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1 **Pre-natal exposure to NO₂ and PM_{2.5} and newborn lung function: an approach based on repeated**
2 **personal exposure measurements**

3
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27

28 **ABSTRACT**

29 Context

30 While strong evidence supports adverse effects of pre-natal air pollution on child's lung
31 function, previous studies rarely considered fine particulate matter (PM_{2.5}) or the potential
32 role of offspring sex and no study examined the effects of pre-natal PM_{2.5} on the lung function
33 of the newborn.

34 Aim

35 We examined overall and sex-specific associations of personal pre-natal exposure to PM_{2.5}
36 and nitrogen (NO₂) with newborn lung function measurements.

37 Methods

38 This study relied on 391 mother-child pairs from the French SEPAGES cohort. PM_{2.5} and NO₂
39 exposure was estimated by the average concentration of pollutants measured by sensors
40 carried by the pregnant women during repeated periods of one week. Lung function was
41 assessed with tidal breathing analysis (TBFVL) and nitrogen multiple breath washout (N₂MBW)
42 test, performed at 7 weeks. Associations between pre-natal exposure to air pollutants and
43 lung function indicators were estimated by linear regression models adjusted for potential
44 confounders, and then stratified by sex.

45 Results

46 Mean exposure to NO₂ and PM_{2.5} during pregnancy was 20.2 µg/m³ and 14.3 µg/m³,
47 respectively. A 10 µg/m³ increase in PM_{2.5} maternal personal exposure during pregnancy was
48 associated with an adjusted 2.5 ml (2.3%) decrease in the functional residual capacity of the
49 newborn (*p*-value=0.11). In females, functional residual capacity was decreased by 5.2 ml
50 (5.0%) (*p*=0.02) and tidal volume by 1.6 mL (*p*=0.08) for each 10 µg/m³ increase in PM_{2.5}. No
51 association was found between maternal NO₂ exposure and newborns lung function.

52 Conclusions

53 Personal pre-natal PM_{2.5} exposure was associated with lower lung volumes in female
54 newborns, but not in males. Our results provide evidence that pulmonary effects of air
55 pollution exposure can be initiated in utero. These findings have long term implications for
56 respiratory health and may provide insights into the underlying mechanisms of PM_{2.5} effects.

57 Key words

58 Newborn, lung function, personal exposure, air pollution, pregnancy

59 Introduction

60 Although the maturation of the lungs is not complete until late adolescence, the lungs
61 undergo a series of well-orchestrated events that begins early in utero through complex
62 processes involving interrelated systems (e.g. neuroendocrine, immune autonomic) such that
63 they are ready to function following birth (Pinkerton and Joad 2006; Schittny 2017).
64 Intrauterine and early post-natal periods are windows of time that are vulnerable to

74 environmental exposures because of the high growth rate of organs combined with immature
75 detoxification systems. Growing evidence indicates that exposure to traffic-related air
76 pollutants during the developmental period has adverse effects on child respiratory health,
77 including reported associations between fine particulate matter with an aerodynamic
78 diameter less than 2.5 microns (PM_{2.5}), coarse particulate matter with an aerodynamic
79 diameter less than 10 microns (PM₁₀), and nitrogen dioxide (NO₂), with respiratory symptoms
80 and lung function (Cai et al. 2020; Garcia et al. 2021; Korten et al. 2017; Schultz et al. 2017).

81
82 Pre-natal exposure to traffic-related air pollutants has been associated with lung function
83 (Bose et al. 2018; Bougas et al. 2018; Cai et al. 2020; He et al. 2019; Latzin et al. 2009; Lee et
84 al. 2018; Milanzi et al. 2018; Morales et al. 2015; Mortimer et al. 2008; Usemann et al. 2019).
85 However, most of these studies have relied on spirometry tests conducted after the child has
86 reached 5 years of age. The importance of early lung development on the lifelong lung
87 trajectory, including lung growth and peak lung function in early adulthood, is well established
88 (Schultz et al. 2018; Stern et al. 2007) and measuring newborn lung function using
89 noninvasive techniques has proven feasible and relevant to the field (Latzin et al. 2009). Fine
90 traffic-derived particles can cross the placenta and have direct or indirect effects on the
91 developing fetus (Bongaerts et al. 2020, 2021; Nääv et al. 2020), but most of the literature
92 has focused on pre-natal ambient NO₂ and PM₁₀, with limited data associating lung
93 development and PM_{2.5} exposures (Jedrychowski et al. 2010; Lee et al. 2018; Milanzi et al.
94 2018). Another limitation lies in the use of ambient models based upon residential addresses
95 to estimate the exposures of study participants. This approach does not account for various
96 microenvironments visited by the participant nor for time spent indoors, leading to the
97 possibility of substantial exposure misclassification. To our knowledge, no study has examined
98 associations of personal pre-natal exposure to PM_{2.5} and NO₂ with lung function of the
99 newborn.

100
101 Identifying determinants of early infant lung function has long term implications for
102 respiratory health and might further help in developing preventive programs for at-risk
103 children. Recent studies have underlined the possibly sex-specific nature of respiratory effects
104 of pre-natal air pollutants exposure (Bose et al. 2018; Leon Hsu et al. 2015; Schultz et al.
105 2017). Human and animal studies show differences in lung growth and airway development
106 between male and female fetuses lending support to differential responses to environmental
107 toxicants (Bolte et al. 2021; Carey et al. 2007; Liptzin et al. 2015; Torday et al. 1981).

108
109 To address these research gaps, we examined the impact of pre-natal PM_{2.5} and NO₂, as
110 measured by repeated personal sampling, on lung function of the newborn in a prospective
111 couple-child cohort. We hypothesized that lung function responses to air pollutants exposure
112 would differ between males and females.

