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Associations between combined urban and lifestyle factors and respiratory health in European children

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Declaration of interests

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

Abstract

Introduction: Previous studies identified some environmental and lifestyle factors independently associated with children respiratory health, but few focused on exposure mixture effects. This study aimed at identifying, in pregnancy and in childhood, combined urban and lifestyle environment profiles associated with respiratory health in children.

Methods: This study is based on the European Human Early-Life Exposome (HELIX) project, combining six birth cohorts. Associations between profiles of pregnancy (38 exposures) and childhood (84 exposures) urban and lifestyle factors, identified by clustering analysis, and respiratory health were estimated by regression models adjusted for confounders.

Results: Among the 1,033 included children (mean±standard-deviation (SD) age: 8.2±1.6 years old, 47% girls) the mean±SD forced expiratory volume in 1s (FEV₁) and forced vital capacity (FVC) were 99±13% and 101±14%, respectively, and 12%, 12% and 24% reported ever-asthma, wheezing and rhinitis, respectively. Four profiles of pregnancy exposures and four profiles of childhood exposures were identified. Compared to the reference childhood exposure profile (low exposures), two exposure profiles were associated with lower levels of FEV₁. One profile was characterized by few natural spaces in the surroundings and high exposure to the built environment and road traffic. The second profile was characterized by high exposure to meteorological factors and low levels of all other exposures and was also associated with an increased risk of ever-asthma and wheezing. A pregnancy exposure profile characterized by high exposure levels to all risk factors, but a healthy maternal lifestyle, was associated with a lower risk of wheezing and rhinitis in children, compared to the reference pregnancy profile (low exposures).

Conclusion: This comprehensive approach revealed pregnancy and childhood profiles of urban and lifestyle exposures associated with lung function and/or respiratory conditions in children.

Our findings highlight the need to pursue the study of combined exposures to improve prevention strategies for multifactorial diseases such as asthma.

Keywords: environment; exposome; respiratory health; asthma; children

1 **1. Introduction**

2 A growing body of evidence suggests that prenatal and childhood windows of exposure are a
3 cornerstone in the development of chronic diseases over the life course (Mastorci et al., 2021).
4 Lungs develop until early adulthood, but important structural developments take place in early-
5 life, including fetal life. During this vulnerable period for the development of organs, harmful
6 factors may influence life-long risks for impaired lung function and respiratory diseases,
7 including asthma and chronic obstructive pulmonary disease (Bui et al., 2018; Sanna et al.,
8 2022).

9 The prevalence and incidence of respiratory and allergy-related diseases widely increased in
10 the second half of the last century. As an example, the prevalence of asthma has doubled (or
11 even tripled) in developed countries in less than 50 years (Eder et al., 2006). While genetic
12 predispositions are known to be involved in allergic diseases, this huge increase in a relatively
13 short period of time points out the role of environmental and lifestyle factors, in particular those
14 that have changed in this period. In recent decades, a large number of studies have demonstrated
15 associations between some environmental factors and respiratory diseases, such as exposure to
16 tobacco (Burke et al., 2012; Sunde et al., 2022), air pollution (Lu et al., 2023; W. Zhang et al.,
17 2022; Y. Zhang et al., 2022) and aeroallergens (house-dust mites, molds, ...) (Wright and
18 Phipatanakul, 2014). Other factors such as climate factors (Guilbert et al., 2023; Li et al., 2014),
19 greenness (Cavaleiro Rufo et al., 2021) and diet (Garcia-Marcos et al., 2013) are suspected to
20 be involved in the development of respiratory diseases and need to be further investigated. Most
21 of the studies conducted to date considered a limited number of exposures, while these
22 exposures are potentially correlated and could have combined effects on health (Robinson et
23 al., 2018; Tamayo-Uria et al., 2019).

24 The concept of exposome, defined as all environmental exposures from conception onwards
25 (Wild, 2005) emphasizes the need of more holistic methods to characterize environmental

26 exposures to improve our understanding of the etiology of complex multifactorial diseases. In
27 particular, because people are continuously exposed to a wide range of environmental factors,
28 considering simultaneously a large set of exposures in exposure-health association studies is
29 warranted to better reflect real-life exposure patterns. Among existing statistical methods able
30 to simultaneously account for multiple exposures, clustering analyses that identify subgroups
31 of individuals sharing the same exposure profiles have previously been applied to identify
32 environmental and behavioral factors associated with asthma in adults (Guillien et al., 2022)
33 and with blood pressure in children (Warembourg et al., 2019). To the best of our knowledge,
34 no study applied clustering analysis to specifically identify early-life urban and lifestyle
35 environmental profiles associated with child respiratory health. This method could shed more
36 light on respiratory risk factors and may help decision makers to identify potential interventions
37 that jointly address the impact of several exposures on child health.

38 The aim of the present study was to identify profiles of pregnancy and childhood urban and
39 lifestyle factors and to further assess their association with respiratory conditions (asthma,
40 wheezing, rhinitis) and lung function parameters (forced expiratory volume in 1s (FEV₁) and
41 forced vital capacity (FVC)) in a population of European children.

42

43 **2. Methods**

44 *2.1. Study population*

45 This study is based on the European Human Early-Life Exposome (HELIX) project, which is a
46 collaborative project combining six existing longitudinal birth cohorts: BiB (Born in Bradford)
47 in United Kingdom, EDEN (Etude des Déterminants pré et postnatals du développement et de
48 la santé de l'Enfant) in France, INMA (Infancia y Medio Ambiente) in Spain, KANC (Kaunas
49 Cohort) in Lithuania, MoBa (Norwegian Mother, Father and Child Cohort Study) in Norway
50 and RHEA (Mother-Child Cohort in Crete) in Greece. Briefly, children born in 2007-08 for

51 BiB and RHEA, 2003-05 for EDEN, 2005-07 for INMA and MoBa and 2007-09 for KANC
52 were recruited and follow-ups are still ongoing. Overall, the six cohorts recruited a total of
53 31,472 mother-child pairs during pregnancy. In the frame of the Helix project, a new follow-up
54 was organized in 2013-2016 (children were between 6 and 12 years of age), based on a
55 standardized protocol across the 6 cohorts. During this follow-up, 1,301 mother-child pairs
56 were selected to be fully characterized for a broad suite of environmental exposures and to be
57 clinically examined. This subcohort was composed of about 200 children from each of the 6
58 cohorts, randomly selected from individuals of the entire cohort who met the eligibility criteria,
59 which were described in a previous study (Maitre et al., 2018). From this subcohort, only
60 children with acceptable and reproducible spirometry test were selected (n=1,033). Informed
61 consent was obtained from all participants or their legal referee.

