

Prenatal phenol exposure and child behaviour: insights into the hypothalamic–pituitary–adrenal axis from two prospective mother–child cohorts



Matthieu Rolland, Mariona Bustamante, Paulina Jedynak, Cathrine Thomsen, Amrit K Sakhi, Maria Foraster, Mireia Gascon, Maria Dolores Gómez-Roig, Elisa Llorba, Ioar Rivas, Isabelle Ouellet-Morin, Muriel Ferrer, Alex Morillas, Sylvain Carras, Sam Bayat, Sarah Lyon-Caen, Oscar J Pozo, Martine Vrijheid, Jordi Sunyer, Rémy Slama, Payam Davvand, Claire Philippat

Summary

Background Synthetic phenols are widely used chemicals with potential neurodevelopmental toxicity. Human studies are often limited by small sample sizes and exposure misclassification. Identifying the biological pathways affected by these substances is crucial for understanding key drivers of toxicity. We aimed to study associations between prenatal exposure to synthetic phenols and child behaviour, exploring the potential mediating role of maternal steroid hormones.

Methods We pooled data from two European cohorts: the Barcelona Life Study Cohort (BiSC; Barcelona, Spain, 2018–21, N=1080) and Suivi de l'Exposition à la Pollution Atmosphérique durant la Grossesse et Effets sur la Santé (SEPAGES; Grenoble, France, 2014–17, N=484). Mothers older than 18 years having a singleton pregnancy of less than 19 weeks gestational age were eligible for inclusion in the cohorts; those having multiple pregnancies were excluded. Repeated urine samples (up to 24 in BiSC; up to 42 in SEPAGES) collected in the second and third trimesters were pooled and analysed for 12 synthetic phenols. Child behavioural outcomes were assessed at 18 months in BiSC and 24 months in SEPAGES using the Child Behavior Checklist for Ages 1–5–5 (CBCL). Concentrations of total cortisol, total cortisone, and 11-dehydrocorticosterone—steroid hormones involved in the hypothalamic–pituitary–adrenal axis—were measured from maternal hair samples. Associations between phenol exposure and behavioural outcomes were estimated by adjusted linear regression analysis, and mediation by steroid hormones was assessed with regression-based causal mediation analysis within the counterfactual framework.

Findings 1024 mother–child pairs were included in the study: 607 from BiSC and 417 from SEPAGES. Maternal exposure to methylparaben in the third trimester of pregnancy was associated with higher internalising scores (change in score of 0.44 [95% CI 0.10–0.79] points) and externalising scores (0.67 [0.12–1.24]) in the CBCL. In boys, maternal exposure to bisphenol S in the third trimester was linked to increased internalising scores (0.92 [0.15 to 1.75]; $p=0.019$) and could be linked to increased externalising scores (1.14 [–0.09 to 2.44]; $p=0.070$). In girls, second-trimester butylparaben and propylparaben exposure were associated with lower internalising (–1.03 [–1.84 to –0.09], $p=0.033$) and externalising (–0.68 [–1.23 to –0.12]; $p=0.019$) scores. No mediation by steroid hormones was observed.

Interpretation Prenatal exposure to phenols might influence early behavioural development, with sex-specific patterns. There was no strong evidence of mediation by maternal steroid hormones, suggesting the involvement of alternative pathways in the biological effects of phenols. Together with previous findings, these results highlight the need for stricter regulation of these compounds to reduce prenatal exposure.

Funding French Agency for Food, Environmental and Occupational Health & Safety, the EU's Horizon 2020 research and innovation programme, and the French Fund – Fondation de France.

Copyright © 2025 The Author(s). Published by Elsevier Ltd. This is an open access article under the CC BY-NC license (<http://creativecommons.org/licenses/by-nc/4.0/>).

