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1 **Residential exposure to outdoor air pollution and adult lung function, with focus on**
2 **small airway obstruction**

3

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29 **Abstract**

30 Although a growing body of evidence suggests that chronic exposure to outdoor air pollution
31 is linked to a decline in lung function, data on flow at low lung volumes that may be more
32 specific of small airway obstruction are still scarce. We aimed to study the associations
33 between residential exposure to air pollution and lung function, with specific focus on small
34 airways obstruction.

35 We assessed 2995 French participants (aged between 40 and 65) in the ELISABET cross-
36 sectional survey. Residential exposures to nitrogen dioxide (NO₂), particulate matter with a
37 diameter <10 µm (PM₁₀) and sulphur dioxide (SO₂) were assessed. The spirometric
38 parameters were forced expiratory volume in 1 s (FEV1), forced vital capacity (FVC), and
39 forced expiratory flow between 25% and 75% of FVC (FEF25-75) and at 75% of FVC (FEF75).
40 Coefficients in linear regression models were expressed as the z-score [95% confidence
41 interval] for an increment of 5 µg/m³ in NO₂ and 2 µg/m³ in PM₁₀ and SO₂.

42 NO₂ was associated with significantly lower values of FEV1 (-0.10 [-0.15;-0.05]), FVC (-0.06 [-
43 0.11;-0.02]), FEV1/FVC (-0.07 [-0.11;-0.03]), FEF25-75 (-0.09 [-0.14;-0.05]) and FEF75 (-0.08
44 [-0.12;-0.04]). PM₁₀ was associated with significantly lower values of FEV1 (-0.10 [-0.15;-
45 0.04]), FVC (-0.06 [-0.11;-0.01]), FEV1/FVC (-0.06 [-0.11;-0.01]), FEF25-75 (-0.08 [-0.13;-
46 0.03]) and FEF75 (-0.08 [-0.12;-0.04]). SO₂ was associated with significantly lower values of
47 FEV1 (-0.09 [-0.16;-0.02]), FEV1/FVC (-0.07 [-0.13;-0.01]), FEF25-75 (-0.09 [-0.15;-0.02]) and
48 FEF75 (-0.08 [-0.14;-0.03]) but not FVC (-0.05 [-0.11;0.009]).

49 Even though spatial variations in pollutant levels were low, residential exposure to outdoor air
50 pollution was associated with lower lung function, including lower FEF25-75 and FEF75
51 suggesting small airway obstruction.

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55 **Highlights**

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57 We study two cities where pollution levels are below the European Union's limits.

58 Residential exposure to air pollution was associated to lower lung function.

59 Data on the possible association with small airway function are still scarce.

60 Outdoor air pollution was associated with an impairment in small airway function.

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74 **Introduction**

75 Exposure to outdoor air pollution is associated with various respiratory outcomes, including a
76 decline in lung function (1) - an early predictor of cardiorespiratory morbidity and mortality (2).

77 A growing body of evidence suggests that chronic exposure to nitrogen dioxide (NO₂) and
78 particulate matter with an aerodynamic diameter <10 µm (PM₁₀) is linked to a decline in FEV₁,
79 FVC and FEV₁/FVC - especially in Europe (3). Exposure to NO₂ and PM₁₀ has been linked to
80 lower FEV₁ (2, 4–6), FVC (2, 4, 5) and FEV₁/FVC values (5) in adults. However, only two
81 studies have investigated the associations between the sulphur dioxide (SO₂) - one of the main
82 markers of industrial pollution - and lung function. The studies found that SO₂ was associated
83 with a lower FEV₁ (4, 6) and a lower FVC (4).

84 Small airway obstruction may reduce flow at low volume, leaving flow at high lung volumes
85 much less affected. Therefore, small airway function can be probed by measuring indices of
86 forced expiratory manoeuvres, such as the forced expiratory flow (FEF) between 25% and
87 75% of FVC (FEF_{25–75}) and at 75% of FVC (FEF₇₅) (7). Although small airway disorders are
88 frequently implicated in early-stage chronic obstruction (8) and in asthma (9), data on the
89 putative association with chronic exposure to outdoor air pollution are still very scarce (10).

90 In previous research, we found that a short-term exposure to outdoor air pollution was
91 associated with lower FEV₁/FVC, FEF_{25–75} and FEF₇₅ values (11). Hence, we aimed to study
92 the relationship between residential exposure to road-traffic-related and industrial pollutants
93 (NO₂, PM₁₀, and SO₂) and lung function including FEF_{25–75} and FEF₇₅ that may be more
94 specific of small airway obstruction.