62 *2.2. Respiratory outcomes*

63 During the follow-up (i.e. 6-12 years of the children), all included children performed a
64 spirometry test (EasyOne spirometer; NDD [New Diagnostic Design], Zurich, Switzerland)
65 according to a common standardized protocol across the six cohorts to assess FEV₁ and FVC.
66 Data quality control was applied to retain only the curves with valid criteria, as described in a
67 previous study (Agier et al., 2019). Finally, we used the Global Lung Initiative 2012 reference
68 equations to compute the FEV₁ and FVC in percent of the predicted value (ie, standardized for
69 child age, height, gender and ethnicity) (Quanjer et al., 2012).

70 Regarding respiratory conditions of children, occurrence of asthma, wheezing and rhinitis were
71 assessed through questionnaires adapted from the International Study on Asthma and Allergy
72 in Childhood (ISAAC) and Mechanisms of the Development of ALLergy projects (MeDALL)
73 (Bousquet et al., 2011) projects during the interview with the mother at the follow-up
74 examination, the same day as the spirometry test. Ever asthma was defined by a positive answer
75 to “Has your child ever been diagnosed by a doctor as having asthma?”; wheezing in the last

76 12 months was defined by a positive answer to: “Has your child had wheezing or whistling in
77 the chest in the last year?”; and rhinitis in the last 12 months was defined by a positive answer
78 to: “In the last year, has your child had problems with sneezing, or a runny, or blocked nose
79 when he/she did not have a cold or the flu?”.

80 *2.3. Characterization of the exposome*

81 A wide range of exposure variables were collected in the frame of the HELIX project. For this
82 study, we focused on urban environmental and lifestyle factors assessed twice, first during the
83 pregnancy and secondly in childhood (from the Helix study visit). Briefly, environmental
84 variables were assessed with geographic information system-based models at residential
85 address (during pregnancy and during childhood) and school address (only for childhood
86 exposures) of the children. Pregnancy exposures were average on the entire pregnancy period
87 and childhood exposure were collected during the study visit (children were 6-12 years old,
88 depending of the cohort). Environmental variables covered atmospheric pollutants (nitrogen
89 dioxide (NO₂), particulate matter of less than 2.5 µm in aerodynamical diameter (PM_{2.5}),
90 particulate matter of less than 10 µm in aerodynamical diameter (PM₁₀), absorbance of PM_{2.5}
91 (PM_{abs}) filters; 16 variables), built environment (building density, street connectivity,
92 accessibility, facilities, land use evenness index, walkability index, population density; 26
93 variables), indoor air (NO₂, PM_{2.5}, PM_{abs}, benzene and TEX (toluene, ethylbenzene, xylene); 5
94 variables), meteorological variables (mean air temperature, humidity, atmospheric pressure; 9
95 variables), ultraviolet (UV) (vitamin-D UV levels; 3 variables), road traffic (traffic load, traffic
96 density and distance to nearest road; 8 variables), road traffic noise (night-time and 24h road
97 noise levels; 5 variables), surrounding natural space (Normalized Difference Vegetation Index
98 (NDVI), major green space and major blue space; 9 variables) and water disinfection by-
99 product (DBPs) (Trihalometanes, Chloroform and Bromodichloromethane; 3 variables).
100 Lifestyle (alcohol, diet, physical activity, sleep and pets; 38 variables) were collected through

101 standardized and validated questionnaires. In total, 122 exposures were assessed, 38 during the
102 pregnancy period and 84 during the childhood period, as presented in Table 1. The detailed
103 assessment methods, correlations between exposures and descriptive statistics of all exposures
104 are described in previous studies (Maitre et al., 2018; Robinson et al., 2018; Tamayo-Uria et
105 al., 2019) and in Appendices.

106 *2.4. Covariates*

107 Information about children and mothers' sociodemographic characteristics as well as pregnancy
108 parameters were collected through questionnaires based and mother's interview. Covariates
109 included center of recruitment, child's sex, age and height, ethnicity defined by both parents
110 native to the cohort country (yes, no), breastfeeding duration, season of conception, presence
111 of older siblings (none, one, two or more), parental education level (primary school, secondary
112 school, university degree or higher), maternal age, maternal pre-pregnancy body mass index
113 (BMI), postnatal passive smoking status and prenatal maternal active and passive smoking
114 status, as identified in a previous study based on exposome-respiratory health associations in
115 the Helix population (Agier et al., 2019). Additionally, socioeconomic factors (family affluence
116 score, family contact, participation in organizations and house crowding) and season of
117 examination were used as covariates in the present study.

118 *2.5. Statistical analyses*

119 All continuous variables were transformed to approach normality, or categorized when it was
120 not possible. Exposure variables and covariates were imputed using the method of chained
121 equations and 20 complete datasets were computed (White et al., 2011). All continuous
122 exposure variables were centered and standardized by cohort to overcome the different
123 distribution between the cohorts.

124 The following analyses were performed independently on pregnancy exposures and childhood
125 exposures. First, the kproto method, an extension of the kmeans for mixed (including both

126 continuous and categorical) data, was fitted to identify profiles of pregnancy and childhood
127 exposures (Huang, 1998). Then, we used a previously defined framework to combine multiple
128 imputation with cluster analysis (Basagaña et al., 2013). The framework implemented in the
129 miclust R package for the kmeans algorithm was modified to use kproto (Huang, 1998) and is
130 detailed in the Appendices. This algorithm also included a variable selection step to reduce the
131 dimension of the exposure dataset. The profiles identified from pregnancy and childhood
132 exposures were named “profile Px” and “profile Cx”, respectively. The description of each
133 identified profile was presented through barplots where each bar relates to one exposure factor
134 and represents the difference between the exposure mean level in the corresponding profile with
135 the exposure mean level in the whole population for continuous exposure. Same methodology
136 was used for categorical exposures, using the prevalence instead of the mean. Some exposures
137 (walkability index, index of greenness, presence of blue space and green space, intakes of fish,
138 fruits, legumes, vegetables, folic acid, physical activity, presence of pets, sleep duration and
139 social factors) have been inverted so that a bar going to the left is *a priori* expected to be
140 associated with a protective effect on respiratory health, and a bar going to the right is *a priori*
141 expected to be associated with deleterious effect on respiratory health.