Introduction

Neurodevelopmental disorders, which affect many children and adolescents and are increasing in prevalence, have long-term consequences for mental health. Effective reduction strategies require the identification of modifiable risk factors, such as exposure to synthetic phenols—a widely used class of chemicals commonly found in

personal care products, some food items, and packaging, which are of particular concern owing to their endocrine-disrupting activity. Emerging research has identified associations between exposure during pregnancy to synthetic phenols—including, but not restricted to, bisphenol A—and neurodevelopmental outcomes in children,¹ including child behaviour.^{2,3} However, little is known regarding the

Lancet Planet Health 2025;
9: 101330

Published Online December 9,
2025

<https://doi.org/10.1016/j.lanplh.2025.101330>

University Grenoble Alpes, Inserm, CNRS, Team of Environmental Epidemiology applied to Reproduction and Respiratory Health, Institute for Advanced Biosciences (IAB), Grenoble, France (M Rolland MSc, P Jedynak PhD, S Lyon-Caen MSc, R Slama PhD, C Philippat PhD); ISGlobal, Barcelona, Spain (M Bustamante PhD, P Jedynak, M Foraster PhD, M Gascon PhD, I Rivas PhD, M Ferrer MSc, A Morillas MSc, M Vrijheid PhD, J Sunyer MD PhD, Prof P Davvand MD PhD); Universitat Pompeu Fabra (UPF), Barcelona, Spain (M Bustamante, P Jedynak, M Foraster, M Gascon, I Rivas, M Ferrer, A Morillas, M Vrijheid, J Sunyer, Prof P Davvand); CIBER Epidemiología y Salud Pública (CIBERESP), Madrid, Spain (M Bustamante, P Jedynak, M Foraster, M Gascon, I Rivas, M Ferrer, A Morillas, M Vrijheid, J Sunyer, Prof P Davvand); PHAGEX Research Group, Blanquerna School of Health Sciences, Universitat Ramon Llull (URL), Barcelona, Spain (M Foraster); Norwegian Institute of Public Health, Oslo, Norway (C Thomsen PhD, A K Sakhi PhD); Unitat de Suport a la Recerca de la Catalunya Central, Fundació Institut Universitari per a la Recerca a l'Atenció Primària de Salut Jordi Gol i Gurina (IDIAPJGol), Manresa, Spain (M Gascon); BCNatal, Barcelona Center for Maternal Fetal and Neonatal Medicine (Hospital Sant Joan de Déu and Hospital Clínic), University of Barcelona, Spain (M D Gómez-Roig MD PhD); Institut de Recerca Sant Joan de

Déu, Barcelona, Spain
(M D Gómez-Roig); Spanish Network in Maternal, Neonatal, Child and Developmental Health Research (RICORS-SAMID, RD24/0013/0004), Instituto de Salud Carlos III, Madrid, Spain (M D Gómez-Roig); Department of Obstetrics and Gynaecology, Women and Perinatal Health Research Group, Institut de Recerca (IR SANT PAU), Hospital de la Santa Creu i Sant Pau, Barcelona, Spain (E Llurba MD PhD); Spanish Network in Maternal, Neonatal, Child and Developmental Health Research (RICORS-SAMID, RD24/0013/0004), Instituto de Salud Carlos III, Madrid, Spain (E Llurba); School of Criminology, University of Montreal, The Research Center of the Montreal Mental Health University Institute and the Research Group on Child Maladjustment, Montréal, QC, Canada (I Ouellet-Morin PhD); Biobank BB-0033-00069, Univ Grenoble Alpes, Inserm U1209, CNRS UMR5309, Institute for Advanced Biosciences, CHU Grenoble-Alpes, Grenoble, France (S Carras PhD); Department of Pulmonology and Physiology, Grenoble University Hospital, La Tronche, France (S Bayat MD PhD); IMIM (Hospital del Mar Medical Research Institute), Barcelona, Spain (O J Pozo PhD); Institute of Environmental Assessment and Water Research, CSIC, Barcelona, Spain (I Rivas)

Correspondence to:
Dr Claire Philippat, University Grenoble Alpes, Inserm, CNRS, Team of Environmental Epidemiology applied to Reproduction and Respiratory Health, Institute for Advanced Biosciences (IAB), 38700 Grenoble, France
claire.philippat@inserm.fr

