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# Early-life exposure to mixtures of Endocrine-Disrupting Chemicals and a Multi-domain Health Score in preschool children

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Tables and figure are displayed at the end of the manuscript (after references).

## Abstract:

**Background:** Early-life exposure to endocrine-disrupting chemicals, such as phenols and phthalates, is suspected to impact various dimensions of child health. Using a multi-outcome approach, this study aimed to estimate their cumulative effect on the child cardiometabolic, respiratory and neurodevelopmental health.

**Methods:** In 373 children of 3 years old from the SEPAGES cohort, a multi-domain health score was built from twenty-three health parameters. Fourteen metabolites of parabens, phenols, and phthalate/DINCH were measured several times during pregnancy (trimester 2

27 and 3) and infancy (2 and 12 months of age). Two mixture models, quantile g computation (q-  
28 gcomp) and Bayesian Kernel Machine Regression (BKMR), estimated associations between  
29 increased concentration of parabens, phenols, and phthalates/DINCH and the child health  
30 score.

31 **Results:** Q-gcomp showed that the paraben mixture and the phthalate mixture were associated  
32 with a poorer health score ( $\beta = -0.11$ , 95% Confidence Interval (CI): -0.22, 0.00 ;  $\beta = -0.14$ ,  
33 95% CI: -0.27, -0.01, respectively), while no significant association was found for the mixture  
34 of phenols ( $\beta = -0.06$ , 95% CI: -0.18, 0.06). A trend for an association was observed between  
35 the whole mixture (parabens, phenols and phthalates combined) with a poorer health score ( $\beta$   
36 = -0.14, 95% CI: -0.32, 0.04). Similar patterns of association, while subject to large  
37 uncertainty, have been observed with BKMR.

38 **Discussion:** This study provides further evidence for the adverse health effects of early-life  
39 exposure to parabens and phthalates. Based on their potential impact on multiple areas of  
40 child health, public health policies targeting these chemical compounds are recommended.

41 **Key words (1 to 7):** endocrine disruptors, chemical mixtures, outcome-wide, Holistic Health,  
42 pregnancy, childhood.

## 43 1. Introduction

44 Early-life exposure to endocrine-disrupting compounds (EDCs) is a growing concern due to  
45 their influence on hormone regulation (1) and broader health impact (2–4). EDCs are  
46 metabolized into different compounds, classified into families and subfamilies based on their  
47 chemical properties and sources (e.g. phenols, phthalates, per- and polyfluoroalkyl substances  
48 (PFAS)). Among EDCs, phenols and phthalates stand out due to their widespread presence  
49 and short half-lives. Synthetic phenols and phthalates are commonly found in plastic products  
50 (e.g. food packaging, PVC), food items, personal care items and building materials. These  
51 substances are used by many manufacturers, with new compounds regularly coming onto the  
52 market, such as the phthalate alternative 1,2-cyclohexane dicarboxylic acid, diisononyl ester  
53 (DINCH). Despite their short half-lives, the omnipresence of phenols and phthalates leads to  
54 heightened concerns about their potential health effects. These non-persistent chemical  
55 compounds may disrupt thyroid (5,6) and steroid hormones (7,8). Chronic exposure during  
56 critical life stages, such as pregnancy and infancy, may impact child development and  
57 increase chronic disease risks (9).

58 Most of the existing literature has focused on estimating the effect of exposure to EDCs on  
59 single health outcome or domain. Extensive research was conducted on reproductive and  
60 developmental health (10), and more recently on metabolic disorders, asthma, and allergies  
61 (11,12). Adopting a more holistic approach, it is now of interest to evaluate the impact of  
62 chemical compounds across multiple health domains within a single model. This approach  
63 could identify the chemical compounds with pleiotropic health effects, i.e. effects on multiple  
64 health outcomes, and support the development of more targeted and effective public health  
65 recommendations (13). Recent studies have explored different “multi-outcome” strategies to  
66 study the overall health impact of EDCs, such as outcome-wide models (14), multimorbidity  
67 indicators (15,16), and composite health scores combining clinical and subclinical parameters  
68 (17). Under the assumption that exposure to EDCs negatively affects each health parameter  
69 considered, which is supported by the literature (4), the composite health score is particularly  
70 advantageous in studies on young children, who have not yet developed clinical  
71 multimorbidity (18). In addition, compared to an outcome-wide analysis, this approach  
72 minimizes biases associated with multiple testing through the use of a single metric.

73 Studying phenols and phthalates poses challenges, such as the accurate assessment of  
74 exposure and the estimation of their mixture effect. Given their short half-lives (6 to 48  
75 hours), frequent measurements are essential for representative exposure estimates. Many  
76 studies have relied on single urine samples, despite evidence that it may lead to significant  
77 attenuation bias in health effect estimates, ranging from 40 to 80% according to the chemical  
78 temporal variability (19). In contrast, pooling urine samples collected over multiple  
79 consecutive days offers a more effective solution, reducing this bias to below 20% and  
80 improving the representativeness of exposure measurement across the full week (19,20).  
81 Furthermore, exposure may vary weekly due to factors like seasonal product use (e.g.  
82 sunscreens in summer) and lifestyle changes, underscoring the importance of measuring  
83 EDCs at multiple time points over the study period. Another challenge in studying EDCs is  
84 their “cocktail” or “mixture” effects, i.e. the joint effects of multiple chemical compounds  
85 (21). Most research to date has used single-pollutant models, which primarily inform per-  
86 compound regulation and fall short in preventing the use of substitutes with unknown toxicity  
87 (22,23). By estimating the effects of chemical mixtures, we could identify groups of  
88 compounds that collectively impact health. This approach is especially relevant for chemical  
89 compounds from common sources, such as parabens which are mostly found in personal care  
90 products, as it could support per-family public health strategies.