142 Secondly, for each health outcome, regression-based models (linear for FEV₁ and FVC, logistic
143 for presence of asthma, wheezing and rhinitis) were fitted to assess the association between the
144 mutually-adjusted exposure profiles and the outcome variables. The reference profile was
145 chosen as the one having the lowest prevalence of *a priori* deleterious exposures. All of these
146 models were adjusted for the covariates defined above. All analyses were performed using the
147 R software (version 3.4) and *mice* package for multiple imputation and *clustMixType* for
148 clustering analyses.

149

150 **3. Results**

151 *3.1. Description of the population*

152 Among the 1,301 children examined in the frame of the Helix project, 1,033 had valid
153 spirometry values and were selected for this analysis. Briefly, 53% of children were boys and
154 the mean age \pm standard deviation (SD) of children was 8.1 ± 1.6 years old when respiratory
155 outcomes were collected (Table 2). The distribution of children per cohort was overall
156 homogenic with about 15% for most of the cohort and slightly more for INMA (18%) and
157 MOBA (23%). The mean maternal age was 30.9 ± 4.8 years and 15% of mothers were active
158 smokers during pregnancy. The characterization of the exposome was detailed in a previous
159 study (Agier et al., 2019) and in Appendices.

160 Regarding respiratory parameters, children had a mean \pm SD of FEV₁% at $99 \pm 13\%$ (range:
161 61-139) and a mean \pm SD FVC% of $101 \pm 14\%$ (range: 60-147). Finally, 123 (12%) children
162 had ever asthma, 124 (12%) reported wheezing in the last 12 months and 246 (24%) reported
163 rhinitis in the last 12 months.

164 *3.2. Identification of pregnancy and childhood exposure profiles*

165 Four exposure profiles were identified from the 38 pregnancy exposures, each including from
166 197 (19%) to 335 (32%) children, and each including children from all cohorts (Table A.1).
167 The distribution of pregnancy exposures in each profile is presented in Figure 1 and Table A.2.
168 Briefly, profile P1 (reference profile) was mainly characterized by children with low levels of
169 exposure to all risk factors except for water DBPs and high temperature during the prenatal
170 period. The profile P2 was mainly characterized by children with high levels of exposure to all
171 risk factors, but an overall healthy lifestyle (high practice of physical activity and high intake
172 of fruit, vegetables and fish) of their mothers during pregnancy. Children belonging to profile
173 P3 had overall low levels of exposure to all risk factors but moderate exposure to unhealthy
174 lifestyle habits during the prenatal period. Finally, the profile P4 was mainly characterized by
175 children with highest exposure to almost all exposures during the prenatal period.

176 Regarding childhood exposures, four exposure profiles were identified from the 84 exposures,
177 each including 191 (18%) to 322 (31%) children, and each including children from all cohorts
178 (Table A.1). The distribution of childhood exposures in each profile is presented in Figure 2
179 and Table A.3. The profile C1 (reference profile) was mainly characterized by children with
180 lower mean exposure levels to all risk factors during childhood as compared to children from
181 other profiles except for humidity. The profile C2 was also characterized by children with
182 globally low exposure to all exposures during childhood except high exposure to high UV dose
183 and high temperatures. Children belonging to profile C3 were characterized by the most adverse
184 levels of exposure to air pollutants (both indoor and outdoor), unhealthy lifestyle habits and low
185 exposure to high UV doses and high temperatures during childhood. Finally, children from
186 profile C4 had the most deleterious exposure to natural spaces (e.g. lack of green and blue
187 spaces in their surroundings) and highest exposure to the built environment (e.g. high
188 population density and high building density) and road traffic during childhood.

189 The median [interquartile] probability of attribution of individuals to the same profile in all
190 imputed dataset (n=20) was 80% [65-69] for the pregnancy exposures and 100% [100-100] for
191 the childhood exposures, illustrating the low uncertainty introduced by missing data imputation.

192 There was an association between pregnancy and childhood exposure profiles (Figure 3; Chi-
193 squared test, $p < 0.001$). Briefly, as compared to children belonging to childhood exposure
194 profile P2 and P4, children belonging to pregnancy exposure profile P1 and P3 were less often
195 assigned to childhood exposure profile C4, but more often assigned to childhood exposure
196 profile C1 and C2.

197 *3.3. Association between exposure profiles and respiratory health*

198 All profile-outcomes association studies were presented in Tables 3 and 4 for the lung function
199 and respiratory conditions, respectively.

200 No association was found between pregnancy profiles and children lung function. One
201 childhood profile, the profile C4, characterized by children with the most deleterious exposure
202 to natural spaces (e.g. poor number of green and blue spaces in their surrounding) and highest
203 exposure to the built environment and road traffic presented lower levels of FEV₁ (beta [95%CI]
204 = -2.55 [-5.04;-0.07], p=0.04), compared to the reference (low exposure) profile. Moreover,
205 children in the childhood profile C2, characterized by globally low exposure to all exposures
206 except high exposure to high UV dose and high temperatures also tended to have lower level
207 of FEV₁ (beta [95%CI] = -2.34 [-5.06;0.38], p=0.09).

208 Regarding respiratory conditions, this last profile, the profile C2, was also associated with
209 increased risk of ever-asthma for children (OR [95%CI] = 2.93 [1.36;6.31], p=0.01). Profile P2,
210 characterized by high levels of exposure to all risk factors, but an overall healthy lifestyle of
211 the mothers (high practice of physical activity and high intakes of fruits, vegetables and fish),
212 during pregnancy, was associated with a lower risk of wheezing and rhinitis in the last 12
213 months (OR [95%CI] = 0.38 [0.18;0.77], p=0.01 and 0.64 [0.39;1.05], p=0.08, respectively),
214 compared with children from the reference profile. Finally, a non-significant trend for an
215 association was observed between profile C3, characterized by children with the most adverse
216 levels of exposure to air pollutants (both indoor and outdoor), unhealthy lifestyle habits and low
217 exposure to high UV doses and high temperatures, and a lower risk of rhinitis (OR [95%CI] =
218 0.65 [0.39;1.07], p=0.09).