113
114

115 **Materials and methods**

116 Study population

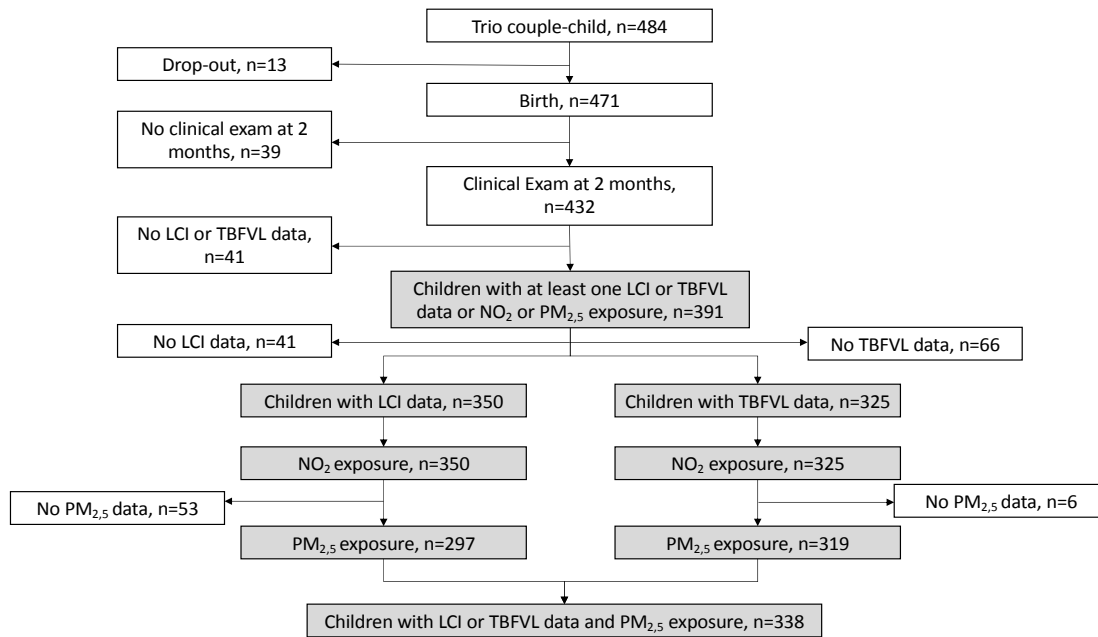
117 This study relied on the French prospective SEPAGES (Suivi de l'Exposition à la Pollution
118 Atmosphérique durant la Grossesse et Effet sur la Santé) couple-child cohort, that recruited
119 484 pregnant women from the Grenoble metropolitan area, from 2014 to 2017 (Lyon-Caen et
120 al. 2019). The inclusion criteria were being pregnant by less than 19 gestational weeks, older

121 than 18 years old, having a singleton pregnancy, being affiliated to the French national
122 security system, planning to deliver in one of the four maternity clinics of Grenoble and living
123 in the study area. Questionnaires, interviews and clinical examinations during and after
124 pregnancy were used to collect sociodemographic and medical information on the children
125 and parents. For the purposes of our study, we focused on 391 mother-child pairs with both
126 exposure to air pollutants during pregnancy and child lung function assessments at 2 months
127 (Figure 1). The SEPAGES cohort received approval from the Ethics Committee (CPP) Sud-Est V,
128 the National Commission on Informatics and Liberty (CNIL). Both the mother and the father of
129 the expected child gave written informed consent prior to inclusion.

130

131

132 Figure 1: Flowchart for the selection of the study population



133
 134 TBFVL: Tidal Breathing Flow Volume Loops; LCI: Lung Clearance Index; NO₂: Nitrogen dioxide;
 135 PM_{2.5}: Particulate matter with a diameter of less than 2,5 micrometres

136
 137
 138

139 Personal air pollution exposure assessment

140 Each woman carried wearable devices to measure her personal exposure to NO₂ (passive
141 sampler from Passam AG, Männedorf, Switzerland) and PM_{2.5} (MicroPEM active air sampler,
142 RTI International, Research Triangle Park, NC, USA) (Chartier et al. 2017) during 1 to 3
143 separate weeks during pregnancy. Each woman pregnancy exposure to NO₂ and PM_{2.5} was
144 estimated by averaging the measured concentrations from the personal sensors carried by
145 the woman. Each measurement week lasted from 4 to 10 days, with 99% of samples lasting
146 greater than 7 days. Participants were instructed to leave devices on during the measurement
147 week and to keep the devices close to them (within 2m) when it had to be removed (e.g.
148 sleeping, bathing). NO₂ concentrations were measured by spectrophotometer using
149 previously established methods (Hafkenscheid et al. 2009). The MicroPEM collects both real-
150 time PM mass concentration data and a PM sample on a 25 mm PTFE filter for gold-standard
151 gravimetric analysis (Cho et al. 2016). All filters were pre- and post-weighed at RTI
152 International, using a microbalance (Mettler Toledo UMX2) housed in a temperature- and
153 humidity-controlled environmental chamber (21 C, 35% RH). Real-time personal PM_{2.5}
154 concentrations were processed with the MicroPEM Docking Station software (RTI
155 International, RTP, NC) at 10-s intervals and were calibrated with the corresponding
156 gravimetric filter measurements. The instruments were calibrated once before starting each
157 measurement with MicroPEM Docking Station software (RTI International, RTP, NC) (Cho et al.
158 2016).