91 The current study aimed to estimate the association between early-life exposure to mixtures of  
92 parabens, mixtures of phenols and mixtures of phthalate/DINCH metabolites and a multi-  
93 domain health score covering the cardiometabolic, respiratory and neurodevelopmental health  
94 in 3-year-old children.

## 95 2. Methods

96 The methodology used for this project is illustrated in Figure 1 and detailed below.

### 97 a. Study population

98 This analysis is based on the SEPAGES cohort (Suivi de l’Exposition à la Pollution  
99 Atmosphérique durant la Grossesse et Effet sur la Santé) (24). Recruitment, conducted  
100 between July 2014 and 2017, included 484 pregnant women from ultrasonography practices  
101 in the Grenoble area, France. Participants met the following criteria: less than 19 weeks of  
102 gestation, over 18 years of age, expecting a single child, planning to deliver at a Grenoble  
103 maternity clinic, and residing within the study area. Ethical approvals were obtained from

104 relevant committees (CNIL: Comité Nationale de l'Informatique et des Libertés; CPP: Comité  
105 de Protection des Personnes Sud-Est V), and participants provided written consent for  
106 themselves and their children.

107 The study population includes 373 children who participated in the 3-year visit and had at  
108 least one cardiometabolic, one respiratory/allergic, and one neurodevelopmental parameter  
109 available (see the list of parameters in part 2.c) along with urine samples collected for at least  
110 one time point for chemical concentrations (see part 2.b). Main analyses were conducted on  
111 n=318 children (phenols) or n=330 children (phthalates), with available chemical  
112 measurements at all time points (see the flow chart in Figure S1 of the supplementary  
113 materials). Notably, excluded mother-child pairs had lower parental education than included  
114 ones (see Table S1).

#### 115 b. Synthetic parabens, phenols, phthalates and DINCH

116 As listed in **Table 1**, eight phenol metabolites (including four parabens), eleven phthalate  
117 metabolites, and two non-phthalate plasticizers (DINCH) were measured in maternal and  
118 infant urine samples. Non-fasting urine samples were collected twice during pregnancy (at 18  
119 and 34 gestational weeks) and during infancy (at 2 and 12 months). During seven consecutive  
120 days, mothers were instructed to collect three spot urine samples per day (morning, midday,  
121 and evening), and weekly within-subject pools were created (see sampling variability in Table  
122 S2). A similar protocol was followed for children, with one spot urine sample collected per  
123 day for seven days (see Table S2). Assessment of phenols, phthalate, and DINCH metabolites  
124 involved on-line column switching ultra-high performance liquid chromatography (for  
125 phenols) or high-performance liquid chromatography (for phthalates and DINCH), both  
126 coupled with tandem mass spectrometry (UPLC-MS-MS or HPLC-MS-MS), as described  
127 elsewhere (25,26). Additionally, urine specific gravity was measured in each pool using a  
128 handheld Atago PAL 10-S refractometer (Atago). Quality control, included check for possible  
129 contamination in child measurements, can be found in eMethod 1.

130 Compounds with more than 30% below the Limit Of Detection (LOD) were excluded from  
131 the analysis (butylparaben and bisphenol S at all time points, and propylparaben at 2 months),  
132 as well as phthalates metabolites at 2 months measured for only part of the samples due to  
133 budget constraints. For other compounds, chemical concentrations below the LOD or Limit of  
134 Quantification (LOQ) were singly imputed using the compound probability distribution (27).

135 Standardization for sampling conditions (sample transport time, thawing time during the  
136 pooling) and the analytical batch was then performed (28,29) when these conditions affected  
137 the measured concentrations (p-values < 0.2), based on regression models. Finally, molar sum  
138 of Di (2-ethylhexyl) phthalate (DEHP), Di-isononyl phthalate (DiNP) and DINCH  
139 metabolites were estimated, and all concentrations were log-10 transformed.

#### 140 c. Health data

141 As listed in **Table 2**, twenty-three health parameters were assessed in children, mostly at the  
142 3-year follow-up, covering cardiometabolic, respiratory, and neurodevelopmental health (see  
143 eMethod 2 for details).

144 **Cardiometabolic health** was assessed by a cohort clinical research assistant, including  
145 diastolic and systolic blood pressure (BP), heart rate (measured with a SureSigns-VSi monitor  
146 VSi, Philips, Amsterdam, Netherlands), and body fat estimated by bioelectrical impedance  
147 (with an empty bladder using the BodyStat 1500 MDD, Isle of Man, UK) coupled with  
148 skinfold thickness measurements (subscapular and triceps skinfolds using a skinfold caliper)  
149 and weight measurement. Fat mass percentage was derived from Goran's equation for  
150 improved accuracy in children (30).

151 **Respiratory and allergy-related health** was assessed through lung function using  
152 oscillometry (resistance at 7 Hz (R7), frequency-dependence of resistance (R7-19), area of  
153 the reactance curve (AX), within-breath volume-dependence of resistance ( $\Delta R$ )) (32), skin  
154 prick allergy tests (5 allergens tested), and parent-reported questionnaires administered at 2  
155 months, 12 months, 2 years, and 3 years, asking whether the child had ever had doctor-  
156 diagnosed asthma (yes/no), doctor-diagnosed eczema (yes/no), wheezing (yes/no),  
157 bronchiolitis (yes/no) and bronchitis (yes/no) since birth.

158 **Neurodevelopmental** assessments included cognitive testing (Wechsler Preschool and  
159 Primary Scale of Intelligence, Fourth Edition (WPPSI), measuring verbal and visuospatial  
160 comprehension, and working memory) and three parent questionnaires (the 99-item Child  
161 Behaviour Checklist (CBCL), the Behaviour Rating Inventory of Executive Function –  
162 Preschool version (BRIEF-P), the Social Responsiveness Scale (SRS)). These questionnaires  
163 provided scores on internalizing/externalizing behaviors (CBCL), executive functions  
164 (BRIEF-P: Emergent Metacognition index, Inhibitory Self-Control index, Flexibility index),

165 and social impairment within the autism spectrum disorders (SRS total score). All measures  
166 were performed at the 3-year follow-up, except CBCL, assessed at 2 years.