219 Similar patterns of association between exposure profiles and respiratory health were observed
220 when pregnancy and childhood exposure profiles were considered independently in the
221 regression models (see additional Tables A.4 and A.5).

222 Finally, similar patterns of associations were found when analyses were stratified by child sex
223 (see additional Tables A.6 and A.7).

224

225 **4. Discussion**

226 The present study is the first to comprehensively investigate effects of early-life (prenatal and
227 childhood) urban and lifestyle exposure through exposure profiles on children respiratory
228 health. Results showed that one childhood profile, mainly characterized by low number of
229 natural spaces in the surrounding and high exposure to the built environment and road traffic,
230 was associated with lower levels of FEV₁ in children. A second childhood exposure profile,
231 globally characterized by low exposure to all exposures except high exposure to high UV dose
232 and high temperatures, was associated with higher risk of ever-asthma and lower level of FEV₁
233 in children. Finally, one pregnancy profile, mainly characterized by high levels of exposure to
234 all risk factors, but a healthy maternal lifestyle, and one childhood profile, characterized by
235 high exposure to air pollutants, unhealthy lifestyle and lowest exposure to high temperatures
236 and UV doses, was associated with decreased risk of rhinitis in children.

237 *4.1. The benefit of combining exposures through exposure profiles*

238 Two previous studies, also based on the Helix population, assessed the associations between
239 pregnancy and childhood exposures and rhinitis (Granum et al., 2020) and FEV₁ (Agier et al.,
240 2019) by considering independent association of each exposure. The Exposome Wide
241 Association Studies (ExWAS) identified few urban and lifestyle exposures, and none of the
242 association resisted to correction of the p-value for multiple testing. Using variable selection
243 algorithm, the previous Helix study on rhinitis selected two pregnancy urban exposures, PM_{abs}
244 and inverse distance to nearest road, which were respectively associated with an unexpected
245 decreased risk (OR [95%CI] = 0.5 [0.3;0.9]) and increased risk (OR [95%CI] = 1.3 [1.1;1.6])
246 of rhinitis. In this study, we go a step further than individual associations by considering the
247 joint effect of exposures on children respiratory health. For that, we identified profiles of
248 exposure able to simultaneously account for multiple exposures, which *a priori* better reflect
249 human exposures in their daily life. In environmental epidemiology, a few studies have used

250 clustering method to assess the association between urban exposome and health outcomes
251 (Guillien et al., 2022; Warembourg et al., 2019; Guillien et al., 2020; de Bont et al., 2021). In
252 all these studies, the authors identified some exposure profiles associated with the health
253 outcome while single-exposure association studies reported only a few or sometimes no
254 association when correcting p-value for the multiple testing hypothesis. This observation
255 supports that clustering analysis, where only $k-1$ tests (where k is the number of clusters) are
256 performed for each health outcome, is a way to overcome the statistical power issue raised in
257 ExWAS analysis. Moreover, by considering all exposures simultaneously through profiles of
258 exposure, the clustering analysis is able to account for complex synergistic effects between
259 exposures, that cannot be assessed through regression based-model, especially when considering
260 multiple exposome domains such as urban environment and lifestyle.

261 *4.3 The choice of the clustering method*

262 There is an increasingly rich literature on clustering methods, divided in two categories. The
263 determinist clustering, which includes the kproto method used here, assign each individual to a
264 unique cluster while probabilistic approaches assign a probability to belong to each cluster for
265 each individual. These approaches also differ in terms of assumptions. Determinist clustering
266 relies on a geometric approach where all individuals are assigned to the nearest cluster center,
267 according to a defined metric, and where the cluster centers are firstly randomly assigned and
268 then recalculated for each new assignment. Probabilistic methods assume that the distribution
269 of the overall population hides several distributions corresponding to subpopulations and aim
270 to estimate the parameters of these distributions, most often considered as Gaussian. In this
271 study, we chose to apply the kproto because most of model-based methods rely on supervised
272 methods, meaning that both the exposures and the outcome are considered to identify clusters,
273 which would mean identifying different exposure profiles for each of the 5 health outcomes
274 considered here. Moreover, we were not able to identify any studies comparing deterministic

275 to probabilistic clustering methods, thus it remains unclear which method outperforms the other.
276 We acknowledge that other methods can provide different partitions, which can also be
277 informative on the health outcomes, and we do not claim having found the best one.

278 *4.4. Interpretation of results*

279 One pregnancy profile, characterized by high levels of exposure to all risk factors, especially
280 air pollutants and road traffic, but an overall healthy lifestyle (high practice of physical activity
281 of mothers during pregnancy and high maternal intakes of fruits, vegetables and fish), was
282 associated with a lower risk of wheezing and rhinitis compared with children from the reference
283 profile. Although direct comparisons with previous single-exposure association studies are not
284 possible, these results seem partly contradictory with the large literature supporting increased
285 risk of respiratory diseases and asthma-related symptoms with exposure to air pollutants
286 (Bowatte et al., 2015), especially among children living in areas with high traffic-related air
287 pollution (Delfino et al., 2014). This unexpected result could be driven by the fact that this
288 profile is also characterized by the largest proportion of mothers with healthy diet during
289 pregnancy. The literature about maternal diet and respiratory health in children is still scarce
290 (Donovan et al., 2020), but there are growing evidences to indicate associations. A previous
291 study based on 460 children-mothers pairs in a Mediterranean island in Spain, Menorca,
292 reported a protective effect of healthy diet on asthma-related symptoms on children at age 6.5
293 years (Chatzi et al., 2008). For example, children with mother having high maternal adherence
294 to a Mediterranean diet (vs. low adherence) during pregnancy had less persistent wheeze at 6.5
295 years (OR [95% CI] = 0.23 [0.09-0.60]). Indeed, diet composed of antioxidants and anti-
296 inflammatory nutrients may help reducing the impact of air pollution on health, that is mediated
297 by oxidative stress (Péter et al., 2015; Saenen et al., 2019).