95

96 **Methods**

97 **Study population**

98 The study included participants aged between 40 and 65 in the 2011-2013 *Enquête Littoral*
99 *Souffle Air Biologie Environnement* (ELISABET) cross-sectional survey. The ELISABET
100 study's methodology has been described in detail elsewhere (11–17). Briefly, the study sample

101 was representative of the general population in the Lille and Dunkirk urban areas of northern
102 France. Data were collected at the participant's home or (very occasionally) during a
103 consultation in a healthcare establishment. In all cases, a trained, registered nurse
104 administered a detailed questionnaire and performed spirometry testing. The study protocol
105 was approved by the local independent ethics committee (CPP Nord Ouest IV, Lille, France;
106 reference 2010-A00065-34; ClinicalTrials.gov identifier: NCT02490553), in compliance with
107 the French legislation on biomedical research. All participants provided their written, informed
108 consent to participation in the study.

109

110 Outcome assessment

111 Spirometry was performed according to the 2005 American Thoracic Society (ATS) and
112 European Respiratory Society (ERS) guidelines (18). The spirometers (Micro 6000, Medisoft,
113 Sorinnes, Belgium) were calibrated weekly. The highest recorded values of FEV₁, FVC and
114 FEV₁/FVC were selected for statistical analysis. We also measured FEF₂₅₋₇₅ and FEF₇₅ from
115 the expiration that had the highest sum of FEV₁ and FVC. No bronchodilators were
116 administered. All spirometry data were collected by eight trained nurses, and validated by an
117 experienced specialist physician (JLE). We expressed the spirometry data as z-score that
118 described the difference (in standard deviations) between the measured value and the value
119 predicted by the 2012 Global Lung Initiative equations (19).

120

121 Pollution and neighbourhood data

122 The pollution assessment and neighbourhood data have been described previously ((16), see
123 the Supplementary Materials). Briefly, the annual mean concentrations of NO₂, PM₁₀ (in Lille
124 and Dunkirk) and SO₂ (in Dunkirk only) were estimated between 2010 and 2013 (in Lille) and
125 between 2012 and 2013 (in Dunkirk) by the ATMO–Nord Pas de Calais air monitoring
126 organization, using an atmospheric dispersion modelling system. PM_{2.5} were had not been
127 estimated by ATMO-Nor Pas de Calais at the time for the study period. Each participant's place

128 of residence was located on a grid with a cell size of 25 m. We assessed the annual exposure
129 levels at the place of residence as the mean value of the four closest points in the grid,
130 weighted by the inverse square distance to each point (20). The overall pollution exposure for
131 each participant was then calculated as the average level of pollution over the year of their
132 inclusion and the year before.

133

134 Statistical analyses

135 The pollutant levels and the correlations between pollutant levels were described for each of
136 the two urban areas. The coefficients of linear regression models were expressed as z-scores
137 [95% CI] for an increment of 5 $\mu\text{g}/\text{m}^3$ in NO_2 and 2 $\mu\text{g}/\text{m}^3$ in PM_{10} and SO_2 . We also
138 expressed the coefficients in mL or mL/s for FEF25-75 and FEF75, as a percentage change
139 or percentage for FEV1/FVC, and as a percentage of the value predicted by the 2012 Global
140 Lung Initiative equations (Supplementary Tables 1 to 3). Estimates were adjusted for age
141 (continuous variable), sex (binary variable), height (continuous variable), inclusion year
142 (continuous variable), urban area (Lille or Dunkirk), investigator (class variable with 12
143 modalities for the 12 investigators), smoking status (former smoker, never smoker, current
144 smoker), body mass index (continuous variable), educational level (Primary education only,
145 Secondary education only, 2 to 4 years of higher education, 5 or more years of higher
146 education), and occupational exposure to fumes and dust (continuous variable). A job-
147 exposure matrix was used to yield an index for cumulative exposure to fumes and dust. This
148 cumulative exposure index was calculated for a subject's entire career by adding the exposure
149 indices obtained for each job (21).

150 We tested the interactions between outdoor air pollution on one hand and age, sex, smoking
151 status, educational level, urban area, asthma status, and time resident at current address on
152 the other. In sensitivity analyses, we further adjusted for asthma status and covariates linked
153 to the neighbourhood (income, population density, and the European deprivation index (EDI)).
154 To enable comparisons of effect sizes, the coefficients of the linear regression models

155 developed in previous studies were standardized for the same increment in pollutant levels
156 (Supplementary Tables 4 to 6). We estimated the PM₁₀ level by applying a 1/0.7 conversion
157 factor to the level of particulate matter with an aerodynamic diameter <2.5 µm (PM_{2.5})
158 measured in a previous study in which PM₁₀ data were not available (22, 23). Statistical
159 analyses were performed using R software (version 3.2.3, R Core Team, R Foundation for
160 Statistical Computing, Vienna, Austria, 2015, <http://www.R-project.org>). The threshold for
161 statistical significance was set to $p < 0.05$.