#### 167 d. Covariates

168 A set of covariates was defined with the main confounders between the exposures and the  
169 multi-domain health score as well as the main predictors of each health subdomain, as  
170 detailed in the Directed Acyclic Graph (DAG) in Figure S2 of the supplementary materials.  
171 Because of the moderate sample size, we built a parsimonious model excluding covariates  
172 with no sign of association with the outcome in our data (regression p-value>0.2). The final  
173 set of covariates used included: **1) parental characteristics and health history**: highest  
174 parental education (below Master degree vs Master degree or higher), parental history of  
175 asthma or allergy (none vs at least one parent) assessed during pregnancy, maternal  
176 depression and anxiety during pregnancy (total score from the Hospital Anxiety and  
177 Depression scale), **2) details on pregnancy**: season of conception, maternal tobacco (active  
178 or passive vs none) during pregnancy, **3) child characteristics and environment at 3 years**:  
179 child sex, child height, child postnatal exposure to tobacco (yes/no), child stimulation score  
180 (total scale of the Home Observation Measurement of the Environment (HOME)).

#### 181 e. Pre-treatment of the data

182 Imputation of the missing values on covariates and the 23 health parameters was done using  
183 the method of chained equations (31) (R package *mice* v3.16.0.). Before, we checked that the  
184 percentage of missingness was below 30%, and we log-transformed covariates with a skewed  
185 distribution. It generated 20 imputed datasets, which were checked (see eMethods 3) and then  
186 used to compute the multi-domain health score and perform the association studies.

#### 187 f. Creation of the multi-domain health score

188 Similarly as done in Amine et al. (2023), a **multi-domain health score** (also named as  
189 “general health score” or simply “health score”) averaged three subscores, each representing a  
190 specific health domain (cardiometabolic, respiratory/allergy, and neurodevelopmental health).  
191 Beforehand, each continuous parameter was transformed in a z-score, using a Box-Cox  
192 transformation (R package *MASS* v7.3-57) plus centering and scaling. The cardiometabolic  
193 subscore was defined as  $(-z \text{ fat mass}) + (-z \text{ heart rate}) + (-z \text{ diastolic BP} - z \text{ systolic BP})/2$ ,  
194 similar to the metabolic score used in the Helix population (32). In the same way, the  
195 neurodevelopmental subscore was defined as  $(z \text{ WPPSI} - z \text{ SRS} - z \text{ CBCL} - z \text{ BRIEF})/4$ ,

196 where each test z-score is the average of the z-scores of its considered indexes. Following the  
197 approach of Eisenmann (33) the respiratory/allergic subscore was defined as the first principal  
198 component of a multiple factorial analysis (R package *FactoMineR* v.2.9.), able to deal with  
199 categorical outcomes.

200 Given the challenge of prioritizing one health domain over another, we assigned equal  
201 weights to each subscore when creating the multi-domain health score. While alternative  
202 weighting schemes could be based on disease burden metrics (e.g., DALYs), economic costs,  
203 or long-term impact, determining an appropriate approach requires further research. We thus  
204 opted for an equal-weight method as a straightforward and unbiased choice.

205 By construct, the multi-domain health score is low-to-moderate for children who exhibit low-  
206 to-moderate health in cardiometabolic, respiratory/allergy and neurodevelopmental domains  
207 simultaneously, as well as for children who are severely affected in one health domain while  
208 being unaffected or poorly affected in the other two. The multi-domain health score  
209 determinants were described using a multivariable linear regression model using all covariates  
210 (listed in part 2.d).

#### 211 g. Strategy of analysis for the association study

212 The association between mixtures of EDCs and the multi-domain health score was performed  
213 using two complementary statistical approaches: quantile g-computation (q-gcomp) (34) and  
214 Bayesian Kernel Machine Regression (BKMR) (35). These two models allow for an effect  
215 estimation of increasing all exposures simultaneously, with additive linear effects for q-  
216 gcomp, and possible interactions and non-linearity for BKMR. Because each model (q-gcomp  
217 and BKMR) has its own assumptions, comparing their results provides additional support to  
218 validate the findings (36).

219 In **q-gcomp**, continuous exposures are transformed in quartiles, and the overall mixture effect  
220 is estimated as a weighted sum of the effects of the quantized exposures (*qgcomp* R package,  
221 v2.15.2). This approach evaluates the impact of simultaneously increasing all exposures by  
222 one quartile. Mathematically, if  $Y_i$  represents the continuous outcome for individual  $i$ , the  
223 regression model is expressed as  $Y_i = \beta_0 + \psi S_i + \beta C_i + \epsilon_i$ , where:  $\beta_0$  is the intercept,  $S_i$  is  
224 the exposure index (defined below),  $\psi$  represent the overall mixture effect,  $C_i$  is the matrix of  
225 covariates with corresponding vector of coefficients  $\beta$ , and  $\epsilon_i$  is the error term. The exposure  
226 index is defined as  $S_i = \sum w_j X_{ij}^q$ , where  $w_j$  is the weight assigned to  $j$ th exposure and  $X_{ij}^q$  is

227 the quantized version of the  $j$ th exposure for individual  $i$ . While the weights can be used to  
228 assess individual chemical contributions, these estimates should be interpreted cautiously,  
229 especially when correlated exposures are considered (34). Due to the moderate sample size,  
230 we did not include non-linear terms nor pairwise interactions in q-gcomp.

