	1.13 (0.89 - 1.43)	0.32	1.00
Lag 3	1.06 (0.83 - 1.35)	0.61	1.00
Lag 4	1.13 (0.89 - 1.42)	0.32	1.00
Exposure period	1.04 (0.86 - 1.25)	0.69	1.00
O ₃ (concentration of 40µg/m ³)			
Lag 1	1.00 (0.82 - 1.22)	0.97	0.97
Lag 2	1.08 (0.89 - 1.31)	0.46	0.46
Lag 3	1.03 (0.85 - 1.25)	0.77	0.77
Lag 4	1.07 (0.88 - 1.31)	0.51	0.51
Exposure period	0.96 (0.81 - 1.13)	0.61	0.61
PM ₁₀ (concentration of 20µg/m ³)			
Lag 1	1.01 (0.80 - 1.27)	0.94	0.99
Lag 2	1.11 (0.87 - 1.40)	0.40	0.90
Lag 3	1.08 (0.86 - 1.36)	0.48	0.90
Lag 4	1.07 (0.85 - 1.35)	0.56	0.90
Exposure period	1.07 (0.90 - 1.28)	0.42	0.90

422 *Definition of abbreviations:* CI = confidence interval

423 *Confidence interval without correction in multiple comparison procedure.

424 † For conditionnal logistic regression.

425 ‡ Corrected P Value with Benjamini Yekutieli's method.

426

427 Table 4. Association between exposure to at least one peak of pollution and the occurrence
 428 of primary spontaneous pneumothorax, during the exposure period.

Variables	OR (95% CI)*	P value†	P _{cor} value‡
O₃ (8-hour average 120 µg/m³)			
Lag 1	1.35 (0.95 - 1.91)	0.09	0.20
Lag 2	1.31 (0.89 - 1.93)	0.17	0.23
Lag 3	1.34 (0.91 - 1.98)	0.14	0.23
Lag 4	1.03 (0.70 - 1.54)	0.87	0.87
Exposure period	1.08 (0.83 - 1.42)	0.57	0.57
PM₁₀ (daily average 50 µg/m³)			
Lag 1	0.88 (0.58 - 1.32)	0.52	0.90
Lag 2	0.96 (0.64 - 1.43)	0.82	0.99
Lag 3	0.86 (0.56 - 1.30)	0.46	0.90
Lag 4	0.81 (0.53 - 1.25)	0.33	0.90
Exposure period	0.87 (0.65 - 1.16)	0.33	0.90

429 *Definition of abbreviations:* CI = confidence interval

430 *Confidence interval without correction in multiple comparison procedure.

431 † For conditionnal logistic regression.

432 ‡ Corrected P Value with Benjamini Yekutieli's method.

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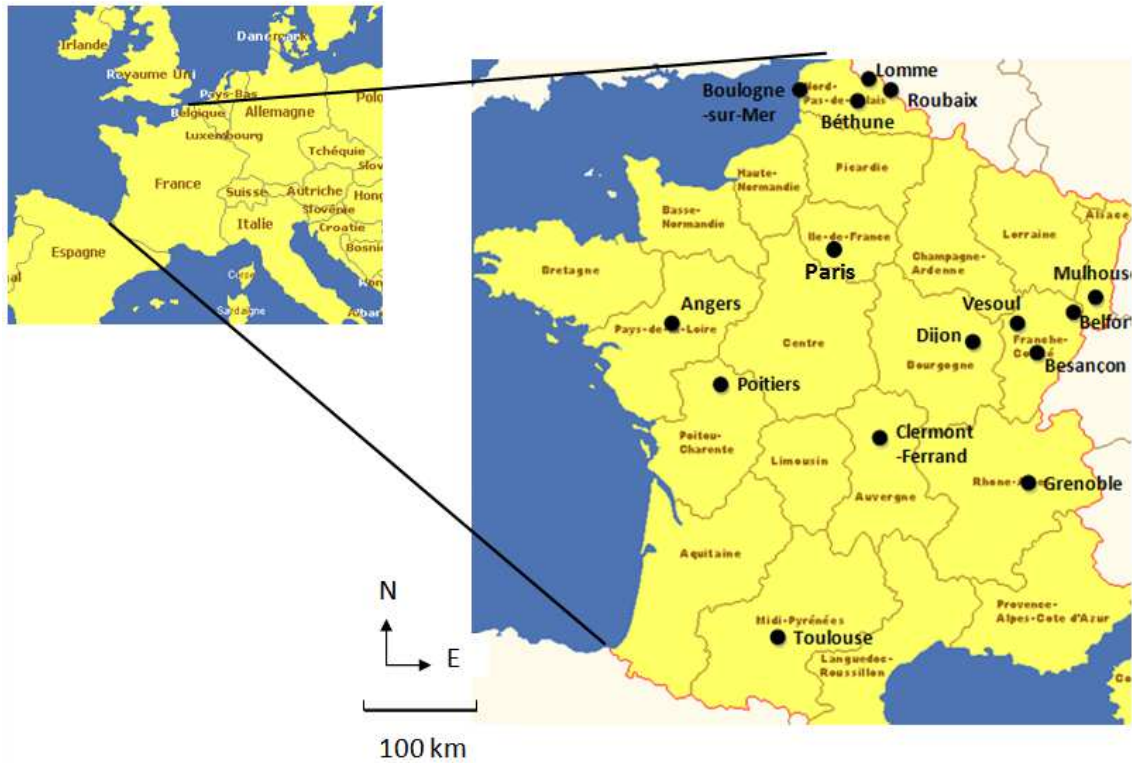
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440 **FIGURES**