159

160

161 Lung function

162 Lung function parameters were measured in the infants (mean age 7 weeks), using an infant
163 face mask (AMBU Size 1 Infant) during natural sleep (following regular feeding) in supine
164 position with the head midline, following to ATS/ERS guidelines (Bates et al. 2000). The first
165 20 to 30 breaths were removed from analysis to allow for stabilization of the infant's
166 breathing pattern. Ten minutes of tidal breathing was then recorded, and three
167 measurements of nitrogen multiple-breath washout (N₂MBW) were performed.

168

169 *Tidal breathing*

170 The first 50 regular breaths of tidal breathing were used, excluding sighs and 10 breaths
171 before and after a sigh. Then, mean tidal breathing parameters of flow, volumes and flow-
172 volume loop were calculated following to the ERS/ATS guidelines (Bates et al. 2000).
173 Outcomes were tidal volume (V_T), minute ventilation (MV), respiratory rate (RR) and the time
174 to peak tidal expiratory flow (t_{PTEF})/expiratory time (t_E) ratio.

175

176 *Multiple-breath washout*

177 Lung volume and ventilation heterogeneity were measured by means of N₂MBW technique
178 with pure oxygen (O₂), using the Exhalyzer© and Spiroware© (Ecomedics). Functional
179 Residual Capacity (FRC) and Lung Clearance Index (LCI), the latter being defined by the
180 number of lung volume turnovers required to reduce the concentration of N₂ below 2.5%,
181 were recorded. Up to 3 satisfactory measures were obtained. All tests were carefully
182 reviewed and accepted using the following criteria: regular breathing during quiet sleep, V_T
183 within target, no swallowing or sigh in the first 5 breaths, no sign of leak and N₂ concentration
184 below 2.5 % for at least 3 consecutive breaths (end of test criteria).

185 Use of pure oxygen may induce transient hypoventilation (hV) characterized by transient
186 decrease in tidal volume (Gustafsson et al. 2017). For each N2MBW measure, we calculated
187 the degree of hypoventilation defined by the maximum drop of V_T in the first 15 breaths
188 following O_2 exposure as compared to the mean V_T in breaths before O_2 exposure. Then, the
189 observed LCI and FRC values were corrected for the degree of hypoventilation by using the
190 residuals of the mixed linear regression (to account for repeated measures by subjects) of the
191 degree of hypoventilation on LCI or FRC (Mortamais et al. 2012).

192
193 A total of 865 valid tests were retained, with a median [Q1; Q3] of 3[2; 3] tests per child. Both
194 for LCI and FRC, the averaged hV_{corrected} value per subject was used.

195 196 Statistical analyses

197 Separate linear regressions for each pollutant (NO_2 , $PM_{2.5}$) and each lung function parameter
198 (LCI, FRC, V_T , MV, RR, t_{PTEF}/t_E) were used to study the associations between pre-natal
199 exposures and newborn lung function. Regressions were adjusted for *a priori* selected
200 confounders and predictors of newborn lung function and comprised child characteristics
201 including age (continuous), sex, height at 2 months (continuous), gestational age at birth
202 (continuous), season of birth (4 categories), tobacco smoking exposure (yes/no, defined as
203 maternal active or passive smoking during pregnancy or passive exposure of the child after
204 birth), and breastfeeding at 2 months as well as parental characteristics including parents
205 highest educational level (< master's degree, \geq master's degree), paternal or maternal
206 asthma, paternal or maternal rhinitis, delivery mode (vaginal delivery, c-section). To assess
207 whether maternal exposure to air pollutants effects on newborns lung function differed
208 between females and males, sex-stratified models and models with interaction terms were
209 fitted. Penalized splines models using cubic regression splines with 12 knots were used to
210 estimate the shape of the relationship between air pollutants and lung function. The optimal
211 degree of freedom was defined by minimizing AIC and nonlinearity was evaluated with a Wald
212 test. We relied on the following threshold for results interpretation: main effects were
213 considered statistically significant for p -values ≤ 0.05 , interaction terms were considered
214 suggestive of an interaction for p -values less than 0.20.

215 216 Sensitivity analyses

217 Sensitivity analyses were conducted by excluding 1) one fourth of the newborns with the
218 highest degree of hypoventilation ($n=80$ for NO_2 analyses and $n=70$ for $PM_{2.5}$ analyses) in
219 order to minimize potential measurement error on lung function parameters, 2) women with
220 only one measurement week of air pollutants during pregnancy to minimize potential
221 measurement error on air pollution exposure and 3) by excluding the lowest (below 1st
222 percentile) and highest values (above the 99th percentile) of the outcomes and exposures,
223 resulting in the exclusion of 4% to 5% of the population of each analysis.

224
225
226 Analyses were carried out using SAS (version 9.4) R (version 3.6.0) software.

227 228 **Results**

229
230 Among 391 children included, 55% were males, 28% were exposed in utero or post-natally to
231 tobacco smoking, 84% were born by vaginal delivery and 86% were still breastfed at 2