231 On the other hand, **BKMR** represents a non-parametric Bayesian approach using a kernel  
232 function to estimate the relationship between several exposures and an outcome (R package  
233 *bkmr* v.0.2.2.). Mathematically, if  $Y_i$  represents the continuous outcome for individual  $i$  and  
234  $\mu_i = E(Y_i)$ , the modeling framework is given by  $\mu_i = h(X_{i1}, \dots, X_{iM}) + \beta C_i$ , where  $h$  is a  
235 flexible function of the exposures  $X_{ij}$ , and  $C_i$  is the matrix of covariates with corresponding  
236 vector of coefficient  $\beta$  (linear assumption). The exposure-response function  $h(\cdot)$  is  
237 characterized using a Gaussian kernel, expressed as  $K(X, X') = \exp \{-\sum_m r_m (X_m - X'_m)^2\}$ ,  
238 where  $X$  and  $X'$  represent vectors of exposures from two different individuals, and  $r_m \geq 0$  are  
239 tuning parameters. This kernel function shrinks the estimated effects of two individuals with  
240 similar exposure mixtures towards each other. The mixture overall effect is computed for all  
241 chemical compounds fixed to a given quantile, compared to when they are all fixed to the 10<sup>th</sup>  
242 quantile. The inclusion of 0 within the credible interval is used to evaluate the certainty of the  
243 mixture effect. As this model performs variable selection at each iteration ( $r_m$  can be equal to  
244 0), the contribution of each chemical compound in the mixture can be estimated through the  
245 mean Posterior Inclusion Probabilities (PIP).

246 One separate model was fitted for each family of compounds (parabens, phenols,  
247 phthalates/DINCH) and the whole mixture (parabens, phenols and phthalates combined). As  
248 the outcome was assessed only once (at 3 years of age), we did not perform a repeated  
249 measures analysis, but rather integrated chemical measurements from all time points as  
250 separate predictors in the model. To handle the multiplicity of predictors in the model  
251 including all chemical families (parabens, phenols and phthalates) in BKMR, the hierarchical  
252 selection was used (“h-BKMR”) considering one group for each compound. All models were  
253 adjusted for the covariates listed in part 2.d, and fitted for each imputed dataset before  
254 combining the results, using Rubin’s rule for q-gcomp and merging all simulations for BKMR  
255 (37,38).

256 Several complementary analyses were performed to deepen the association study, including 1)  
257 the investigation of windows-specific effects by fitting separate models for each time point

258 (trimester 2, trimester 3, 2 months (parabens and phenols only) and 12 months), 2) the  
259 investigation of potential sex-specific association, by fitting sex-stratified analyses, 3) the  
260 description of domain-specific health effects, by investigating the association separately for  
261 each subscore (cardiometabolic, respiratory, neurodevelopmental), 4) the description of  
262 chemical-specific associations, by fitting adjusted linear regressions between each single  
263 chemical compound with the multi-domain health score (“uni-pollutant” models).

264 Various sensitivity analyses were used to further assess the robustness of the findings to 1)  
265 extreme values, using winsorization on the 2% lowest and 2% highest values for the multi-  
266 domain health score (39), 2) adjustment factors, by considering the minimal adjustment set  
267 (i.e. excluding predictors of the outcome, see the DAG in Figure S2), 3) removal of children  
268 with potential measurements error in blood pressure (remaining n=359), 4) the use of  
269 concentrations corrected for urine specific gravity, even if this approach is discussed as it may  
270 bias health effect estimates (40), 5) the use of the conjugated form of the compound when  
271 contamination was suspected (bisphenol A at 2 and 12 months and methylparaben at 12  
272 months, see eMethods 1), for the uni-pollutant analysis only.

273 Analyses were done with R version 4.2.1.

## 274 3. Results

### 275 a. Description of the population

276 As shown in **Table 3**, the study population comprised 373 children, with a median age of 3.07  
277 years (percentile 25; 75: 3.04; 3.13) at the time of the clinical visit, and 46% of the  
278 participants were female. At birth, mothers had a median age of 32 years (percentile 25; 75:  
279 30; 35), and for 74% of families, at least one parent had a high degree of education (Master  
280 degree or higher). Chemical concentration levels (before log<sub>10</sub>-transformation) are  
281 summarized in **Figure 2** and detailed in Table S3 and S4, with additional information  
282 available in previous studies (41,42). Between-compound concentrations in a given time point  
283 (e.g. different phthalate compounds at 12 months) were more strongly correlated than within-  
284 compound concentrations across time (i.e. measurements of a given phthalate compound at 2  
285 and 12 months of age) (Figure S3). A table describing each health parameter is available in  
286 the supplementary materials (Table S5). Before imputation, half covariates and health  
287 parameters had less than 2% of missing values, and the highest missingness was reached for  
288 parameters of lung function (18-23%) (Table 3 and S5).

289                   b. Description of the multi-domain health score

290 For the respiratory/allergic subscore, we observed a similar contribution from each outcome,  
291 although ever-asthma diagnosis had a slightly greater weight (see Table S6 and Figure S4).  
292 For neurodevelopmental and cardiometabolic subscores, each outcome contributed equally by  
293 design, as they were based on an unweighted mean of z-scores. Although the three subscores  
294 (cardiometabolic, respiratory/allergic, and neurodevelopmental) were poorly correlated  
295 ( $\rho < 0.1$ , see Table S7), we observed that the multi-domain health score significantly  
296 increased with all health parameters included (Table S8).

297 As shown in **Figure 3**, the multi-domain health score built had a normal distribution (Shapiro  
298 test p-value = 0.42) with a median (percentiles 25; 75) of 0.02 (-0.42; 0.42) (see also Table  
299 S9). The following characteristics were associated with a better multi-domain health score:  
300 higher child height, higher child stimulation score, and male sex, while a poorer score was  
301 associated with parental history of asthma or rhinitis and higher maternal anxiety and  
302 depression score (Table S10).