162

163 **Results**

164 The analyses included 2995 adults with data on air pollution, FEV₁ and FVC (Figure 1). Data
165 on FEF₂₅₋₇₅ and FEF₇₅ were available for 2968 individuals. Participants lacking data on
166 smoking status, height, and occupational exposure to fumes and dust were not included.
167 Likewise, participants with a height below 140 cm, with unacceptable spirometry data or having
168 lived for less than one year at their current residential address (n=282, Figure 1) were not
169 included.

170 The characteristics of the participants included in the final analysis are summarized in Table
171 1. Among the 2995 adults, 1543 lived in Lille and 1452 in Dunkirk, the mean age was 53 years,
172 47.1% of the participants were men, 50.2% had never smoked, 23.5% were obese (BMI ≥ 30
173 kg/m²), and 10.1% had not attended high school. In comparison with participants in Lille,
174 participants in Dunkirk had a higher BMI ($P < 0.0001$), a lower education level ($P < 0.0001$) and
175 a higher FEV₁/FVC ($P = 0.003$), and had lived longer at their current residential address
176 ($P < 0.0001$).

177 Air pollution levels were below the limit value set by the European Union (Figure 2). The NO₂
178 and PM₁₀ levels were higher in Lille than in Dunkirk ($P < 0.0001$, Figure 2). As evidenced by the
179 interquartile ranges, the variability of air pollution levels assigned to the participants' residential
180 addresses was relatively small but was greater in Lille than in Dunkirk. Levels of NO₂ and PM₁₀
181 were positively correlated in both Lille and Dunkirk ($r = 0.84$ and $r = 0.85$, respectively, $P < 0.0001$

182 for both). In Dunkirk, NO₂ and SO₂ levels were positively correlated (r=0.81, P<0.0001), as
183 were PM₁₀ and SO₂ levels (r=0.74, P<0.0001).

184

185 Association between outdoor air pollution and lung function

186 The lung function results are summarized in Table 2. NO₂ was associated with lower FEV₁ (-
187 0.10 [-0.15;-0.05]), FVC (-0.06 [-0.11;-0.02]), FEV₁/FVC (-0.07 [-0.11;-0.03]), FEF₂₅₋₇₅ (-0.09
188 [-0.14;-0.05]) and FEF₇₅ (-0.08 [-0.12;-0.04]) values. PM₁₀ was associated lower FEV₁ (-0.10
189 [-0.15;-0.04]), FVC (-0.06 [-0.11;-0.01]), FEV₁/FVC (-0.06 [-0.11;-0.01]), FEF₂₅₋₇₅ (-0.08 [-
190 0.13;-0.03]) and FEF₇₅ (-0.08 [-0.12;-0.04]) values. SO₂ was associated with lower values for
191 FEV₁ (-0.09 [-0.16;-0.02]), FEV₁/FVC (-0.07 [-0.13;-0.01]), FEF₂₅₋₇₅ (-0.09 [-0.15;-0.02]) and
192 FEF₇₅ (-0.08 [-0.14;-0.03]) but not for FVC (-0.05 [-0.11;0.009]).

193

194 Sensitivity analysis

195 After further adjustment for asthma status, the effect size of the associations tended to
196 decrease; the overall conclusions were the same, however (Supplementary Table 7). The
197 results of further adjustments for covariates linked to the neighbourhood are summarized in
198 Supplementary Tables 8 to 10. After adjustment for the neighbourhood median income, NO₂
199 remained significantly associated with all the outcomes. PM₁₀ remained significantly associated
200 with all the outcomes other than FVC. SO₂ was not significantly associated with a decrease in
201 lung function. After adjustment for the neighbourhood population density, NO₂, PM₁₀ and SO₂
202 remained significantly associated with all the outcomes other than FVC. After adjustment for
203 the neighbourhood EDI, NO₂ remained significantly associated with all the outcomes other
204 than FVC. PM₁₀ remained significantly associated with lower FEF₂₅₋₇₅ and FEF₇₅ values.
205 SO₂ remained significantly associated with lower FEV₁, FEF₂₅₋₇₅ and FEF₇₅ values.

206

207 Interaction analysis

208 Asthma status significantly modified the association between SO₂ exposure and FVC
209 (Supplementary Table 11); SO₂ was associated with a lower FVC in participants with asthma
210 and in those without; although the association's effect size was stronger and significant among
211 participants with asthma only. Smoking status significantly modified the association between
212 NO₂, PM₁₀ and SO₂ exposure and FEF75 (Supplementary Tables 12 to 14), between PM₁₀ and
213 SO₂ exposure and FEF25-75, and between SO₂ exposure and FEV1/FVC. All these
214 associations were negative, and were generally weaker in never-smokers. With regard to
215 smoking status, the associations were generally stronger in current-smokers than in former
216 smokers. The urban area (Lille or Dunkirk) did not significantly modify the effect of outdoor air
217 pollution on lung function (data not shown). All the other interactions tested did not achieve
218 statistical significance.