See Online for appendix

Research in context

Evidence before this study

We searched PubMed for journal articles published in English from database inception to May 1, 2025, using the search terms ("synthetic phenols" OR "bisphenol" OR "paraben" OR "triclosan") AND ("pregnancy" OR "maternal exposure" OR "prenatal exposure") AND ("neurodevelopment" OR "child behavior"). 133 results were retrieved by the search. Most epidemiological studies on the effects of phenols on child neurodevelopment focused on bisphenol A, a chemical that has been banned from several applications in the EU, from food packaging materials. Few studies considered other phenols, such as bisphenol S, a replacement product with similar properties to bisphenol A. Most studies had small-to-moderate sample sizes (N=140–708) and relied on a small number of spot urine samples (three or fewer) to assess exposure, resulting in substantial exposure misclassification and reduced statistical power. Moreover, none conducted robust mediation analyses to explore the underlying biological pathways of neurotoxicity—an essential step in strengthening the biological plausibility of observed effects and enhancing our understanding of toxicity mechanisms.

Added value of this study

The large sample size and the urine sampling design—in which up to 24 or 42 samples were obtained from individuals in each of the two cohorts—limited exposure misclassification and increased power compared with previous studies. Additionally, using two

biological pathways underlying these associations. Clarifying such mechanisms is relevant for regulatory purposes, as the classification of endocrine disruptors in the EU is based on both mechanistic evidence and observed adverse health effects.⁴

Several studies have highlighted associations between prenatal phenol exposure and hormonal pathways¹ as well as direct effects on brain structure;⁵ however, to our knowledge, formal mediation analysis has not been conducted. The potential role of the hypothalamic–pituitary–adrenal (HPA) axis, which is crucial in the response to stress,⁶ has received insufficient attention, whereas elevated cortisol concentrations in pregnancy have been associated with increased behavioural problems in children.⁷ Associations between maternal symptoms linked with the HPA axis—such as stress, anxiety, or depression—and an increased risk of mental health and behavioural problems in children have also been reported.⁸

Environmental factors can affect the HPA axis. An *in silico* study showed that bisphenol A acts as a glucocorticoid receptor agonist.⁹ Animal studies have linked perinatal exposure to bisphenol A with increased corticosterone and adrenocorticotropic hormone concentrations, decreased glucocorticoid receptor concentrations, and neurodevelopmental impairments in the offspring, suggesting mediation potential through the HPA axis.¹⁰ Additionally, in studies with moderate sample sizes (n<200), higher

cohorts with different populations and settings strengthened the robustness and generalisability of our findings. Although key for fetal brain development, the mediating role of hypothalamic–pituitary–adrenal (HPA) axis hormones in the neurodevelopmental effects of phenols have, to our knowledge, not been studied to date. Such studies are crucial for meeting EU regulatory standards, for which evidence of endocrine disruption effects is required to classify chemicals as endocrine disruptors. We found that exposure to methylparaben (in boys and girls) and bisphenol S (in boys only)—both of which are typically overlooked when studying the health effects of phenols—was positively associated with both internalising and externalising scores, suggesting an increase in behavioural problems in young children. These associations did not seem to be mediated by HPA hormones, suggesting the involvement of other pathways.

Implications of all the available evidence

In line with studies on other health outcomes, our results suggested that bisphenol S is unlikely to be a safe alternative to bisphenol A. Moreover, methylparaben—the most prevalent phenol with the highest exposure levels—had the strongest associations with behavioural outcomes, highlighting a potential neurodevelopmental risk from common exposures. Together, these findings support the need for stricter regulatory evaluation and strategies to reduce prenatal exposure. Further research is needed to elucidate the underlying biological mechanisms.

concentrations of bisphenol A during pregnancy were associated with decreased salivary cortisol concentrations in women¹¹ and male infants¹² and increased concentrations in female infants.¹² Data on bisphenol A analogues and other synthetic phenols—such as parabens and triclosan—remain scarce, although some were found to affect glucocorticoid pathways in an *in silico* study.¹³

We aimed to examine associations between prenatal exposure to synthetic phenols and behavioural outcomes in children aged between 18 and 24 months, and to investigate the potential mediating role of the HPA axis in these associations.