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444 **Figure 1: Geographical location of the fourteen participating centers**

445 Seven university teaching hospitals, namely Angers, Besançon, Clermont-Ferrand, Dijon,
446 Grenoble, Poitiers and Toulouse; and seven general, non-academic hospitals, namely Belfort,
447 Béthune, Boulogne sur Mer, Lomme, Roubaix, Mulhouse and Vesoul. Maximal distance
448 between two hospitals: north-south 798km; east-west 593km.

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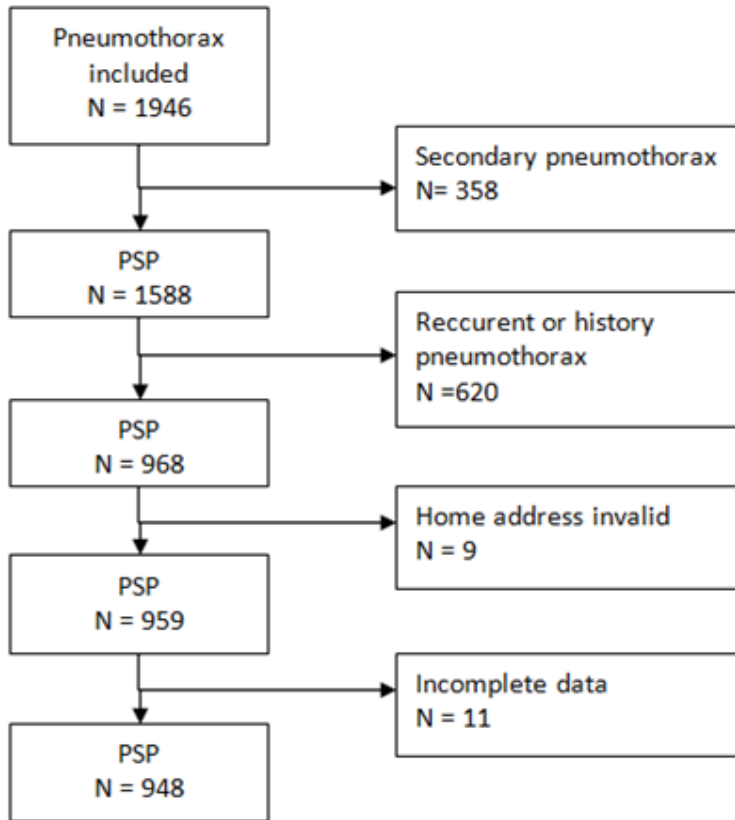
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456 **Figure 2: Flow chart of the population include**