298 Regarding childhood exposures, one profile (C4), characterized by the most deleterious
299 exposure to natural spaces (e.g. low number of green and blue spaces in their surrounding) and

300 highest exposure to the built environment and road traffic, was associated with lower FEV₁
301 level which demonstrates the deleterious impact of combined risk factors. Even if not
302 statistically significant, the childhood profile C2, characterized by globally low exposure to all
303 exposure families but high exposure to high UV dose and high temperatures, also had lower
304 level of FEV₁. Children from this profile also had increased risk of ever asthma and wheezing,
305 providing additional support for a deleterious impact of this exposure profile on respiratory
306 health. These results suggest a short and mid-term effects of meteorological factors (assessed
307 during the day, the week and the month prior to clinical examination in this study) on respiratory
308 health, that might be easier to evidence in the absence of other risk factors such as air pollution.
309 Finally, the profile C3, characterized by the most adverse levels of exposure to air pollutants
310 (both indoor and outdoor), unhealthy lifestyle habits and low exposure to high UV doses and
311 to high temperatures shows a trend for a decreased risk of rhinitis in children. These results,
312 which seems controversial regarding air pollutants and lifestyle, support the potential existing
313 interactions between exposures and the need to use more comprehensive and holistic methods
314 that consider all exposures as a whole to better understand exposome-health associations. Here,
315 this association may be driven by the low exposure to high temperature and UV doses. Even if
316 the impact of these meteorological factors on respiratory health in children is not clearly
317 established, there are growing evidence for a beneficial effect of moderate exposure to UV on
318 asthma (Cherrie et al., 2021; Hart et al., 2011) and for deleterious respiratory health effects
319 associated with increased ambient temperature, including lower lung function (Li et al., 2014),
320 higher exacerbation rate in children with asthma (Schinasi et al., 2022) and rhinitis (Norbäck et
321 al., 2018).

322 *4.5. Strengths and weaknesses*

323 Our study has several strengths. First, the multi-center design of this study encompassing 6
324 European countries, led to a study population covering a wide range of outdoor exposures and

325 lifestyle habits, which is a strength in terms of the generalizability of the results. Secondly, this
326 study covers a wide range of exposures at several time points. Here, we considered pregnancy
327 and childhood which are critical windows of exposure where lungs are particularly vulnerable
328 with long lasting consequences of noxious exposures (Barouki et al., 2012; Bousquet et al.,
329 2015). By analyzing five respiratory outcomes, including two objective lung function
330 parameters (FEV₁ and FVC) and three prevalent respiratory conditions (ever asthma, wheezing
331 and rhinitis), the consistency of associations across the different respiratory health outcomes
332 was used in results interpretation. Finally, as previously discussed, the methodology performed
333 in this study overcame many of the issues associated with exposome studies, especially the
334 unstraightforward issue of multiple comparisons, while providing results on exposures that are
335 more representative of real life.

336 Nevertheless, this study also suffers from some limitations. First, the number of participants
337 remains limited (n=1,033) and could imply a lack of statistical power. Then, we acknowledge
338 that some measurement errors, possibly different from one cohort to another, is unavoidable in
339 environmental epidemiology studies. The methodological complexity related to the
340 consideration of multiple centers and the potential confounding by center when it comes to
341 assessing associations with health outcomes has already been addressed (Basagaña et al., 2018).
342 Here, we standardized all continuous variables within cohort to limit this issue. In that way, we
343 removed the between-center differences and focused on the variation of the levels of exposure
344 within each cohort. Moreover, although the spirometry tests were performed by trained
345 technicians, following the same standardized protocols defined from current guidelines
346 (Quanjer et al., 2012), and an extensive quality control has been applied (Agier et al., 2019),
347 some measurement errors in FEV₁ and FVC could have arose as spirometry, which is a forced
348 expiratory test, is often difficult to perform in children. Then, as demonstrated in a previous
349 study (Maitre et al., 2018), the excluded participants of this study presented some differences

350 from the included participants which could affect the representativeness of the studied
351 population, but should not affect the association between the identified exposure profiles and
352 respiratory outcomes. Furthermore, avoidance of exposure in the presence of child specific
353 disorder can't be totally excluded and could lead to a reverse causality phenomenon. Here, this
354 potential selection bias is limited because the study is based on population-based cohorts and
355 not on a population of moderate-to-severe patients with asthma where avoidance of
356 environmental triggers is more often implemented. Then, we simultaneously considered a wide
357 range of exposures while avoidance would be specific to a single exposure or family of
358 exposure. In addition, despite a large set of urban exposures collected in this study, some
359 relevant exposures are missing. For example, indoor exposures and aeroallergens such as
360 pollens were not available while it would be of interest in the context of allergy-related
361 outcomes (De Roos et al., 2020; Lu et al., 2022; Mattila et al., 2021). The chemical exposome
362 was not considered in this outdoor-lifestyle exposome study, but because chemical exposures
363 are not related to most of the outdoor exposome (Tamayo-Uria et al., 2019) this should not
364 impact the association estimates of the outdoor exposome profile. Also, genetic factors, that are
365 involved in asthma and allergic diseases susceptibility (Stikker et al., 2023), were not
366 considered in our study. Indeed, we aimed at identifying environmental and lifestyle factors
367 that might be responsible of the huge increase of asthma and allergic diseases prevalence
368 observed since the second half of the last century. Once environmental and lifestyle factors
369 associated with respiratory health will be well identified, further studies investigating
370 gene*environment interactions might be of great interest. An additional limitation is related to
371 the challenge of interpreting associations with exposure profiles accounting for many exposures
372 and to compare these associations with results of single-exposure association studies where
373 potential confounding by co-exposures and synergistic effects are not considered. Finally,
374 analyses regarding childhood exposure-child health associations presented here are cross-

375 sectional. This issue mainly impacts the associations studied with ever-asthma when the
376 timeline between exposure in childhood and child health outcomes can't be defined. Further
377 projects considering multiple timepoints for exposure and respiratory health are needed to yield
378 more insights into the presumed causal relationships.

379

380 **5. Conclusions**

381 This study is among the firsts to use a holistic method that simultaneously considers a large
382 range of environmental factors through pregnancy and childhood exposure profiles, to further
383 investigate the effect of combined environmental exposures on children respiratory health. The
384 results highlighted two childhood exposure profiles associated with lower levels of FEV₁, one
385 of which was also associated with a higher risk of ever-asthma and wheezing. This study also
386 identified a prenatal exposure profile associated with a lower risk of wheezing and rhinitis in
387 children. In terms of public health, these results suggest that a better understanding of combined
388 exposures associated with health might shed light on the etiology of complex multifactorial
389 diseases, which in turn can provide clues for more efficient preventive measures.