Methods

Study design and population

This study pooled harmonised data from two mother–child cohorts: the Barcelona Life Study Cohort (BiSC; Barcelona, Spain, 2018–21, N=1080) and Suivi de l'Exposition à la Pollution Atmosphérique durant la Grossesse et Effets sur la Santé (SEPAGES; Grenoble, France, 2014–17, N=484; appendix p 30). Only mother–child pairs for whom pooled urine samples (from the mother) and a completed Child Behavior Checklist for Ages 1.5–5 (CBCL) questionnaire (for the child) were available were included in the study. The eligibility criteria for both cohorts were the mother having a singleton pregnancy of less than 19 weeks gestational age at inclusion; being aged 18 years

or older; being fluent in French (SEPAGES) or in Spanish or Catalan (BiSC); being registered in the national social security systems (and therefore entitled to access public health-care services); and planning to deliver the child in the recruitment area. Women having a multiple pregnancy were excluded. The studies were approved by the relevant ethical committees (appendix p 3), and at least one parent of the expected child provided written informed consent for themselves and their child before inclusion. The statistical analysis plan¹⁴ and the cohort protocols^{15,16} have been previously published.

Exposure assessment

During both the second and third trimesters, women collected three urine samples per day for 7 consecutive days in SEPAGES (a maximum of 42 samples) and two urine samples per day for 6 consecutive days in BiSC (a maximum of 24 samples; appendix p 31). Median gestational ages at sampling were 18·9 weeks (IQR 17·4–20·9) and 35·7 weeks (34·4–37·0). For each participant, samples collected over the week were pooled. These pooled samples were used to quantify total urinary concentrations of 12 compounds: 11 phenols (bisphenols A, S, F, B, and AF, and methylparaben, ethylparaben, propylparaben, butylparaben, triclosan, and benzophenone-3) and the related compound triclocarban. These compounds were selected on the basis of their plausibility to affect child behaviour (ie, through endocrine disruption), their high production volume, or their use as substitutes for regulated phenols, and the feasibility of their analysis using ultra-high-performance liquid chromatography coupled with tandem mass spectrometry (appendix p 4).

Child behaviour

The CBCL, a widely used questionnaire assessing emotional and behavioural problems in children aged 1·5–5 years, was completed by mothers at home when the child was aged 18 months (BiSC) or by a field worker when the child was aged 24 months (SEPAGES). Higher scores on the questionnaire indicate more problematic behaviours. We used the raw scores on the internalising (eg, anxiety, depression, and withdrawal; theoretical range 0–48) and externalising (eg, aggression and hyperactivity; theoretical range: 0–72) scales owing to their high reliability in identifying children at risk of emotional and behavioural problems.

Maternal HPA axis hormones

We collected 3 cm of scalp side hair samples from mothers at a median gestational age of around 31·9 weeks (IQR 31·1–32·4) in BiSC and around birth (median gestational age 42 weeks [41·1–42·9]) in SEPAGES. These samples correspond to hair growth during the previous 3 months. For both cohorts, measurements were conducted by the same laboratory using liquid chromatography coupled with tandem mass spectrometry (appendix p 4). We measured the concentrations of seven hormones

related to the HPA axis: cortisol, 20 α -dihydrocortisol, 20 β -dihydrocortisol, cortisone, 20 α -dihydrocortisone, 20 β -dihydrocortisone, and 11-dehydrocorticosterone (appendix p 32). We calculated the molar sums of cortisol (from cortisol, 20 α -dihydrocortisol, and 20 β -dihydrocortisol; denoted total cortisol) and cortisone (from cortisone, 20 α -dihydrocortisone, and 20 β -dihydrocortisone; denoted total cortisone). 11-Dehydrocorticosterone was studied individually.