219

220 **Discussion**

221 **Key findings**

222 We investigated the effect of residential exposure to traffic-related and industrial pollutants on
223 lung function including FEF25-75 and FEF75 that may be more specific of small airway
224 obstruction. Even though the spatial variations in pollutant levels were low, we found that both
225 NO₂ and PM₁₀ were associated with significantly lower FEV1, FVC, FEV1/FVC, FEF25-75 and
226 FEF75 values, and SO₂ was associated with significantly lower FEV1, FEV1/FVC, FEF25-75
227 and FEF75 values.

228

229 **Comparison with previous studies**

230 FVC

231 The effect sizes observed in the present study are compared with those reported in the
232 literature in Supplementary Tables 4 to 6. The effect sizes for the associations between NO₂
233 and FVC and between PM₁₀ and FVC were quite similar to the literature values (4, 5, 23),
234 despite inter-study differences in populations, pollutant measurement methods, and exposure

235 ranges. Hence, these associations appear to be highly consistent. In a study performed in
236 Tasmania, the negative association between NO₂ and FVC was not significant; however, the
237 effect size and the confidence intervals were in line with our results (24). In contrast, the
238 ESCAPE study performed in eight European countries evidenced significant negative
239 associations for NO₂ and PM₁₀, although the size of the effect on FVC was much lower (2).

240 FEV1 and FEV1/FVC

241 Although associations between outdoor air pollution and FEV₁ or FEV₁/FVC have previously
242 been reported, the effect sizes varied markedly, and the associations were always weaker than
243 in the present study. The above-cited studies found negative associations between NO₂ and
244 FEV₁, between PM₁₀ and FEV₁ (2, 4–6) and between SO₂ (one of the main markers of industrial
245 pollution) and FEV₁ (4, 6). Negative associations between NO₂ and FEV₁/FVC (5, 6), and
246 between PM₁₀ and FEV₁/FVC (5) have also been described. Conversely, other studies did not
247 find an association between PM₁₀ or PM_{2.5} and FEV₁/FVC (6, 23). In the Tasmanian study cited
248 above, NO₂ was associated (but not significantly) with lower FEV1 and FEV1/FVC values,
249 although the confidence intervals were quite consistent with our results (24).

250 FEF 25-75 and FEF 75

251 In a prospective study of 4742 adults in Switzerland, a 10 µg/m³ decline in PM₁₀ levels over an
252 11-year period was associated with a slowing in the annual rate of decline in FEV1 and FEF25-
253 75 values (10). The Tasmanian study also observed a negative (but non-significant)
254 association between NO₂ exposure and FEF25-75, i.e. similar to that observed in the present
255 study (24). To the best of our knowledge, the link between air pollutants and FEF75 has not
256 previously been investigated. Most epidemiological studies do not use FEF25-75 or FEF75 as
257 indices of peripheral airway obstruction because these measurement display significant inter-
258 and intra-individual variability. In the ELISABET project, we used recent equipment and the
259 latest reference equations to analyze these two markers in a modern population; this approach
260 probably reduced the inter-individual variability in these flow measurements. Furthermore, the
261 forced exhalation manoeuvres were standardized, and the acceptability of forced exhalation

262 data was rigorously examined. All the flow-volume curves were recorded by a small number
263 of nurses. A single expert (blinded to the subject's identity and other data) visualized all the
264 flow-volume curves, and scrupulously applied the ATS/ERS guidelines on curve acceptability.
265 These precautions made it possible to (i) significantly reduce the variability of these distal flows
266 and (ii) optimally evaluate distal obstruction and the severity of the small airway disorders.

267 Possible explanations of inconsistent result for obstructive syndrome

268 Overall, the effect size for the relationship between air pollution and obstructive syndrome
269 seems inconsistent. The methods and device used for spirometry vary from one study to
270 another. For example, some studies used a sealed bell device (2, 5) that might measure flow
271 less accurately and might thus induce a non-differential measurement bias and weaker
272 associations. Another possible explanation relates to differences in the methods used to model
273 air pollution levels such as atmospheric dispersion modelling system, satellite-based land-use
274 regression (LUR) models, LUR models or spatial proximity models can influence the
275 associations between pollution and lung function. Likewise, geocoding methods used to assign
276 pollution estimates at the individual level can also influence the associations between pollution
277 and lung function (25). Nevertheless, variability in exposure measurements should also
278 influence associations with FVC.

279 **Subgroups analyses**

280 Asthma

281 Variations over time in expiratory lung function are greater extent in people with asthma than
282 in healthy people (26). Interestingly, we found that asthma status modified the association
283 between SO₂ and FVC. SO₂ was associated with a lower FVC in participants with asthma and
284 in those without, and the associations were stronger and statistically significant in participants
285 with asthma only. Although a previous study did not find a significant interaction with asthma
286 status, the researchers reported negative, non-significant associations between NO₂ and PM₁₀
287 with FVC in participants with ever-asthma and in participants without asthma; the associations
288 were stronger in the ever-asthma group (2).