303                   c. Chemical mixtures associated with the multi-domain health score

304 As shown in **Figure 4** and Table S11, the q-gcomp mixture model showed that higher  
305 concentrations to mixtures of parabens and phthalates/DINCH were associated with a poorer  
306 multi-domain health score. A one-quartile increase in all chemical compounds from the  
307 phthalate/DINCH mixture was associated with a poorer health score ( $\beta = -0.14$ , 95%  
308 Confidence Interval (CI): -0.27; -0.01), similarly as increased concentration of the paraben  
309 mixture ( $\beta = -0.11$ , 95% CI: -0.22; 0.00). On the other hand, no significant association was  
310 found for the phenol mixture ( $\beta = -0.06$ , 95% CI: -0.18; 0.06). When parabens, phenols and  
311 phthalates were studied in a combined mixture (“whole mixture”), a trend for an association  
312 was observed with a poorer health score ( $\beta = -0.14$ , 95% CI: -0.27; 0.01). The results of the  
313 BKMR models were more uncertain, with wide credibility intervals that crossed the null (see  
314 Figure 4). Therefore, we interpreted these findings according to the direction of the  
315 association only. Consistently, the results pointed to poorer health scores with increased  
316 exposure to mixtures, providing support for the q-gcomp findings.

317 In the analysis evaluating each time window separately (see Figures S5 and S6), we found  
318 that the highlighted associations with a poorer health score in q-gcomp were replicated in  
319 trimester 2 of pregnancy for the phthalates/DINCH mixture ( $\beta = -0.10$ ; 95% CI: -0.19; 0.00),

320 and at 12 months for the paraben mixture ( $\beta = -0.05$ ; 95% CI: -0.11; 0.01). In addition,  
321 significant associations for the phenol mixture and the whole mixture with a poorer health  
322 score, which were not observed in the main models, were observed specifically in trimester 2  
323 ( $\beta = -0.08$ ; 95% CI: -0.15; 0.00,  $\beta = -0.11$ ; 95% CI: -0.23; 0.01, respectively).

324 Using q-gcomp, the observed associations showed similar patterns of association in girls and  
325 boys for parabens and phthalates/DINCH (Figure S7). Additional associations were observed  
326 specifically in girls, but not in the whole population, for the phenol mixture and for the whole  
327 mixture (parabens, phenols and phthalates). BKMR confirmed the girl-specific association for  
328 the phenol mixture and suggested another girl-specific association for the phthalates/DINCH  
329 mixture (Figure S8). However, the wide credible intervals obtained in BKMR contained 0.

330 Analysis on specific health domains confirmed that the associations observed with the multi-  
331 domain health score were also reflected on several health subscores (cardiometabolic,  
332 respiratory/allergic, neurodevelopmental), although these associations were not always  
333 statistically significant (see Figure 5). Specifically, the association observed for the paraben  
334 mixture with the multi-domain health score was mainly driven by the neurodevelopmental  
335 subscore ( $\beta = -0.21$ , 95% CI: -0.40, -0.02), but it was also supported by the  
336 respiratory/allergic subscore ( $\beta = -0.11$ , 95% CI: -0.31, 0.09). Regarding phthalates,  
337 associations were mainly driven by the neurodevelopmental subscore ( $\beta = -0.23$ , 95% CI: -  
338 0.45, -0.01) and supported by the cardiometabolic subscore ( $\beta = -0.13$ , 95% CI: -0.35, 0.09).

339 The chemical compounds highlighted by the uni-pollutant analysis (Figure S9 and Tables  
340 S12-S13) were predominantly those contributing most to the mixtures using q-gcomp and  
341 BKMR (Figure S10 and Tables S14-S15) and included maternal concentration of monoethyl  
342 phthalate (MEP) (trimester 2 and 3), monobenzyl phthalate (MBzP) (trimester 2) and  
343 ethylparaben (trimester 3), as well as the infant concentration of propylparaben (12 months).

344 Overall, the findings of q-gcomp remained unchanged in the sensitivity analyses (see Figure  
345 S11 online). Similar results were obtained after removing children with potential  
346 measurement errors in blood pressure and after winsorizing extreme values on the outcome.  
347 Models restricted to the minimal set of confounders confirmed the results with overall  
348 stronger effect sizes as compared to the main model. When using chemical concentrations  
349 corrected for urine specific gravity, the mixture effect of phthalates was shifted towards the  
350 null, while the other significant findings remained unchanged. Using conjugated forms for

351 bisphenol A (2 and 12 months) and methylparaben (12 months) did not change the results in  
352 the uni-pollutant analysis (null associations), as displayed in Figure S9 online.

## 353 4. Discussion

354 This novel study estimates the overall effect of early-life exposure to parabens, phenols and  
355 phthalates on child health through a comprehensive approach using: 1) a multi-outcome  
356 strategy to estimate the cumulative effects across multiple health domains (cardiometabolic,  
357 respiratory and neurodevelopmental), 2) mixture models to estimate the joint effects of  
358 chemical compounds coming from similar sources, and 3) accurate and representative  
359 measures of overall chemical exposure via repeated measurements from early pregnancy to  
360 the first year of life. Our findings indicate that increased concentrations to mixtures of  
361 parabens and phthalates in early-life were associated with a poorer health score in children at  
362 3 years of age. This study provides additional evidence to support adverse health effects of  
363 early-life exposure to parabens and phthalates on multiple areas of child health.