Statistical analysis

Outcome transformation and interpretation

As CBCL scores were right-skewed, we applied a square-root transformation to improve the normality of model residuals. Because regression coefficients from models using transformed outcomes are difficult to interpret, we calculated the expected CBCL score change at the median as a marginal effect, using the formula $[\text{median}(\sqrt{\text{CBCL}}) + \beta]^2 - [\text{median}(\sqrt{\text{CBCL}})]^2$. This calculation provided an approximate change in raw CBCL score for a child with a median score.¹⁷

Exposure and hormone preprocessing

Biomarkers detected in less than 2% of samples (ie, fewer than 21 of 1024 women; bisphenols AF, B, F, and triclocarban) were excluded from further analysis. For compounds with detection rates lower than 70% (ie, fewer than 717 of 1024 women had detectable concentrations; bisphenol S and butylparaben), concentrations were categorised as below or above the limit of detection (LOD). For the remaining biomarkers, values below the LOD were singly imputed on the basis of their estimated distribution. All phenol and hormone concentrations were log₁₀-transformed (to express effect estimates per ten-fold increase and ensure consistency across variables), and standardised to account for analytical batch and other protocol-related factors (eg, thawing or transport time, depending on compound and cohort; appendix p 7).

Data description

For between-cohort comparisons, we used Pearson's χ^2 test for categorical variables and the Wilcoxon rank sum test for continuous variables. Correlations between exposure biomarkers were assessed using Spearman's rank correlation coefficients.

Associations between phenols and CBCL scores

Adjusted linear regression analyses were conducted to identify associations between individual phenols and CBCL scores, with separate models for the second and third trimesters. In the main analysis, concentrations were treated as continuous variables. To assess the linearity of these associations, we used generalised additive models (GAMs) with penalised thin plate regression splines (mgcv::s(bs="tp", k=10)) adjusted for the same covariates. We compared each GAM to its corresponding linear model using likelihood ratio tests, providing a direct test for

	Overall (N=1024)	BiSC (N=607)	SEPAGES (N=417)	p value
Maternal BMI (kg/m ²)*				
18.5 to 24.9	687 (71%)	375 (67%)	312 (75%)	<0.0001
<18.5	48 (5%)	20 (4%)	28 (7%)	..
≥25.0	238 (24%)	164 (29%)	74 (18%)	..
Missing	51	48	3	..
Maternal age (years)	33.9 (31.0 to 36.8)	35.0 (32.0 to 38.0)	32.3 (30.0 to 35.3)	<0.0001
Maternal education level				
Below university	156 (15%)	134 (22%)	22 (5%)	<0.0001
University (below master's degree)	323 (32%)	168 (28%)	155 (37%)	..
University (master's degree or higher)	543 (53%)	305 (50%)	238 (57%)	..
Missing	2	0	2	..
Maternal ethnicity				
European	894 (88%)	495 (82%)	399 (97%)	<0.0001
Latin American	101 (10%)	101 (17%)	0	..
Other†	25 (2%)	11 (2%)	14 (3%)	..
Missing	4	0	4	..
Maternal anxiety (Z score)‡	0.00 (−0.70 to 0.60)	−0.18 (−0.70 to 0.55)	0.00 (−0.70 to 0.60)	0.88
Missing	80	67	13	..
Parity				
Nulliparous	587 (57%)	393 (65%)	194 (47%)	<0.0001
Multiparous	437 (43%)	214 (35%)	223 (53%)	..
Passive smoking during pregnancy§				
Yes	305 (31%)	229 (39%)	76 (19%)	<0.0001
No	674 (69%)	357 (61%)	317 (81%)	..
Missing	45	21	24	..
Alcohol intake during pregnancy¶				
Yes	262 (27%)	169 (29%)	93 (23%)	0.014
No	724 (73%)	404 (71%)	320 (77%)	..
Missing	38	34	4	..
Folic acid intake during pregnancy				
Yes	705 (82%)	338 (76%)	367 (88%)	<0.0001
No	156 (18%)	108 (24%)	48 (12%)	..
Missing	163	161	2	..
Active smoking during pregnancy				
Yes	68 (7%)	45 (8%)	23 (6%)	0.38
No	912 (93%)	554 (92%)	358 (94%)	..
Missing	44	8	36	..
Timing of second trimester urine sample (gestational weeks)	18.9 (17.4 to 20.9)	20.3 (18.4 to 22.6)	17.7 (16.4 to 18.9)	<0.0001
Missing	172	135	37	..
Timing of third trimester urine sample (gestational weeks)	35.7 (34.4 to 37.0)	36.7 (35.7 to 37.7)	34.0 (33.3 to 35.3)	<0.0001
Missing	112	70	42	..
Hair collection (gestational weeks)	33.0 (31.7 to 41.9)	31.9 (31.1 to 32.4)	42.0 (41.1 to 42.9)	<0.0001
Missing	98	98	0	..
Time between hair collection and hormone assessment (months)	12 (5 to 49)	6 (4, 11)	51 (45 to 59)	<0.0001
Missing	155	98	57	..
Total cortisol (nmol/g)	0.024 (0.016 to 0.037)	0.027 (0.020 to 0.037)	0.019 (0.010 to 0.037)	<0.0001
Missing	171	102	69	..
Season of birth				
Winter	202 (20%)	116 (19%)	86 (21%)	0.55
Other	822 (80%)	491 (81%)	331 (79%)	..
Sex of the child				
Male	528 (52%)	299 (49%)	229 (55%)	0.075
Female	496 (48%)	308 (51%)	188 (45%)	..