390

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419

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List of figures

Figure 1. Description of pregnancy profiles

Barplots representing the distribution of continuous (at the top) and categorical (at the bottom) variables of each exposure family. Each bar represents the difference between the mean level of one exposure in the corresponding profile with the mean level of the same exposure in the whole population for continuous exposure. Same methodology was used for categorical exposures, using the prevalence instead of the mean. Exposures highlighted with a * at the end of their label have been inverted so that a bar going to the left is *a priori* expected to be associated with a protective effect on respiratory health, and a bar going to the right is *a priori* expected to be associated with deleterious effect on respiratory health.

NDVI: normalized difference vegetation index; PM_{2.5}: particulate matter of less than 2.5 µm in aerodynamical diameter; PM₁₀: particulate matter of less than 10 µm in aerodynamical diameter; PM_{abs}: absorbance of particulate matter of less than 2.5 µm in aerodynamical diameter; NO₂: nitrogen dioxide.

Figure 2. Description of childhood profiles

Barplots representing the distribution of continuous (at the top) and categorical (at the bottom) variables of each exposure family. Each bar represents the difference between the mean level of one exposure in the corresponding profile with the mean level of the same exposure in the whole population for continuous exposure. Same methodology was used for categorical exposures, using the prevalence instead of the mean. Exposures highlighted with a * at the end of their label have been inverted so that a bar going to the left is *a priori* expected to be associated with a protective effect on respiratory health, and a bar going to the right is *a priori* expected to be associated with deleterious effect on respiratory health.

KIDMED: Mediterranean Diet Index; NO₂: nitrogen dioxide; BTEX: benzene, toluene, ethylbenzene and xylene; NDVI: normalized difference vegetation index; UV: ultraviolet;

PM_{2.5}: particulate matter of less than 2.5 µm in aerodynamical diameter; PM₁₀: particulate matter of less than 10 µm in aerodynamical diameter; PM_{abs}: absorbance of particulate matter of less than 2.5 µm in aerodynamical diameter.

Figure 3. Sankey diagram of distribution of children in pregnancy and childhood profiles

Profile P1 (reference profile) was mainly characterized by children with low levels of exposure to all risk factors except for water DBPs and high temperature during the prenatal period. The profile P2 was mainly characterized by children with high levels of exposure to all risk factors, but an overall healthy lifestyle (high practice of physical activity and high intake of fruit, vegetables and fish) of their mothers during pregnancy. Children belonging to profile P3 had overall low levels of exposure to all risk factors but moderate exposure to unhealthy lifestyle habits during the prenatal period. Finally, the profile P4 was mainly characterized by children with highest exposure to almost all exposures during the prenatal period.

Profile C1 (reference profile) was mainly characterized by children with lower mean exposure levels to all risk factors during childhood as compared to children from other profiles except for humidity. The profile C2 was also characterized by children with globally low exposure to all exposures during childhood except high exposure to high UV dose and high temperatures. Children belonging to profile C3 were characterized by the most adverse levels of exposure to air pollutants (both indoor and outdoor), unhealthy lifestyle habits and low exposure to high UV doses and high temperatures during childhood. Finally, children from profile C4 had the most deleterious exposure to natural spaces (e.g. lack of green and blue spaces in their surroundings) and highest exposure to the built environment (e.g. high population density and high building density) and road traffic during childhood.

Table 1. Description of pregnancy and childhood exposures

	Pregnancy		Childhood		Total number of exposures
	number of exposures	exposures	number of exposures	exposures	
Atmospheric pollutants	4	NO ₂ , PM _{abs} , PM ₁₀ , PM _{2.5}	12	NO ₂ (one day, one week and one year before examination; at home), PM _{abs} (one day, one week and one year before examination; at home), PM ₁₀ (one day, one week and one year before examination; at home), PM _{2.5} (one day, one week and one year before examination; at home)	16
Built environment	9	Building density (300m buffer), connectivity density (300m buffer), landuse Shannon's Evenness Index, meters of public transport mode lines (300m buffer), number of public transport mode stops (300m buffer), number of facilities (300m buffer), number of different type facilities (300m buffer), population density, walkability index	17	Building density (home and school), connectivity density (300m buffer, home and school), landuse Shannon's Evenness Index (home and school), meters of public transport mode lines (300m buffer, home and school), number of public transport mode stops (300m buffer, home and school), number of facilities (300m buffer, home and school), number of different type facilities (300m buffer, home and school), population density (home and school), walkability index (home)	26
Indoor air	-	-	5	Concentrations of Benzene, BTEX (sum), NO ₂ , PM _{abs} and PM _{2.5} at home	5

Meteorological variables	3	Relative humidity, pressure, temperature	9	Relative humidity (one day, one week and one month before examination; at home), temperature (one day, one week and one month before examination; at home), vitamin-D ultraviolet dose (one day, one week and one month before examination; at home)	12
Road traffic	3	Inverse distance to nearest road, traffic density on nearest road, total traffic load of all roads (100m buffer)	5	Inverse distance to nearest road (home), traffic density on nearest road (school), total traffic load of all roads (100m buffer; home), total traffic load of major roads (100m buffer; home and school)	8
Road traffic noise	1	Sound pressure level of 24h period	4	Sound pressure level during night (home and school), Sound pressure level of 24h period (home and school)	5
Surrounding natural space	3	NDVI (100m buffer), presence of bluespace (300m buffer), presence of greenspace (300m buffer)	6	NDVI (100m buffer; home and school), presence of bluespace (300m buffer; home and school), presence of greenspace (300m buffer; home and school)	9
Water disinfection by-products	3	Bromodichloromethane, chloroform, total trihalometanes	0	-	3
Lifestyle	12	Alcohol, cereals, dairy, fast-food, fish, folic acid during 1st trimester, fruits, legumes, meat and vegetables intakes, moderate physical activity during third trimester, vigorous physical activity during third trimester	26	Added fat, bakery, bread, breakfast cereals, caffeinated drinks, cereals, dairy, fast-food, fish and seafood, fruits, meat, organic food, potatoes, processed meat, ready-made food, soda beverages, sweets, vegetables	38

			and yogurt intakes, sum of KIDMED indices, presence of cats at home, presence of dogs at home, presence of pets at home, sleep duration the whole week, moderate and vigorous physical activity, sedentary behavior
Total	38	84	122

Pregnancy exposures were averaged during the whole pregnancy, and childhood exposures were averaged during the year before study visit (where children were 8-11, depending on the cohort), unless otherwise stated.