289 Smoking status

290 Smoking is linked to a decrease in lung function in adults (27), and smoking cessation prevents
291 an excessive decline in lung function (28). We therefore looked at whether smoking status
292 influenced our findings. Indeed, smoking status significantly modified the association between
293 outdoor air pollution on some (but not all) lung function parameters. The negative associations
294 were generally weaker in never-smokers than in smokers, and weaker in former smokers than
295 current-smokers. Our results might explained by a greater vulnerability to the effects of
296 pollution in current smokers, given that smoking and pollution exposure drive major
297 inflammatory responses in the lung and thus in favour a decline in lung function (1, 28).
298 However, our results were not consistent with a previous study in which the associations
299 between PM₁₀, NO₂ and SO₂ with FEV₁ were (i) greater in former smokers and (ii) smaller and
300 similar in current and never-smokers (6). A study by Rice *et al.* reported a borderline-significant
301 relationship between PM_{2.5} exposure and a lower FEV₁ in former smokers, relative to never-
302 smokers; no association was found in current smokers (23). Rice *et al.* hypothesized that “*the*
303 *current-smokers may be less susceptible because the daily injury by active smoking may*
304 *overwhelm any incremental damage by long-term pollution exposure*” (23). Hence, reports on
305 the interaction between smoking and lung function are not consistent, and further studies are
306 needed to better evaluate the conjoint effects of smoking and outdoor air pollution exposure
307 on lung function.

308 **Sensitivity analyses**

309 Neighbourhood characteristic such as socioeconomic factor or population density may be
310 confounder in the association between air pollution and health. Socioeconomic status is often
311 a cause of residual confusion because it is associated with various health outcomes (29) and
312 with air pollution exposure (30). In a sensitivity analysis adjusted for the neighbourhood’s
313 median income and median EDI index and density, most of the associations between outdoor
314 air pollution and lung function remained statistically significant strengthening our results.

315 Nevertheless, the neighbourhood population density might be strongly correlated with many
316 sources of air pollution, and so adjusting for this factor is questionable.

317 **Mechanisms**

318 A decrease in lung function is also associated with biological factors, such as a high level of
319 oxidant stress (31), and a growing body of evidence suggests that outdoor air pollution
320 increases oxidative stress (1). Furthermore, it would be interesting to consider the impact of
321 genetic factors on associations between outdoor air pollution and lung function (i.e. gene-
322 environment interactions) because the genetic background can partly explain inter-individual
323 differences in lung function (32). Investigating these biological and genetic factors might
324 provide a better understanding of the effect of air pollution on lung function.

325

326 **Strengths and limitations**

327 Most previous studies examined the association between PM₁₀ and lung function, rather than
328 PM_{2.5}. However, fine particles and ultrafine particles might be more toxic due variously to
329 deeper penetration into the bronchi, a larger contact area, and their chemical composition (33).
330 To complete our present work, data on both ultrafine particles and PM_{2.5} would be needed.
331 Furthermore, the identification of a causal relationship between air pollutant and lung function
332 is a major challenge because of the complex interactions between outdoor air pollutants.
333 Indeed, PM₁₀ and NO₂ are highly correlated in the ELISABET study the Pearson correlation
334 were 0.87 in Lille and 0.83 in Dunkirk. (16)

335 One strength of the present study was our use of a dispersion model based on up-to-date
336 scientific data (such as land use) to estimate air pollution levels at each participant's residential
337 address. However, a non-differential misclassification bias might have been present because
338 data on time-activity patterns were not available in our study. Furthermore, our study did not
339 take account of indoor air pollution. Given that this measurement error applies to all study
340 participants, it would only attenuate the observed effects. To compare our association between
341 PM₁₀ and lung function with a previous study (23), a conversion factor to estimate the PM₁₀

342 level from the data on PM_{2.5} was used and so this comparison should be interpreted with
343 caution

344 This study has other limitation. The cross-sectional design means that exposure did not
345 necessarily precede decline of lung function, and so causation cannot be inferred. Finally, on
346 the grounds of the correlation of lung function parameters and not dependant statistical tests,
347 we cannot take into account multiple test in our analysis.

348

349 **Conclusion**

350 The results of the present study suggest that residential exposure to relatively low levels of air
351 pollution (i.e. in two urban areas where pollution levels are below the limits set by the European
352 Union) has an effect on lung function - emphasizing the need to reduce air pollution levels
353 further. Second, our study provided new evidence that residential exposure to outdoor air
354 pollution can be associated with an impairment in small airway function in adults.

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385

386 **Competing interest**

387 AH, SH, DC, MR, FO, NCK, JG, RM, JLE and LD declare that they have no conflicts of interest.
388 PA reports personal fees from Servier, personal fees from Total, personal fees from
389 Genoscreen, personal fees from Fondation Alzheimer, outside the submitted work.