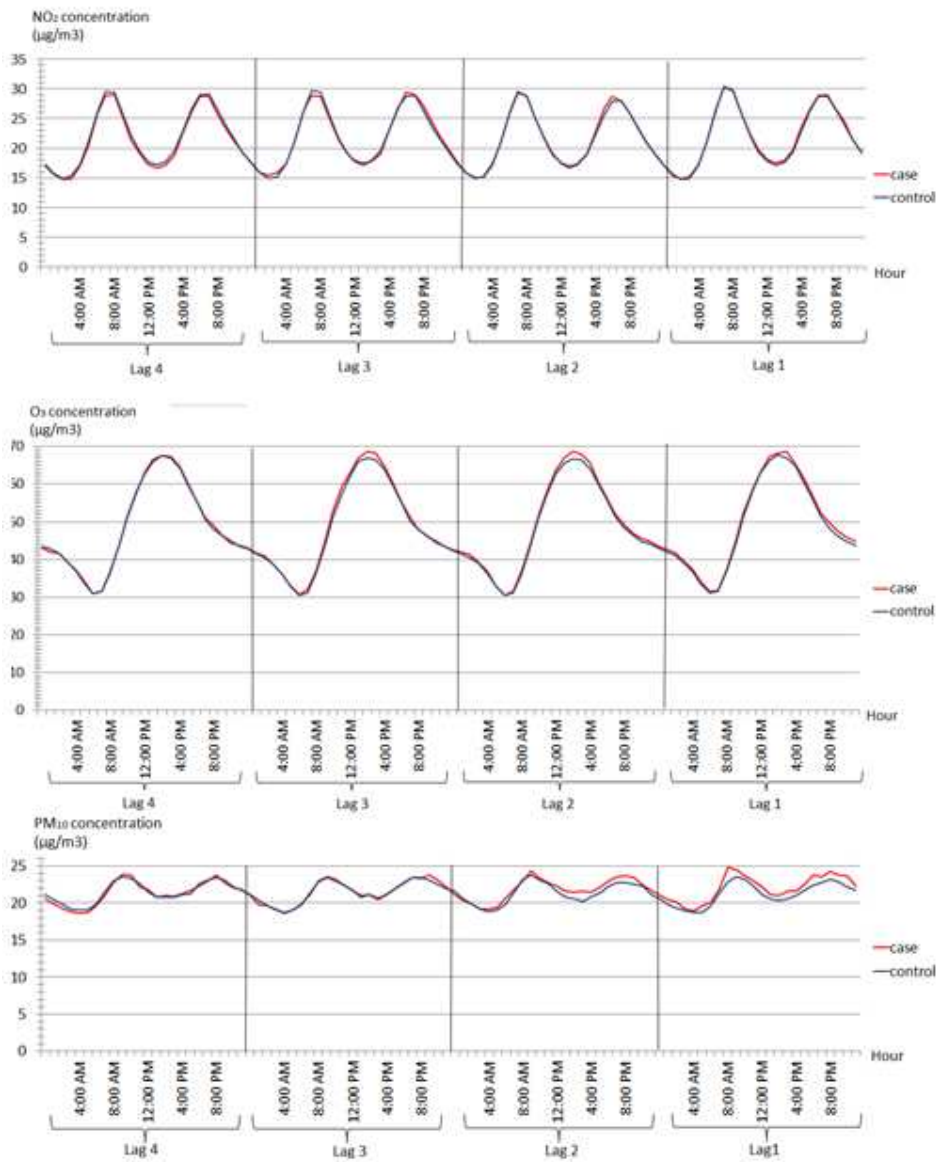
457 *Definition of abbreviations: PSP=primary spontaneous pneumothorax*