NO₂: nitrogen dioxide; PM_{abs}: absorbance of PM_{2.5} filters, PM₁₀: particulate matter with an aerodynamic diameter of less than 10µm, PM_{2.5}: particulate matter with an aerodynamic diameter of less than 2.5 µm; BTEX: benzene, toluene, ethylbenzene, xylene; NDVI: Normalized Difference Vegetation Index.

Table 2. Description of the population

Characteristic	N = 1,033
Cohort	
BIB	147 (14%)
EDEN	159 (15%)
INMA	185 (18%)
KANC	144 (14%)
MOBA	242 (23%)
RHEA	156 (15%)
Child sex	
Female	489 (47%)
Male	544 (53%)
Age of child (years)	8.07 (1.58)
Height (m)	1.29 (0.10)
Both parents native to the cohort country	868 (84%)
Breastfeeding duration (days)	4.95 (1.15)
Trimester of conception	
January-March	327 (32%)
April-June	213 (21%)
July-September	217 (21%)
October-December	276 (27%)
Presence of older siblings	
None	476 (46%)
One	375 (36%)
Two or more	182 (18%)
Highest parental education level	
Primary school	87 (8.4%)
Secondary school	301 (29%)
University degree or higher	645 (62%)
Maternal age (years)	30.9 (4.8)
Maternal pre-pregnancy BMI (kg/m ²)	24.6 (4.8)
Postnatal passive smoking status of the child	
No exposure	663 (64%)
Exposure	370 (36%)
Maternal active Tobacco Smoke pregnancy	152 (15%)
Maternal active Tobacco Smoke pregnancy (cig/day)	0.54 (1.97)
Maternal passive Tobacco Smoke during pregnancy	408 (39%)
Season of exam	
Winter	315 (30%)
Spring	241 (23%)
Summer	241 (23%)
Autumn	236 (23%)
Contact with family	
Less than once a week	56 (5%)

Once a week	304 (29%)
(Almost) daily	673 (65%)
Social participation	
None	557 (54%)
1 organization	309 (30%)
≥2 organizations	167 (16%)
Family Affluence score	
Low	100 (10%)
Middle	380 (37%)
High	553 (53%)
House crowding (number of people)	4.2 (1.0)

Categorical variables are presented as n (%) and continuous variables are presented as mean (standard deviation). BIB: Born In Bradford; EDEN: Étude des Déterminants Pré et Postnatals du Développement et de la Santé de l'Enfant; INMA: Infancia y Medio Ambiente; KANC: Kaunas Cohort; MOBA: Norwegian Mother, Father and Child Cohort Study; RHEA: Mother-Child Cohort in Crete; BMI: body mass index.

Table 3. Association between pregnancy and childhood exposure profiles and lung function

	beta	95% CI	p
FEV1 (%)			
Pregnancy profiles			
Profile P1	0.00		
Profile P2	1.04	[-1.32; 3.39]	0.39
Profile P3	-0.04	[-2.11; 2.03]	0.97
Profile P4	0.25	[-2.09; 2.60]	0.83
Childhood profiles			
Profile C1	0.00		
Profile C2	-2.34	[-5.06; 0.38]	0.09
Profile C3	1.38	[-0.85; 3.60]	0.22
Profile C4	-2.55	[-5.04; -0.07]	0.04
FVC (%)			
Pregnancy profiles			
Profile P1	0.00		
Profile P2	0.77	[-1.71; 3.26]	0.54
Profile P3	-0.04	[-2.22; 2.15]	0.97
Profile P4	0.33	[-2.15; 2.80]	0.80
Childhood profiles			
Profile C1	0.00		
Profile C2	-0.89	[-3.75; 1.98]	0.55
Profile C3	1.24	[-1.11; 3.59]	0.30
Profile C4	-0.96	[-3.58; 1.66]	0.47

Models adjusted for the center of recruitment, the child's sex, age, and height and parental country of birth, breastfeeding duration, season of conception, presence of older siblings, parental education level, maternal age, maternal pre-pregnancy BMI, postnatal passive smoking status, and prenatal maternal active and passive smoking status, season of examination, Family Affluence score, social participation, contact with family and house crowding.

CI: confidence interval; p: p-value; FEV1: forced expiratory volume in 1s; FVC: forced vital capacity.

Profile P1 (reference profile) was mainly characterized by children with low levels of exposure to all risk factors except for water DBPs and high temperature during the prenatal period. The profile P2 was mainly characterized by children with high levels of exposure to all risk factors, but an overall healthy lifestyle (high practice of physical activity and high intake of fruit, vegetables and fish) of their mothers during pregnancy. Children belonging to profile P3 had overall low levels of exposure to all risk factors but moderate exposure to unhealthy lifestyle habits during the prenatal period. Finally, the profile P4 was mainly characterized by children with highest exposure to almost all exposures during the prenatal period.

Profile C1 (reference profile) was mainly characterized by children with lower mean exposure levels to all risk factors during childhood as compared to children from other profiles except for humidity. The profile C2 was also characterized by children with globally low exposure to all exposures during childhood except high exposure to high UV dose and high temperatures. Children belonging to profile C3 were characterized by the most adverse levels of exposure to air pollutants (both indoor and outdoor), unhealthy lifestyle habits and low exposure to high UV doses and high temperatures during childhood. Finally, children from profile C4 had the most deleterious exposure to natural spaces (e.g. lack of green and blue spaces in their surroundings) and highest exposure to the built environment (e.g. high population density and high building density) and road traffic during childhood.