390 LD, RM and SH have contributed to an expert report ordered by the Lille European metropole
391 « Rapport d'expertise à propos de la localisation de la piscine du projet d'aménagement de la
392 gare Saint Sauveur à Lille » [Expert report on the location of the swimming pool of the
393 development project of the Saint Sauveur station in Lille] with no personal fees

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Table 1. Personal and neighbourhood-related characteristics of study population, overall and by urban area.

	All participants (n=2995)	Lille (n=1543)	Dunkirk (n=1452)	P
Age (years), mean \pm SD	53.2 \pm 7.22	53.0 \pm 7.20	53.3 \pm 7.25	0.30
Sex, men, n (%)	1412 (47.1)	717 (49.3)	695 (47.9)	0.44
Smoking status, n (%)				
Never-smokers	1505 (50.2)	760 (49.2)	745 (51.3)	0.50
Former smokers	931 (31.1)	493 (32.0)	438 (30.2)	
Current smokers	559 (18.7)	290 (18.8)	269 (18.5)	
BMI (kg/m ²), n (%)				
<25	1142 (38.1)	650 (42.1)	492 (33.9)	<0.0001 [¶]
[25-30[1150 (38.4)	575 (37.3)	575 (39.6)	
\geq 30	703 (23.5)	318 (20.6)	385 (26.5)	
Educational level, n (%)				
Primary education only	302 (10.1)	125 (8.1)	177 (12.2)	<0.0001 [¶]
Secondary education only	1570 (52.4)	702 (45.5)	868 (59.8)	
2 to 4 years of higher education	564 (18.8)	347 (22.5)	217 (14.9)	
5 or more years of higher education	559 (18.7)	369 (23.9)	190 (13.1)	
Time at current place of residence (years), mean \pm SD	17.8 \pm 10.6	17.0 \pm 10.4	18.7 \pm 10.7	<0.0001 [¶]
Ever-asthma [§] , n (%)	(n=2950) 290 (9.83)	(n=1527) 157 (10.3)	(n=1423) 133 (9.35)	0.39
IRIS median income (\times 1000 euros), median (IQR)	18.7 (16.2; 21.2)	20.7 (16.9; 22.0)	17.0 (16.0; 19.8)	<0.0001 [¶]
IRIS density (1000 inhabitants/km ²), median (IQR)	(n=2994) 3.81 (1.40; 6.94)	4.10 (1.82; 7.69)	(n=1451) 3.48 (0.99; 6.43)	<0.0001 [¶]
IRIS EDI, median (IQR)	(n=2994) 0.54 (0.51; 0.69)	0.51 (0.40; 0.72)	(n=1541) 0.56 (0.46; 0.66)	0.02 [¶]
Outdoor air pollution (μ g/m ³), median (IQR)				
NO ₂	21.9 (19.4; 26.2)	26.0 (22.6; 28.8)	20.3 (18.2; 21.4)	<0.0001 [¶]
PM ₁₀	26.7 (25.8; 27.6)	27.0 (25.7; 28.3)	26.5 (25.8; 27.2)	<0.0001 [¶]
SO ₂	(n=1452) 3.07 (2.14; 3.89)	/	3.07 (2.14; 3.89)	
Lung function, median (IQR)				
FEV ₁ (L)	3.01 (2.51; 3.59)	3.01 (2.50; 3.59)	3.03 (2.52; 3.59)	0.55
FVC (L)	3.96 (3.34; 4.76)	3.96 (3.35; 4.79)	3.95 (3.32; 4.74)	0.64
FEV ₁ /FVC (%)	76.8 (72.2; 80.5)	76.5 (71.9; 80.3)	77.1 (72.5; 80.7)	0.003 [¶]
FEF ₂₅₋₇₅ (L/s)	(n=2968) 2.92 (2.24; 3.70)	(n=1528) 2.89 (2.22; 3.66)	(n=1440) 2.95 (2.26; 3.74)	0.08
FEF ₇₅ (L/s)	(n=2968) 1.12 (0.79; 1.51)	(n=1528) 1.10 (0.79; 1.47)	(n=1440) 1.14 (0.80; 1.55)	0.006 [¶]

N: number, SD: standard deviation, IQR: interquartile range, BMI: body mass index, FEV₁: forced expiratory volume in one second, FVC: forced vital capacity, FEF₂₅₋₇₅: forced expiratory flow between 25% and 75% of FVC, FEF₇₅: forced expiratory flow at 75% of FVC, IRIS: regrouped statistical information block, EDI: European Deprivation Index.

[§] Participants reporting ever-asthma diagnosed by a physician.

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Table 2. Associations between outdoor air pollution and lung function, expressed as z-scores.