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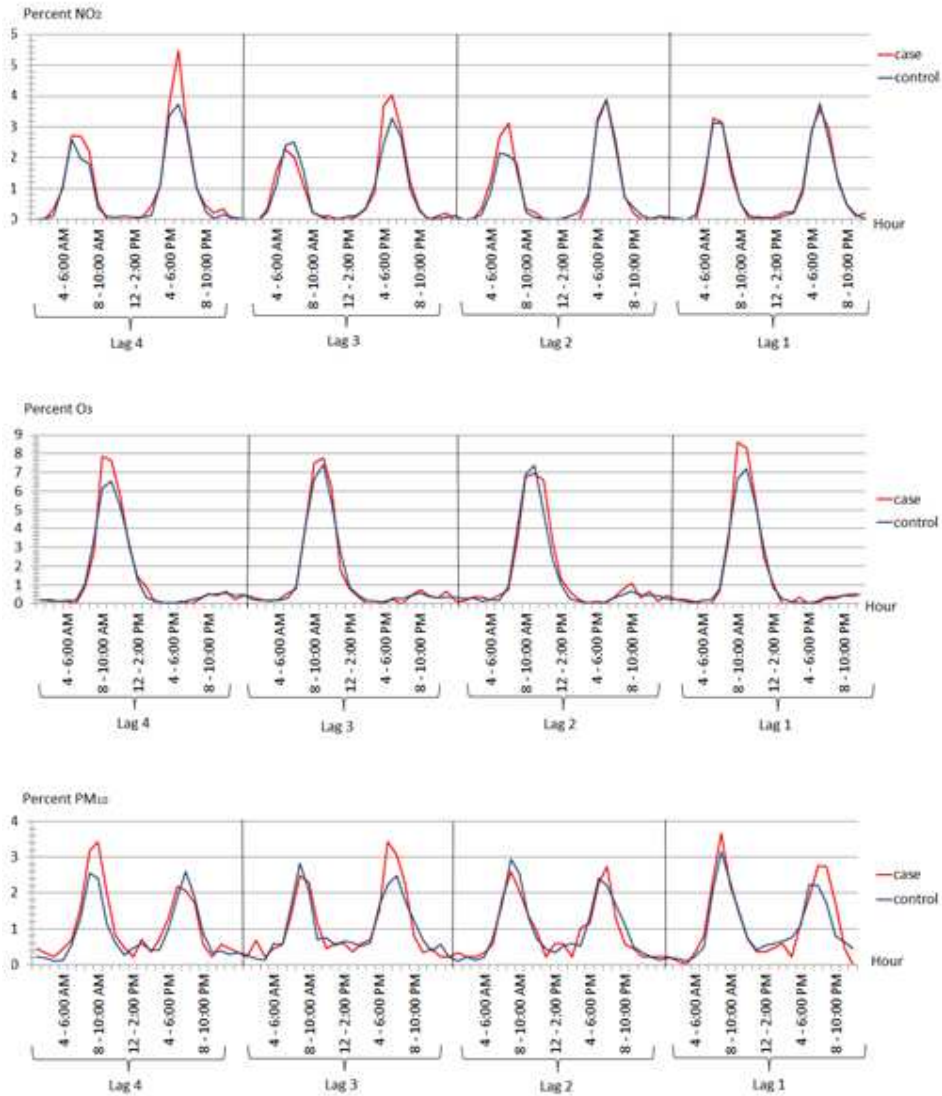
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463 **Figure 3: Hourly mean concentration of nitrogen dioxide (NO₂), ozone (O₃) and particulate**
 464 **matter with a diameter $\leq 10\mu\text{m}$ (PM₁₀) according to the four days on the case and control**
 465 **periods**

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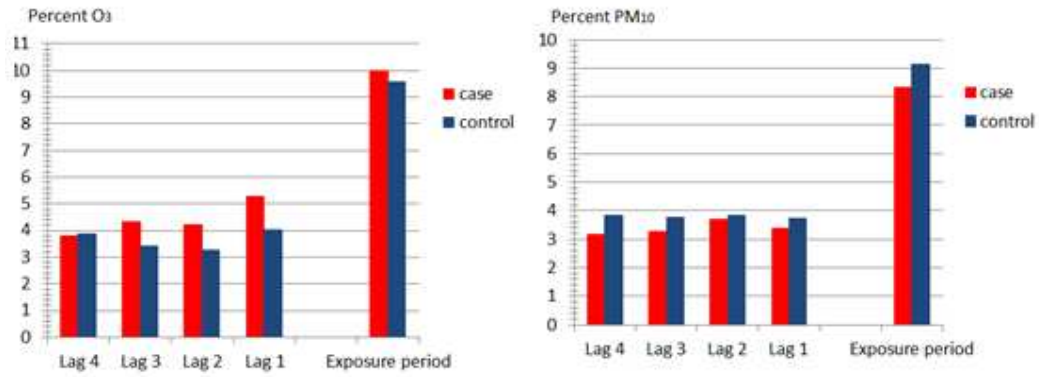
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468 **Figure 4: Percentage of periods, according to the case and control status, exposed to at**
 469 **least one fast increase concentration of pollutants**

470 A. nitrogen dioxide (NO₂) cut-off= 40µg/m³; B. ozone (O₃) cut-off = 40µg/m³; C. particulate
 471 matter with a diameter ≤10µm (PM₁₀) cut-off = 20µg/m³.

472

473



474

475 **Figure 5: Percentage of periods, according to the case and control status, exposed to at**
 476 **least one peak of pollution, on every Lag and exposure period.**

477 A. ozone (O₃) = 120 µg/m³ (8-hour average) ; B. particulate matter with a diameter ≤ 10µm

478 (PM₁₀) = 50 µg/m³ (daily average)

479