(Table 1 continues on next page)

	Overall (N=1024)	BiSC (N=607)	SEPAGES (N=417)	p value
(Continued from previous page)				
Breastfeeding duration (weeks)	35 (17 to 48)	48 (26 to 48)	26 (15, 42)	<0.0001
Missing	18	9	9	
Child in day care at age 12 months				
Yes	378 (45%)	255 (51%)	123 (35%)	<0.0001
No	471 (55%)	241 (49%)	230 (65%)	..
Missing	175	111	64	..
Age at CBCL questionnaire (months)	19.7 (18.7 to 24.6)	18.8 (18.4 to 19.4)	24.7 (24.5 to 25.1)	<0.0001
Externalising behaviour raw scores (points)	11 (7 to 16)	10 (5 to 14)	12 (9 to 17)	<0.0001
Missing	1	0	1	..
Internalising behaviour raw scores (points)	4 (2 to 8)	3 (1 to 6)	6 (3 to 9)	<0.0001

Data are n (%), n, or median (IQR). p values were calculated with Pearson's χ^2 test for categorical variables and the Wilcoxon rank sum test for numerical variables. BiSC=Barcelona Life Study Cohort. CBCL=Child Behavior Checklist for Ages 1.5–5. SEPAGES=Suivi de l'Exposition à la Pollution Atmosphérique durant la Grossesse et Effets sur la Santé. * Assessed at inclusion (gestational age ~12 weeks) in BiSC and before pregnancy in SEPAGES. †For BiSC, no further information was available for the 11 participants classed as being of Other ethnicity. For SEPAGES, the 14 participants of Other ethnicity comprised four African, one Asian, three Oriental Mediterranean, and two southeast Asian participants, as described in the original cohort, and four participants for whom no further detail was available. ‡Anxiety Z scores were derived from the Perceived Stress Scale, the Edinburgh Postnatal Depression Scale, and the Symptom Checklist-90-Revised anxiety subscale in BiSC; and were based on the Hospital Anxiety and Depression Scale, which includes separate subscales for anxiety and depression, in SEPAGES. §Passive smoking during pregnancy was defined as being exposed to tobacco smoke 3 months before and during pregnancy in BiSC, and being exposed to indoor tobacco smoke for at least 1 hour per week during pregnancy only in SEPAGES. ¶Alcohol intake during pregnancy was defined as the consumption of any alcoholic beverages during any trimester of pregnancy in BiSC, and drinking any quantity of alcohol per month when pregnancy was known during SEPAGES. ||Active smoking during pregnancy was defined as any number of cigarettes smoked any time during pregnancy in BiSC, and as smoking at least one cigarette per day any time during pregnancy in SEPAGES.

Table 1: Cohort characteristics

deviation from linearity, including U-shaped or inverted U-shaped patterns. To assess effect modification by the sex of the child, we included an interaction term between sex and exposure. When $p_{\text{interaction}}$ was less than 0.10, we computed an effect estimate for male and female sexes using the full regression model and the variance-covariance matrix. Finally, we analysed the interaction between exposure and cohort, and stratified by cohort when $p_{\text{interaction}}$ was less than 0.10 or when a significant association was observed in the main models, to check the consistency of the results across both cohorts.