232 months (Table 1). Children were aged 49 days on average at lung function examination.
233 Among the 391 children with at least one LCI or TBFVL measurement, 350 had LCI measured
234 and 325 had TBFVL evaluated.
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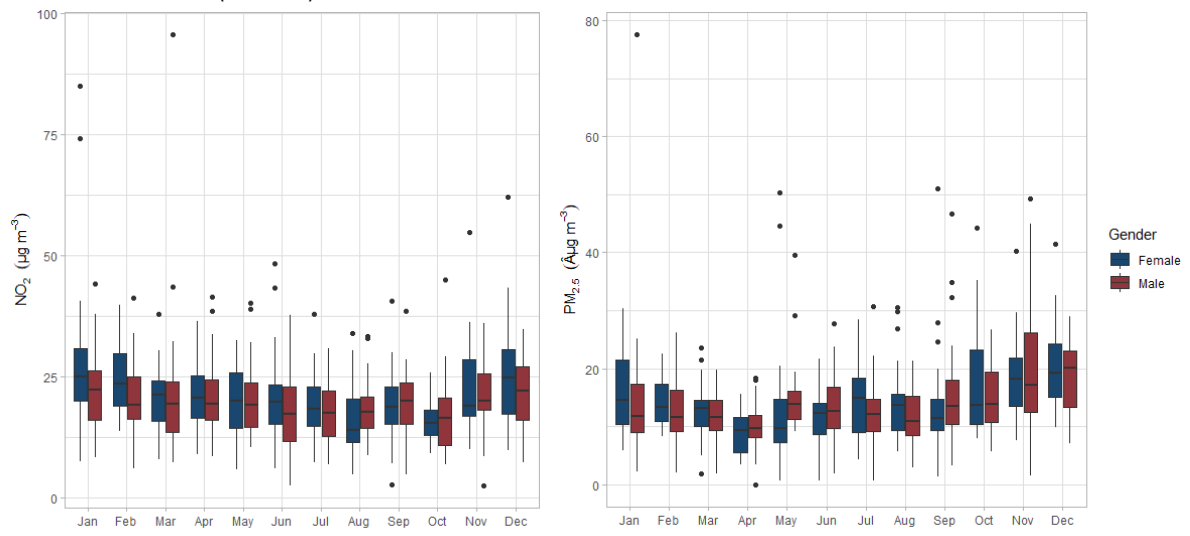
Table 1: Characteristics of the study population, SEPAGES cohort (n=391)

Characteristics	n (%)		
Sex of the child			
	Male	213	(54.5)
	Female	178	(45.5)
Tobacco smoking exposure¹			
	No	282	(72.3)
	Yes	108	(27.7)
Season of birth			
	January-March	83	(21.2)
	April-June	91	(23.3)
	July-September	111	(28.4)
	October-December	106	(27.1)
Parents highest educational level			
	< Master's degree	115	(29.4)
	≥ Master's degree	276	(70.6)
Parental history of asthma			
	No	254	(72.8)
	Yes	95	(27.2)
Parental history of rhinitis			
	No	135	(36.7)
	Yes	233	(63.3)
Still breastfed at 2 months			
	No	53	(13.8)
	Yes	332	(86.2)
Delivery mode			
	Vaginal	330	(84.4)
	Caesarean section	61	(15.6)
Moved during pregnancy			
	No	319	(81.6)
	Yes	72	(18.4)
	n	mean (std)	[min-max]
Child age at exam (days)	391	7.0 (1.1)	[5.4-16.1]
Height at exam (cm)	390	56.4 (2.2)	[50.0-63.2]
Gestational age at birth (weeks)	391	39.3 (1.5)	[30.0-42.0]

239 ¹ defined as maternal active or passive smoking during pregnancy or passive exposure of the
240 child after birth
241
242
243

244 Individual measurements of personal exposure followed a seasonal trend with higher NO₂ and
245 PM_{2.5} exposure levels during the cold season (Figure 2). Average exposure to NO₂ and PM_{2.5}
246 during pregnancy was 20.2 µg/m³ and 14.3 µg/m³, respectively (Table 2). Mean NO₂ exposure
247 was slightly higher for women carrying female foetuses compared to women carrying males
248 (Table 2). These average exposures were calculated, for 95.4% of women for NO₂ and 82% of
249 women for PM_{2.5}, using 2 or 3 weeks of measurements performed during pregnancy (Table
250 S1). Only 4.9% of women for NO₂ and 18% for PM_{2.5} performed only one week of
251 measurement during pregnancy. Most of the measurement weeks were performed during
252 the 2nd (52.1% for NO₂ and 44.3% for PM_{2.5}) or 3rd (44.4% for NO₂ and 52.3% for PM_{2.5})
253 trimesters of the pregnancy (Table S1). The distributions of average exposure to NO₂ and
254 PM_{2.5} during pregnancy were quite similar when restricting the population to women who
255 performed 3 or ≥2 measurements weeks (Table 3).
256
257

258 Figure 2: Seasonal variation of measurements of NO₂ and PM_{2.5} personal exposure in the
259 SEPAGES cohort (n=391)



260
261
262
263

264 Table 2: Personal pre-natal exposure to air pollutants and newborn lung function indicators
 265 measured in 391 mother-child participants of the SEPAGES cohort

	All participants			Females		Males	
	n	mean (std)	[min-max]	n	mean (std)	n	mean (std)
PM _{2.5} pregnancy (µg/m ³)	338	14.3 (6.3)	[2.2-46.7]	158	14.2 (6.5)	180	14.2 (6.1)
NO ₂ pregnancy (µg/m ³)	391	20.2 (7.0)	[5.3-57.6]	178	20.8 (7.6)	213	19.6 (6.5)
LCI	350	7.6 (1.1)	[4.5-11.0]	158	7.3 (1.1)	192	7.8 (1.1)
FRC (ml)	350	106.4(18.1)	[62.2-89.7]	158	103.7(17.5)	192	108.6(18.3)
V _T (ml)	325	34.1 (7.1)	[13.5-55.1]	155	32.5 (7.0)	170	35.6 (6.8)
MV (ml/kg)	325	319.1(54.3)	[155.5-509.7]	155	321.8(58.1)	170	316.7(50.5)
T _{PTEF} /T _E (%)	325	36.4 (9.9)	[18.8-70.7]	155	36.6 (9.5)	170	36.3(10.3)
RR min ⁻¹	325	46.4(11.2)	[25.4-84.6]	155	47.3(12.1)	170	45.5(10.4)