	NO ₂	PM ₁₀	SO ₂
FEV1	N=2995 -0.100 (-0.149, -0.051)***	N=2995 -0.095 (-0.149, -0.040)***	N=1452 -0.092 (-0.160, -0.024)*
FVC	N=2995 -0.061 (-0.105, -0.017)**	N=2995 -0.060 (-0.109, -0.011)*	N=1452 -0.050 (-0.114, 0.009)†
FEV1/FVC	N=2995 -0.067 (-0.109, -0.025)**	N=2995 -0.061 (-0.108, -0.014)*	N=1452 -0.071 (-0.128, -0.013)*
FEF ₂₅₋₇₅	N=2968 -0.091 (-0.138, -0.045)***	N=2968 -0.081 (-0.132, -0.029)**	N=1440 -0.089 (-0.154, -0.025)**
FEF ₇₅	N=2968 -0.081 (-0.120, -0.042)***	N=2968 -0.078 (-0.121, -0.035)	N=1440 -0.081 (-0.136, -0.027)**

FEV1: force expiratory volume in 1 second, FVC: force vital capacity, FEF₂₅₋₇₅: forced expiratory flow between 25% and 75% of FVC, FEF₇₅: forced expiratory flow at 75% of FVC.

The linear regression models' regression coefficients were expressed as z-scores. The models were adjusted for age, sex, height, BMI, year of inclusion, investigator, urban area (Lille or Dunkirk), smoking status, educational level, and occupational exposure to fumes and dust. SO₂ analysis were available only in Dunkirk.

*** p < 0.001; ** p < 0.01; * p < 0.05; † 0.05 ≤ p < 0.1; † p ≥ 0.1

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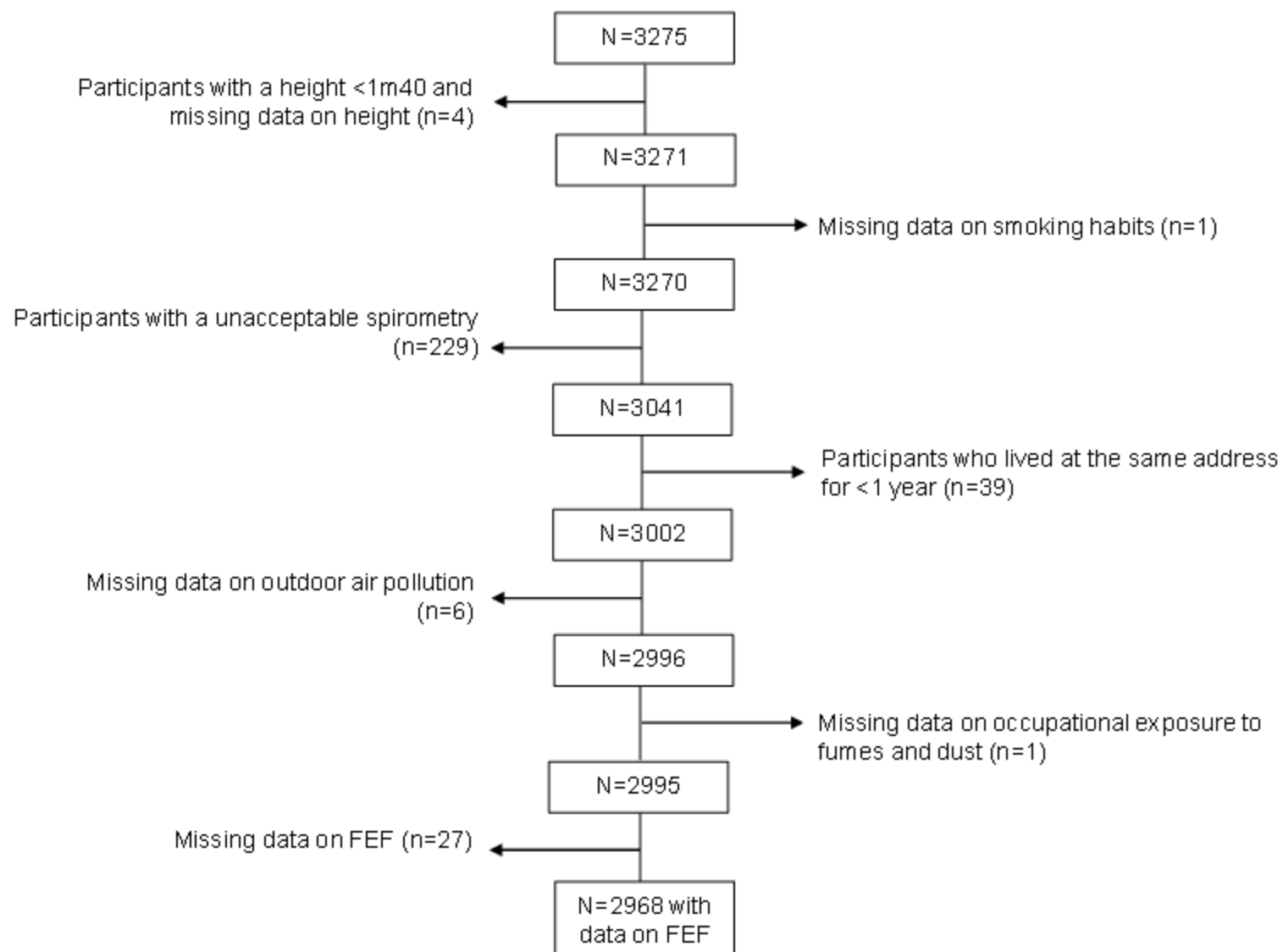
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513 **Figure legends**