Table 4. Association between pregnancy and childhood exposure profiles and respiratory conditions

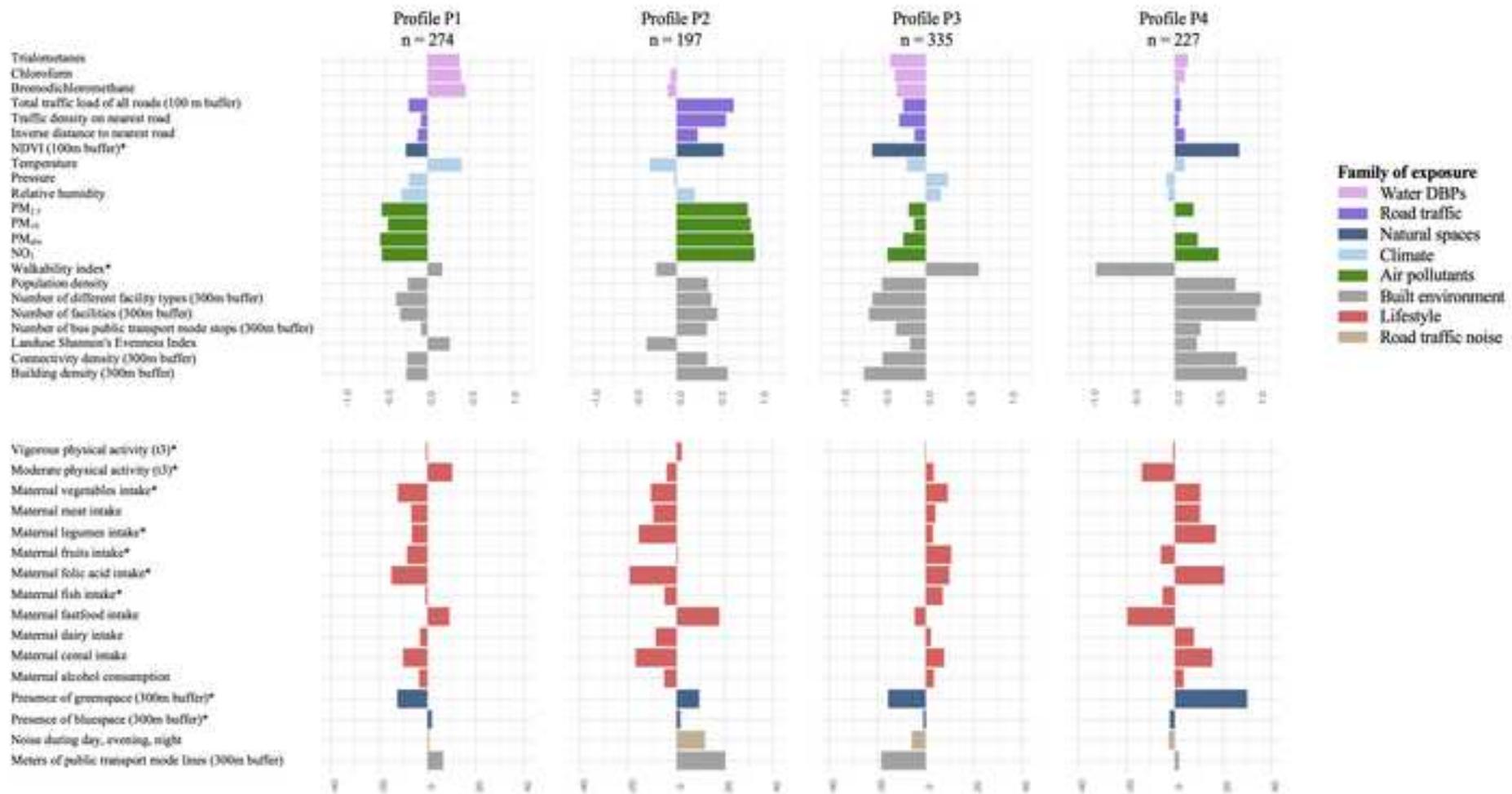
	OR	95% CI	p
Ever-asthma			
Pregnancy profiles			
Profile P1	1.00		
Profile P2	0.74	[0.35; 1.58]	0.44
Profile P3	1.07	[0.62; 1.86]	0.81
Profile P4	0.98	[0.53; 1.82]	0.94
Childhood profiles			
Profile C1	1.00		
Profile C2	2.93	[1.36; 6.31]	0.01
Profile C3	1.26	[0.67; 2.36]	0.48
Profile C4	1.17	[0.56; 2.42]	0.68
Wheezing			
Pregnancy profiles			
Profile P1	1.00		
Profile P2	0.38	[0.18; 0.77]	0.01
Profile P3	0.77	[0.45; 1.32]	0.34
Profile P4	0.93	[0.50; 1.72]	0.82
Childhood profiles			
Profile C1	1.00		
Profile C2	1.79	[0.84; 3.81]	0.13
Profile C3	1.32	[0.72; 2.43]	0.37
Profile C4	1.11	[0.54; 2.30]	0.77
Rhinitis			
Pregnancy profiles			
Profile P1	1.00		
Profile P2	0.64	[0.39; 1.05]	0.08
Profile P3	0.81	[0.53; 1.24]	0.33
Profile P4	0.8	[0.49; 1.30]	0.36
Childhood profiles			
Profile C1	1.00		
Profile C2	1.33	[0.77; 2.29]	0.31
Profile C3	0.65	[0.39; 1.07]	0.09
Profile C4	1.27	[0.76; 2.12]	0.36

Models adjusted for the center of recruitment, the child's sex, age, and height and parental country of birth, breastfeeding duration, season of conception, presence of older siblings, parental education level, maternal age, maternal pre-pregnancy BMI, postnatal passive smoking status, and prenatal maternal active and passive smoking status, season of examination, Family Affluence score, social participation, contact with family and house crowding.

OR: odds-ratio; CI: confidence interval; p: p-value; FEV1: forced expiratory volume in 1s; FVC: forced vital capacity.

Profile P1 (reference profile) was mainly characterized by children with low levels of exposure to all risk factors except for water DBPs and high temperature during the prenatal period. The profile P2 was mainly characterized by children with high levels of exposure to all risk factors, but an overall healthy lifestyle (high practice of physical activity and high intake of fruit, vegetables and fish) of their mothers during pregnancy. Children belonging to profile P3 had overall low levels of exposure to all risk factors but moderate exposure to unhealthy lifestyle habits during the prenatal period. Finally, the profile P4 was mainly characterized by children with highest exposure to almost all exposures during the prenatal period.

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Pregnancy profiles

Childhood profiles