266 LCI: lung clearance index, FRC: functional residual capacity, V_T :tidal volume, MV: minute
 267 ventilation, RR: respiratory rate, tPTEF: time to peak tidal expiratory flow; tE: expiratory time
 268
 269
 270

271 Table 3: Maternal NO₂ and PM_{2.5} exposure levels (µg/m³) during pregnancy estimated using
 272 personal devices, SEPAGES cohort, n=391

	n	mean	sd	Percentiles					IQR
				p5	p25	p50	p75	p95	
NO₂ exposure									
During pregnancy, for all participants	391	20.2	7.0	10.5	15.3	19.3	24.4	42.5	9.1
participants with ≥2 measurements	373	20.2	7.1	10.5	15.3	19.3	24.3	31.8	9.1
participants with 3 measurements	82	21.0	6.9	11.8	15.8	20.4	26.1	31.6	10.3
PM_{2.5} exposure									
During pregnancy, for all participants	338	14.3	6.27	5.9	10.5	13.2	17.2	25.4	6.7
participants with ≥2 measurements	277	14.2	5.81	6.3	10.6	13.2	17.0	24.9	6.4
participants with 3 measurements	1	14	--	--	--	--	--	--	--

273
 274
 275

276 While maternal NO₂ exposure during pregnancy was negatively associated with all parameters
277 of newborn's lung function (except LCI), none of these associations were statistically
278 significant (Figure 3). Sex-specific results for NO₂ did not vary. A 10 µg/m³ increase in PM_{2.5}
279 maternal personal exposure during pregnancy was associated with an adjusted 2.5 ml
280 (representing 2.3% of the average FRC) decrease in the functional residual capacity of the
281 newborn (p-value=0.11) (Figure 3, Table S2). This association was heterogeneous by sex
282 subgroups with a statistically significant decrease of functional residual capacity in females (-
283 5.2 ml (representing 5.0% of the average FRC), CI_{95%} -9.5, -1.0, *p*=0.02), while the estimated
284 association was close to the null for males (0.3 ml (representing 0.3% of the average FRC),
285 CI_{95%} -4.3, 4.8, *p*=0.91) (Figure 3, Table S2). Suggestive associations of PM_{2.5} exposure with
286 increased respiratory rate (2.4 min, for each 10 µg/m³ increase in PM_{2.5}, CI_{95%} -0.7, 5.6,
287 *p*=0.13) and decreased tidal volume (-1.6 mL, for each 10 µg/m³ increase in PM_{2.5}, CI_{95%} -3.4,
288 0.2, *p*=0.08) were found among females, while results were less conclusive for males (-1.2
289 min, CI_{95%} -3.9, 1.6, *p*=0.40 for respiratory rate and 0.1 ml, CI_{95%} -1.7, 1.8, *p*=0.95, for tidal
290 volume) (Figure 3, Table S2). We found evidence for effect modification by sex on the
291 association between PM_{2.5} and respiratory rate (*p*-interaction = 0.09). Other interaction terms
292 with sex did not reach statistical significance (*p*-interaction>0.20) (Table S2). The penalized
293 spline models indicated linear concentration–response relationships between both pollutants
294 and all lung function parameters.

295

296 Sensitivity analyses

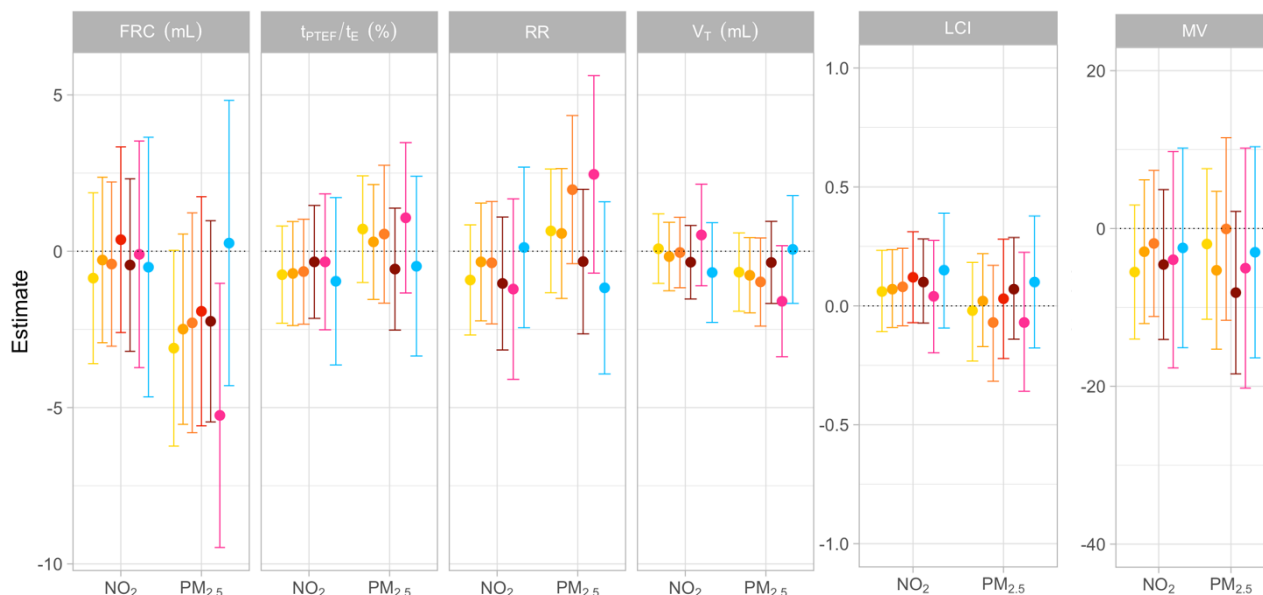
297 Results from sensitivity analyses were generally consistent albeit less significant given
298 reduced power that resulted from excluding participants (Figure 3).