### 364 a. Main findings

365 Our results showed associations between higher concentrations of parabens and phthalates  
366 and a poorer multi-domain health score in children. To our knowledge, only one study from  
367 the Human Early Life Exposome (HELIX) project used a similar composite health score to  
368 explore associations with EDCs (17). While a comparable finding was found between  
369 methylparaben and poorer child health, limited evidence was found with other non-persistent  
370 chemical compounds, likely due to reliance on single urine samples for exposure  
371 measurement. Using a different approach, two multi-outcome studies have also examined the  
372 effects of phthalates on child health (14,15); one with results on respiratory outcomes only,  
373 while the other found varying directional effects across domains, thus lacking evidence of a  
374 broad, unidirectional effect.

375 Our results align with existing literature on the associations between parabens and phthalates  
376 with individual outcomes of the three health domains covered: cardiometabolic, respiratory  
377 and neurodevelopmental health. Several studies suggests that early-life exposure to parabens  
378 and phthalates (especially DEHP and MEP) may be associated with adverse metabolic  
379 outcomes, including adiposity-related measures and increased blood pressure in children  
380 (43,44). Regarding respiratory health and allergies, several reviews or meta-analyses  
381 suggested associations between parabens, several phthalates (especially MBzP and DEHP)

382 and increased risk of asthma and eczema (45–48). In regards to neurodevelopmental health,  
383 some studies suggested that several outcomes were associated with exposure to parabens and  
384 DEHP (49–53), though other studies remained less conclusive (54,55). Using a multi-domain  
385 health score, our findings strengthen the hypothesis that phthalates and parabens could  
386 broadly affect multiple health areas in childhood. This is further supported by supplementary  
387 analyses which indicate suggestive associations with neurodevelopmental and  
388 respiratory/allergic subscores for parabens, and with neurodevelopmental and cardiometabolic  
389 subscores for phthalates/DINCH.

390 Among the suspected mechanisms of action of phenols and phthalates, key processes like  
391 endocrine dysregulation, oxidative stress, inflammation and epigenetic modifications, may  
392 contribute to the development of various chronic diseases across the three health domains  
393 studied. Many phenols and phthalates are classified as endocrine-disrupting chemicals (1,56)  
394 and may interfere with thyroid function and other hormones (7,8), which are critical for the  
395 brain development (57) and child growth (58), and might impact the onset of later chronic  
396 disorders (59–61). Hormonal effects may explain the girl-specific association observed for  
397 phenols, though stratification further reduces statistical power, warranting cautious  
398 interpretation of these sex-specific findings. To our knowledge, the epidemiological literature  
399 on sex-specific effects remains unclear. For example, several studies suggest that BPA  
400 exposure impacts neurobehavioral functioning differently by sex, but studies are inconsistent  
401 in regards to which sex is more affected (62). Additionally, phenols and phthalates may  
402 generate oxidative stress (63) and trigger inflammatory responses (64,65), which are strongly  
403 associated with allergy-related diseases (66,67), metabolic disorders (68,69) and mental  
404 health disorders like depression (70). Lastly, exposure to phenols and phthalates may induce  
405 epigenetic alterations, altering gene expression patterns critical to processes like fetal  
406 development or immune responses, potentially leading to wide-ranging health effects (71,72).  
407 Taken together, these findings suggest that exposure to phenols and phthalates may impact  
408 biological pathways common to multiple health domains, potentially explaining their  
409 pleiotropic effects (i.e. simultaneous effects on multiple health outcomes) (13).

410 By integrating multiple measures of exposures to EDCs during pregnancy and infancy, this  
411 study aimed to model their health effects more comprehensively. Given that phenols and  
412 phthalates are non-persistent chemicals, with half-lives ranging from approximately 6 to 30  
413 hours in the human body (73,74), studies relying on a single urine sample may be subject to

414 attenuation bias in the estimated health effects (20,75). Our first strategy to mitigate  
415 attenuation bias in the association study was to use pooled urine samples collected over an  
416 entire week (20,24). As a complementary approach, we proposed to integrate concentrations  
417 measured at several time points (trimester 2 and 3 of pregnancy, 2 and 12 months of age) in a  
418 unified model to better model effects of the overall exposure. This method resulted in slightly  
419 larger effect sizes compared to when studying specific exposure windows, especially for  
420 phthalates and paraben when using q-gcomp, and for phenols when using BKMR. Thus, these  
421 results support the hypothesis of a cumulative health effect of chemical compounds over time.

422 To assess the robustness of the results, we performed a series of sensitivity analyses, and used  
423 two complementary statistical models (q-gcomp and BKMR). Overall, the sensitivity analyses  
424 confirmed the robustness of the results. However, we observed that the association with  
425 phthalates/DINCH was not robust in models using urine concentrations corrected for specific  
426 gravity. Accounting for urine dilution in such analysis is debated as it may introduce bias  
427 (40). Therefore, these supplementary findings do not fully undermine the credibility of the  
428 main results. In addition, both q-gcomp and BKMR models showed similar association  
429 trends, but BKMR yielded greater uncertainty, with wide credible intervals including zero.  
430 This large uncertainty may arise from its complex design, which can model interactions and  
431 non-linearity. In this context, BKMR might require larger samples sizes or effect sizes  
432 compared to q-gcomp, which is based on a simpler linear regression model. Alternative  
433 mixture models, such as WQS, non-parametric models such as Bayesian additive regression  
434 trees (BART), and multivariate adaptive regression splines (MARS), could have further  
435 validated our results. However, WQS unidirectionality assumption could introduce bias (34),  
436 and simulations have shown that most non-parametric mixture models (including BKMR)  
437 exhibit similar performance (76). Therefore, to simplify the analysis, we selected one  
438 quantile-based model (q-gcomp) and one non-parametric model (BKMR), as commonly used  
439 in similar studies (77,78).