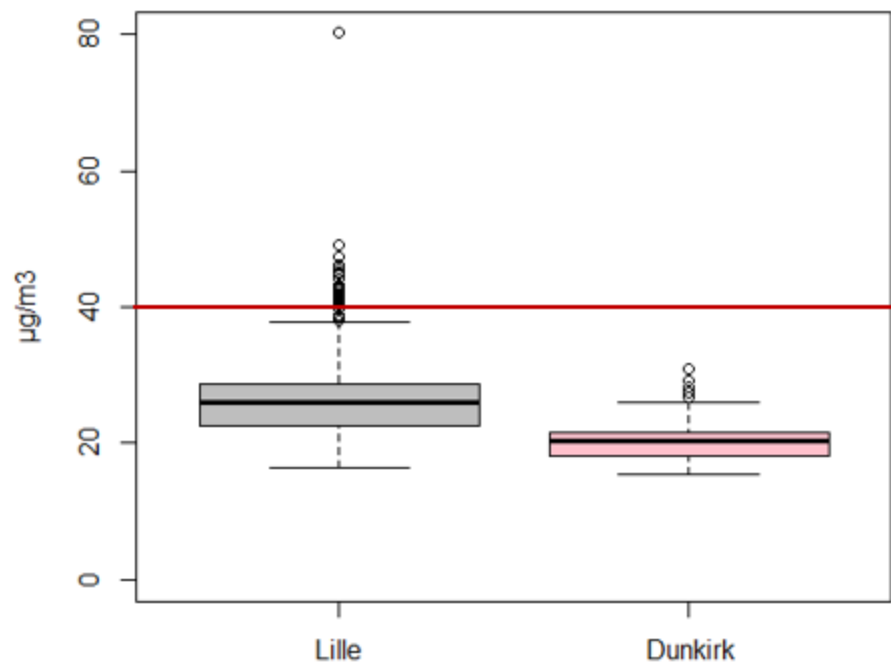
514 **Figure 1.** Study flow chart.

515 **Figure 2.** Description of NO₂ and PM₁₀ levels by urban area.

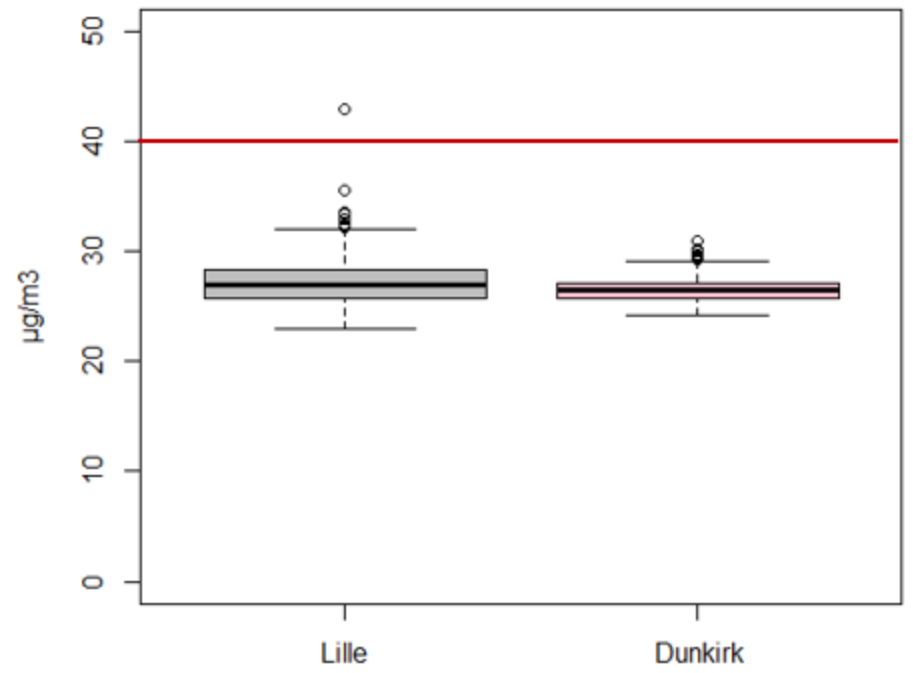
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Description of NO2 levels by urban area



Description of PM10 levels by urban area



— European Union limit value