299

300

301 Figure 3: Association between maternal personal exposure to NO₂ and PM_{2.5} during pregnancy (10 µg/m³ increase) and lung function of the
 302 newborn, SEPAGES cohort, n=391

- Univariate
- Multivariate
- Participants with ≥2 measurement weeks
- Participants without extreme values
- Girls
- Boys



304 **Univariate:** regression models included air pollutant exposure. **Multivariate:** regression models were adjusted for child age (continuous), child sex, gestational age at delivery
 305 (continuous), height at 2 months (continuous), tobacco smoking exposure (yes/no, defined as maternal active or passive smoking during pregnancy or passive exposure of the
 306 child after birth), season of birth (4 categories), parents highest educational level (< master's degree, ≥ master's degree), paternal or maternal asthma, paternal or maternal
 307 rhinitis, breastfeeding (no or <1 month, ≥1 month), delivery mode (vaginal delivery, c-section). **Participants with ≥2 measurement weeks:** 16 participants for NO₂ and 52 for
 308 PM_{2.5} who had only one measurement week during pregnancy were excluded from the multivariate regression models. **Participants without hypoventilation:** newborns with
 309 the highest degree of hypoventilation were excluded from the multivariate regression models. **Participants without extreme values:** Participants with exposures or outcomes
 310 below the 1st percentile or above the 99th were excluded from multivariate regression models (exclusion of approx. 5% of the population). **Females:** multivariate models were
 311 restricted to females. **Males:** multivariate regression models were restricted to males.
 312 FRC: functional residual capacity (ml), LCI: Lung clearance index, MV: minute ventilation (ml/kg), V_T: tidal volume (ml), T_{PTEF}/T_E: time to peak tidal expiratory flow/expiratory
 313 time, RR: respiratory rate per minute.
 314
 315

316 **Discussion**

317 This is the first prospective study to measure personal pre-natal exposure of the mother to
318 NO₂ and PM_{2.5} and to show association with newborn lung function. Our results suggest that
319 females, but not males, born to mothers with higher exposure to PM_{2.5} during pregnancy
320 were at higher risk for lower lung volumes, as reflected by the lower FRC and tidal volume
321 measured at 2 months of age. No significant association was observed with NO₂. These data
322 add to a growing literature linking pre-natal particulate air pollution exposure to children's
323 respiratory health (Latzin et al. 2009). They provide a key advancement in showing that such
324 effects of PM_{2.5} are present as early as the first 2 months of life and further suggest that
325 females might be more sensitive to such effects.
326

327 Comparison with studies in older children, sex differences and mechanistic insights

328 Most of the literature on effects of pre- and post-natal exposure to air pollutants on children
329 lung function measured forced expiratory volumes after 5 years old. This evidence suggests
330 adverse effects of pre- and post-natal PM_{2.5} and NO₂ exposure on lung function level and
331 growth (Jedrychowski et al. 2010; Korten et al. 2017; Lee et al. 2018; Milanzi et al. 2018;
332 Schultz et al. 2018). Besides, there is growing evidence for sex-specific effects of air pollutants
333 on respiratory health, although with mixed results regarding lung function (Bose et al. 2018;
334 Lee et al. 2018; Leon Hsu et al. 2015; Liptzin et al. 2015; Schultz et al. 2017). Lee (Lee et al.
335 2018) and Bose (Bose et al. 2018) investigated pre-natal ambient exposure to PM_{2.5} and
336 nitrate, respectively, and found increased susceptibility for lung function effects in school
337 aged males. On the contrary, our results support potential effects of pre-natal personal PM_{2.5}
338 on decreased FRC and tidal volume and increased RR in females, which suggests a deficit in
339 lung volumes in females, but not in males. Although focused on personal maternal carbon
340 monoxide measurements as a proxy of household air pollution exposure, a study conducted
341 on 384 newborns from rural Ghana suggest that female's lung function would be more
342 sensitive to pre-natal household air pollution exposure than males (Lee et al. 2019). The exact
343 mechanisms that could explain this effect in females and more generally these sex-specific
344 effects of air pollutants on lung function remain to be fully elucidated. Differential
345 development of the lung between males and females has been described in human and
346 animals, indicating earlier surfactant maturation in females and smaller lungs from birth to
347 adolescence (Carey et al. 2007; Ishak et al. 2014). A study showed that intrauterine growth
348 restriction could particularly impact lung development in females with transient delay in post-
349 natal alveolar formation and retinoic acid receptor expression in the lung of female rat pups
350 (Joss-Moore et al. 2013). More generally, the developing human fetal lung transcriptome
351 showed sex-specific differences (Kho et al. 2016) and miRNAs have been shown differentially
352 regulated between sexes during the canalicular and sacular stages of lung development in
353 mice (Mujahid et al. 2013). Although these elements require further investigation, they
354 provide first insights into the biological mechanisms that may be at play.

355 Regarding PM_{2.5}, a study showed that mice pups exposed in the pre-and post-natal period had
356 decreased inspiratory and expiratory volumes and altered lung morphology (Mauad et al.
357 2008). PM_{2.5} are potent oxidant capable of generating reactive oxygen species, which can
358 result in oxidative stress both in the mother and fetus. Fetal oxidative stress can adversely
359 affect post-natal lung maturation, through gene expression modifications (Land and Wilson
360 2005). Epigenetic mechanisms have also been shown sensitive to air pollutants exposure
361 during pregnancy (Abraham et al. 2018; Gruzieva et al. 2019) and could have long term
362 impact on the structure and function of the lung (Joss-Moore et al. 2013; Mukherjee et al.