#### 440 b. Strengths and weaknesses

441 This study has several strengths. First, from a public health perspective, our original results  
442 relying on a multi-domain health score enabled us to identify key risk factors impacting  
443 multiple health domains simultaneously. Using this score helps mitigate the false discovery  
444 rate, as the number of tests is divided by the number of outcomes included, i.e. by twenty-  
445 three. Moreover, we employed a by-family approach to model mixtures, which allowed us to

446 target specific sources of chemical compounds. This targeted method may facilitate more  
447 effective per-family regulation of endocrine-disrupting chemicals. A further asset relates to  
448 the precise and repeated measurements of EDC exposure from weekly-pooled urine samples,  
449 conducted twice during pregnancy and twice during infancy. This strategy allowed us to  
450 better characterize the overall chemical exposure during this critical developmental period and  
451 its potential health effect. Moreover, robustness of our findings was evaluated using two  
452 mixture models, q-gcomp and BKMR, which are based on similar hypotheses but apply  
453 different methodology to model mixtures.

454 However, our study has some limitations. The moderate sample size (n=318 to 330) and the  
455 use of imputations for individual health parameters may have reduced the statistical power to  
456 detect associations, although this should not have biased the results (79). Moreover, the use of  
457 a multi-domain health score limited the results to compounds showing a uni-directional  
458 association across outcomes and may also have obscured effects occurring on a single health  
459 domain. Additionally, we cannot exclude residual confounding from unmeasured variables  
460 such as diet, or selection bias, without the possibility of using techniques such as Inverse  
461 Probability Weighting in all models (especially in BKMR).

#### 462 c. Public health impact

463 This study provides additional evidence that early-life exposure to parabens and phthalates  
464 may impact multiple health domains in children, emphasizing the need for prioritized public  
465 health policies. These findings support public health policies to reduce exposure to these  
466 chemical compounds, especially stricter regulations since interventions targeting  
467 manufacturing have been shown to be more effective than those relying on individual  
468 behavior (80). At the same time, labeling requirements of products and educational initiatives  
469 remain essential to raise public awareness and promote safer consumer choices. In addition,  
470 the findings related to specific chemical mixtures (parabens and phthalates) support a shift  
471 toward per-family regulation of chemical compounds, moving away from the traditional  
472 approach of regulating individual compounds.

## 473 Conclusion

474 We introduced a novel multi-outcome approach that integrate multiple health parameters  
475 covering cardiometabolic, respiratory and neurodevelopmental health domains into a multi-  
476 domain health score. This study extends prior findings by suggesting that early-life exposure

477 to mixture of parabens and mixture of phthalates may jointly impact multiple health aspects of  
478 child health. Thus, it advocates for public health policies targeting these chemical families.

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- 756

## 757 Tables

758 Table 1 – Non-persistent chemical compounds studied

Synthetic phenols	Phthalates/DINCH
Parabens:	
- Methylparaben (MEPA)	- Monoethyl phthalate (MEP)
- Ethylparaben (ETPA)	- Mono-n-butyl phthalate (MnBP)
- Propylparaben (PRPA)	- Mono-isobutyl phthalate (MiBP)
- Buthylparaben (BUPA)	- Monobenzyl phthalate (MBzP)
	- 6-Hydroxy Monopropylheptyl phthalate (ohMPHP)
Other phenols:	
- Benzophenone-3 / Oxybenzophenone (OXBE)	- Di-isononyl phthalate (DiNP)*
- Tricolosan (TRCS)	- Di (2-ethylhexyl) phthalate (DEHP)*
- Bisphenol A (BPA)	- 1,2-cyclohexanedicarboxylic acid, diisononyl ester (DINCH)*
- Bisphenol S (BPS)	

759

760 This table lists all chemical compounds considered for this study, by chemical families.

761 \* DINP, DINCH, and DEHP measures were estimated through molar sums of their  
762 metabolites.763 DEHP: molar sum of Mono(2-ethyl-5oxohexyl) phthalate (MEOHP), Mono(2-ethyl-5-  
764 carboxypentyl) phthalate (MECPP), Mono(2-ethylhexyl) phthalate (MEHP), Mono(2-ethyl-5-  
765 hydroxyhexyl) phthalate (MEHHP), Mono-2-carboxymethyl hexyl phthalate (MMCHP).766 DiNP: molar sum of Mono-4-methyl-7-hydroxyoctyl phthalate (oh-MiNP), Mono-4-methyl-  
767 7-oxooctyl phthalate (oxo-MiNP) and Mono-4-methyl-7-carboxyoctyl phthalate (cx-MiNP)768 DINCH: molar sum of 2-(((Hydroxy-4-methyloctyl)oxy)carbonyl)cyclohexanecarboxylic  
769 Acid (oh-MINCH) and 2-(((4-Methyl-7-oxooctyl)oxy)carbonyl)cyclohexane carboxylic  
770 Acid (oxo-MINCH)

771

772

773 *Table 2 – Health parameters included in the multi-domain health score in children aged 3 years*

Cardiometabolic health	Respiratory health and allergies	Neurodevelopment
- Blood pressure: systolic and diastolic	- Lung function: intra-breath and within-breath oscillometry parameters	- Cognitive abilities (WPPSI)
- Heart rate	- Asthma and allergy-related diseases: ever-asthma*, ever-wheezing, ever-eczema*, ever-bronchiolitis, ever-bronchitis (questionnaires)	- Behavioural disorders (CBCL)
- Percentage of fat mass (bioimpedance and skinfold)	- Allergies (skin prick tests)	- Behavioral manifestations of executive functions (BRIEF-P)
		- Social impairment within the autism spectrum disorders (SRS)

774

775 This table lists all health parameters considered for the creation of the multi-domain health  
 776 score. All parameters were measured at the 3-year visit, except for the CBCL which was  
 777 assessed at 2 years.

778 \* Doctor diagnosed

779 BRIEF-P: Behaviour Rating Inventory of Executive Function – Preschool version, CBCL:  
 780 Child Behaviour CheckList, SRS: Social Responsiveness Scale, WPPSI: Wechsler Preschool  
 781 and Primary Scale of Intelligence, Fourth Edition.

782

Variable	N (%)	n (%) or Median (percentile 25, 75)
<b>PARENTAL CHARACTERISTICS AND HEALTH HISTORY</b>		
Highest parental education	373 (100%)	
Below master degree		98 (26%)
Master degree or above		275 (74%)
Maternal age at conception (years)	373 (100%)	32.4 (30.2, 35.4)
Maternal parity	373 (100%)	
No child		166 (45%)
1 child		168 (45%)
2 children or more		39 (10%)
Parental history of asthma or rhinitis	355 (95%)	
None		118 (33%)
At least one parent		237 (67%)
Maternal anxiety and depression score	360 (97%)	10.0 (7.0, 13.0)
<b>PREGNANCY AND EARLY LIFE</b>		
Season conception	373 (100%)	
January-March		108 (29%)
April-June		74 (20%)
July-September		87 (23%)
October-December		104 (28%)
Pregnancy Tobacco	348 (93%)	
No Tobacco		268 (77%)

Active or passive tobacco 80 (23%)

CHILD AT THE 3-YEARS FOLLOW UP

Child sex	373 (100%)	
Female		171 (46%)
Male		202 (54%)
Child age at the follow-up (years)	372 (100%)	3.07 (3.04, 3.13)
Child height (cm)	373 (100%)	95.3 (92.8, 97.5)
Child passive smoking (ever)	370 (99%)	
Never exposed		285 (77%)
Exposed		85 (23%)
Child stimulation score (HOME)	364 (98%)	25.00 (23.00, 26.00)

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784

785 BMI: Body Mass Index, HOME: Home Observation Measurement of the Environment,

786 WAIS: Wechsler Adult Intelligence Scale – Fourth Edition.

## 787 Figures

### 788 **Figure 1 – Methodological workflow**

789 This figure describe the methodology used for this project.

790

### 791 **Figure 2 – Description of the exposure to parabens, phenols, phthalates, and non-phthalate plasticizers in the study population**

792 Distribution of the chemical concentrations measured in the study population (n=373), along  
793 with Limit of Detection (LOD) and Limit of Quantification (LOQ). When multiple values of  
794 LOD/LOQ were used for a given compound according to the sample (different batches), the  
795 minimum value was plotted. For molar sums (DiNP, DEHP, DINCH), LOQ and LOD were  
796 artificially computed by using the same molar weights. This plot displays the standardized,  
797 imputed, non-log transformed values, at the exception of butylparaben and bisphenol S for  
798 which raw machine values were used (>30 % below limit of detection).

800 DEHP: Di (2-ethylhexyl) phthalate, DiNP: Di-isononyl phthalate, DINCH: 1,2-  
801 cyclohexanedicarboxylic acid, diisononyl ester, MBzP: Monobenzyl phthalate, MEPA:  
802 Methylparaben, MEP: Monoethyl phthalate, MiBP: Mono-isobutyl phthalate, MnBP: Mono-  
803 n-butyl phthalate, oh-MPHP: 6-Hydroxy Monopropylheptylphthalate.

### 804 **Figure 3 - Description of the cardiometabolic (A), respiratory/allergy (B), and mental** 805 **(C) health subscores and the multi-domain health score (D).**

806 Distribution of the cardiometabolic subscore (panel A), respiratory subscore (panel B),  
807 neurodevelopmental subscore (panel C) and the multi-domain health score (panel D), i.e. the  
808 average of the three subscores. All twenty imputed datasets were used.

### 809 **Figure 4 – Associations between chemical mixtures and the multi-domain health score,** 810 **integrating chemical measurements at all time points, estimated by q-gcomp and BKMR**

811 This figure represents the association between each chemical mixtures and the multi-domain  
812 health score estimated by quantile g-computation (q-gcomp) model (panel A) and Bayesian  
813 Kernel Model Regression (BKMR) (panel B). For q-gcomp, the graph shows the overall  
814 effect of each mixture on the multi-domain health score, i.e. the effect for a quartile increase  
815 in all chemical concentrations, with 95% Confidence Interval (CI). For BKMR, it represents  
816 the change in the multi-domain health score for each 10% quantile increase in exposure to  
817 chemical mixture. For both models, each graph represents an independent model (one model  
818 by exposure family), built from chemical measurement from all time points (n=318 to 330).

819 Models were applied to each of the 20 imputed datasets and results were combined using the  
820 Rubin's rule (q-gcomp) or by combining all simulations (BKMR). Adjustment was made on  
821 parental education, parental history of asthma or rhinitis, maternal depression and anxiety  
822 during pregnancy, season of conception, maternal tobacco during pregnancy, child sex, child  
823 height, child exposure to tobacco, child stimulation score.

824 **Figure 5 - Associations between chemical mixtures and each health subscore estimated**  
825 **by q-gcomp**

826 This figure represents the results of the quantile g-computation (q-gcomp) models on each  
827 subscores (cardiometabolic, respiratory, neurodevelopmental), using chemical concentrations  
828 at all time points. It shows the overall effect of each mixture on each subscore, i.e. the effect  
829 for a quartile increase in all chemical concentrations, with 95% Confidence Interval (CI). One  
830 estimate represents an independent model (one model by exposure family), built from  
831 chemical measurement from all time points (n=318 to 330). Models were applied to each of  
832 the 20 imputed datasets and results were combined using the Rubin's rule. Adjustment was  
833 made on parental education, parental history of asthma or rhinitis, maternal depression and  
834 anxiety during pregnancy, season of conception, maternal tobacco during pregnancy, child  
835 sex, child height, child exposure to tobacco, child stimulation score.

836