363 2021). In this regard, early measures of newborn lung function provide a more precise
364 understanding of the effects of in-utero exposure to air pollutants and can thus inform future
365 studies to investigate the underlying biological mechanisms.

367 Comparison with other studies in newborns

368 Very few studies have performed such early measurements of flows and volumes in healthy
369 newborns. Performed after sedation, they are not well accepted by the parents. Without
370 sedation, they are challenging to perform and require some time to get the child in quiet
371 sleep, rigorous procedures and quality controls to obtain reliable data, as well as trained
372 professionals. Yet this is crucial to investigate such effects as early changes in lung function
373 might reflect alterations of lung development with lifetime consequences. In fact, lung
374 function defects in infancy, through its impact on lung function peak achieved in early
375 adulthood, may account for part of COPD in adulthood (Lange et al. 2015). Our findings that
376 increased pre-natal PM_{2.5} exposure in females is associated with reduced FRC and with
377 suggestive decrease in tidal volume and increase in RR are in line with the only previous study
378 on pre-natal air pollution effects on lung function performed in newborns (Latzin et al. 2009).
379 This Swiss study conducted on 241 newborns showed that concentrations of PM₁₀ and NO₂ at
380 ambient monitors were associated with significant increased RR and decreased tidal volume.
381 No effects of PM were found on LCI, both in the Swiss study and in ours. Conversely, Latzin et
382 al. found significant positive associations of PM₁₀ ambient concentrations with MV and mean
383 tidal flows and no association with FRC, while we did show significant lower FRC in females
384 associated with higher pre-natal personal PM_{2.5}, but no association with MV and T_{PTEF}/T_E.
385 Results of the South African birth cohort MACE showed some consistency with ours, with
386 decreased FRC and tidal volume and increased RR and MV, associated with short-term
387 exposure to PM₁₀, while NO₂ related changes were less evident (Muttoo et al. 2022).

389 The tradeoff between personal and outdoor air pollution exposure estimates

390 Most epidemiological studies rely on residential exposure estimates to air pollutants based on
391 ambient exposure models as a surrogate of personal exposure. This approach does not
392 account for exposures at other locations visited by the participant nor for indoor sources.
393 Personal measurements allow to address these two issues, but such measurements are
394 usually obtained for limited time periods, because of their high cost and limited acceptability
395 for extended periods of time. Compared with outdoor estimates, personal measurements to
396 air pollutants could increase the risk of biases from individual behaviors (Weisskopf and
397 Webster 2017). However, in industrialized countries where people stay most of their time
398 indoors, especially pregnant women who spend an increasing time at home towards the
399 latter stages of pregnancy (Nethery et al. 2009), the use of personal measurements might
400 help improving exposure characterization to air pollutants and decreasing exposure
401 measurement error. In the Grenoble metropolitan area, a previous work conducted on
402 pregnant women showed that PM_{2.5} personal measurements were not correlated to the
403 corresponding residential exposure estimates in ambient air, suggesting that personal
404 measurements could be more representative of real exposures, in particular because it
405 captured indoor sources (Ouidir et al. 2015). In the SEPAGES cohort, although personal
406 measurements of air pollutants were available at different trimesters of pregnancy (mainly
407 the 2nd and 3rd trimesters), we did not conduct trimester specific association analyses
408 because we believe this design with a single measurement week per trimester of pregnancy is
409 not relevant to identify critical exposure windows as it does not capture the whole trajectory

410 of air pollution exposure during pregnancy. Designs with continuous estimates of exposure
411 throughout pregnancy are more relevant to flexibly assess critical windows of exposure
412 (Wilson et al. 2017).

413

414 Strengths and limitations

415 Beyond the two key strengths and innovations of this study, which are the repeated personal
416 exposure measurements and the early characterization of lung function in newborns, other
417 assets include the prospective design and the consideration of important confounders. In
418 addition, to our knowledge, this is the first investigation of sex-specific effects of PM_{2.5} on
419 newborn lung function. The moderate sample size of the study might have impacted the
420 statistical power to detect interactions. However, the stratified results suggest differential
421 effects of PM_{2.5} by gender, which might be driven by physiological differences in lung growth
422 between male and female fetuses and underline the necessity to integrate child sex
423 differences in vulnerability (Bolte et al. 2021; Liptzin et al. 2015).

424 Other potential limitations include the fact that only one to three personal measurement
425 weeks were performed and that we did not account for post-natal exposure to PM_{2.5}.
426 However, in a similar study conducted on newborns, post-natal exposure to NO₂ and PM₁₀ did
427 not modify the association with pre-natal exposures (Latzin et al. 2009). As for pre-natal
428 exposure, most participants (95%) performed 2 or 3 weeks of measurements at different
429 seasons, which were averaged over the whole pregnancy, in order to eliminate the seasonal
430 effects. In addition, our results were robust to the exclusion of participants with only one
431 exposure measurement. Regarding lung function tests, measurement errors in FRC and LCI
432 parameters due to hypoventilation induced by pure oxygen during the N2MBW test may have
433 occurred. Nevertheless, we analyzed HV-corrected FRC and LCI parameters and our results
434 were robust to the exclusion of participants with the highest degree of hypoventilation.

435

436

437 **Conclusion**

438 In summary, we studied the association of newborn lung function indicators with personal
439 pre-natal exposure of the mother to NO₂ and PM_{2.5} and pointed out that females, but not
440 males, born to mothers with higher exposure to PM_{2.5} during pregnancy were at higher risk of
441 lower lung volumes. While previous literature showed that air pollution exposure alters lung
442 development, our results provide evidence that such effects can be initiated in utero,
443 especially in females. These early impacts of PM_{2.5} on newborn lung function may program
444 post-natal lung function trajectory and respiratory diseases and provide additional evidence
445 for more stringent reductions of air pollution exposures in pregnant women and children.

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487

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489

490 **Authors' contributions**

491 JL and VS designed the study. AB carried out the analyses. ES formatted figures. JL wrote the
492 original manuscript. IP, RC provided guidance. All authors contributed to the acquisition and
493 processing of the data. IP, AB, JQ, SLC, RC, VS revised the manuscript. All authors read and
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495

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649

Table S1: Design of personal exposure measurement weeks during pregnancy, SEPAGES cohort, n=391

		NO ₂ (391 women)		PM _{2.5} (338 women)	
		n	%	n	%
Number of personal measurement					
Trimester of measurement weeks					
1 measurement		18	4.6	61	18
	T1	0	0	2	3.3
	T2	10	55.5	10	16.4
	T3	8	44.4	49	80.3
2 measurements		291	74.4	276	81.7
	T2, T3	266	91.4	253	91.7
	T1, T3	20	6.9	19	6.9
	T2, T2	5	1.7	4	1.4
3 measurements		82	21.0	1	0.3
	T1, T2, T3	9	11.0	0	0
	T2, T2, T3	71	86.6	1	100
	T2, T2, T2	1	1.2	0	0
	T2, T3, T3	1	1.2	0	0

T1: trimester 1, T2: trimester 2, T3 : trimester 3 of the pregnancy

Table S2: Association between maternal personal exposure to NO₂ and PM_{2.5} during pregnancy (10 µg/m³ increase) and lung function of the newborn, SEPAGES cohort, n=391

Pollutant	Univariate ¹			Multivariate ²			Participants with ≥2 measurement weeks ³			Participants without hypoventilation ⁴			Without extreme values			Females			Males			p-interaction
	n	β	p-value	n	β	p-value	n	β	p-value	n	β	p-value	n	β	p-value	n	β	p-value	n	β	p-value	
NO ₂																						
FRC	350	-0.86	0.53	308	-0.28	0.84	293	-0.41	0.76	228	0.37	0.81	298	-0.44	0.75	141	-0.10	0.96	167	-0.51	0.81	0.85
LCI	350	0.06	0.47	308	0.07	0.38	293	0.08	0.34	228	0.12	0.22	296	0.10	0.25	141	0.04	0.75	167	0.15	0.23	0.30
MV	325	-5.52	0.20	286	-2.94	0.53	270	-1.90	0.69				272	-4.57	0.34	134	-3.96	0.57	152	-2.46	0.70	0.76
T _{PTEF} /T _E	325	-0.75	0.34	286	-0.71	0.40	270	-0.65	0.44				275	-0.34	0.71	134	-0.34	0.76	152	-0.96	0.48	0.87
RR	325	-0.92	0.31	286	-0.34	0.72	270	-0.37	0.71				274	-1.03	0.34	134	-1.21	0.41	152	0.12	0.93	0.89
V _T	325	0.08	0.88	286	-0.17	0.76	270	-0.04	0.94				272	-0.35	0.56	134	0.52	0.53	152	-0.68	0.40	0.40
PM _{2.5}																						
FRC	297	-3.10	0.05	265	-2.49	0.11	213	-2.29	0.20	195	-1.92	0.30	255	-2.24	0.17	124	-5.25	0.02	141	0.26	0.91	0.26
LCI	297	-0.02	0.82	265	0.02	0.81	213	-0.07	0.55	195	0.03	0.82	254	0.07	0.50	124	-0.07	0.65	141	0.10	0.48	0.31
MV	319	-1.97	0.69	282	-5.30	0.30	238	-0.06	0.99				269	-8.13	0.12	133	-5.03	0.51	149	-3.01	0.66	0.94
T _{PTEF} /T _E	319	0.71	0.42	282	0.30	0.75	238	0.55	0.63				272	-0.57	0.56	133	1.07	0.38	149	-0.48	0.74	0.26
RR	319	0.65	0.52	282	0.57	0.59	238	1.97	0.10				272	-0.33	0.77	133	2.46	0.13	149	-1.17	0.40	0.09
V _T	319	-0.67	0.30	282	-0.77	0.21	238	-0.98	0.17				269	0.36	0.59	133	-1.60	0.08	149	0.06	0.95	0.22

n=sample size, β=beta of the regression model, significant or borderline significant results are in bold. FRC: functional residual capacity (ml), LCI: Lung clearance index, MV: minute ventilation (ml/kg), V_T: tidal volume (ml), T_{PTEF}/T_E: time to peak tidal expiratory flow/expiratory time, RR: respiratory rate per minute.

1: regression models included air pollutant exposure

2: regression models were adjusted for child age (continuous), child sex, gestational age at delivery (continuous), height at 2 months (continuous), tobacco smoking exposure (yes/nSo, defined as maternal active or passive smoking during pregnancy or passive exposure of the child after birth), season of birth (4 categories), parents highest educational level (< master's degree, ≥ master's degree), paternal or maternal asthma, paternal or maternal rhinitis, breastfeeding (no or <1 month, ≥1 month), delivery mode (vaginal delivery, c-section).

3: 19 participants for NO_2 and 68 for $\text{PM}_{2.5}$ who had only one measurement week during pregnancy were excluded from the multivariate regression models in order to minimize potential measurement error on air pollutants exposure.

4: newborns with the highest degree of hypoventilation were excluded from the multivariate regression models in order to minimize potential measurement error on lung function parameter