We did not apply formal corrections for multiple comparisons, as the number of tests was small (eight phenols $\times$ two CBCL scores). However, to mitigate the risk of false positives, we focused our interpretation on associations that were consistent across cohorts, behavioural domains, and/or exposure windows.

To assess the combined effects of phenols, we used Bayesian kernel machine regression (BKMR).¹⁸ This method, which is frequently used in environmental epidemiology, accounts for non-linear and interactive effects, and provides estimates of overall mixture associations. Separate models were run for the second and third trimesters using 50 000 iterations. Owing to a limitation of the BKMR approach, biomarkers dichotomised owing to low detection rates (bisphenol S and butylparaben) were excluded. The results were evaluated by plotting the expected change in CBCL scores relative to the tenth percentile increase in all exposure biomarkers. This analysis was conducted for the entire population and was stratified by the sex of the child.

Mediation analysis

We conducted mediation analyses to estimate the role of total cortisol, total cortisone, and 11-dehydrocorticosterone in associations between phenol exposure and child behaviour. These analyses were conducted only for phenols that were associated with CBCL scores ($p < 0.05$) in the main analysis or the sex-specific analysis. Following the counterfactual framework,¹⁹ we did not require significance of individual paths (exposure to mediator or mediator to outcome) before estimating mediation effects, as subtle effects could still produce meaningful indirect effects. We used the R package `f{mediation}`, which relies on two regression models (appendix p 33): one regressing the mediator (hormone concentration) on exposure (phenol concentration) and covariates; and the second regressing the outcome (CBCL score) on the exposure, the mediator, and covariates. On the basis of these models, the natural indirect effect (ie, part of the effect of exposure on CBCL score mediated by the hormone) was computed using parametric bootstrapping (1000 simulations).

Missing data

Participants with missing exposure or CBCL data were excluded from association models; those for whom hormone data were also missing were excluded from mediation models. Covariate missingness was addressed via multiple imputation by chained equations (20 imputations) using a random forest algorithm. For BKMR models we used single imputation, relying on the median for continuous variables and the mode for categorical variables, owing to computational constraints.

Standardised concentrations* (µg/L)									
Measured concentrations (µg/L)					BiSC				
BiSC					SEPAGES				
N	>LOD	p5	p50	p95	N	>LOD	p5	p50	p95
Trimester 2									
Benzophenone-3	455	454 (100%)	0.91	5.18	140	415	415 (100%)	0.25	1.14
Bisphenol A	455	390 (86%)	<LOD	2.52	25.2	415	412 (99%)	0.67	2.00
Bisphenol S	455	267 (59%)	<LOD	0.50	3.55	415	101 (24%)	<LOD	<LOD
Butylparaben	455	<LOD	<LOD	<LOD	0.62	415	<LOD	<LOD	<LOD
Ethylparaben	455	455 (100%)	0.85	2.53	48.8	415	414 (100%)	0.26	0.70
Methylparaben	455	455 (100%)	4.48	14.9	231	415	415 (100%)	2.68	12.3
Propylparaben	455	398 (87%)	<LOD	0.52	37.2	415	334 (80%)	<LOD	0.40
Triclosan	455	425 (93%)	<LOD	0.79	126	415	408 (98%)	0.21	0.91
Trimester 3									
Benzophenone-3	523	523 (100%)	0.82	4.89	128	409	407 (100%)	0.24	0.99
Bisphenol A	523	453 (87%)	<LOD	2.90	25.3	409	402 (98%)	0.52	1.78
Bisphenol S	523	291 (56%)	<LOD	0.43	3.30	407	109 (27%)	<LOD	<LOD
Butylparaben	523	<LOD	<LOD	<LOD	0.49	409	<LOD	<LOD	<LOD
Ethylparaben	523	523 (100%)	0.93	2.70	30.83	409	407 (100%)	0.21	0.73
Methylparaben	523	523 (100%)	5.16	17.6	1160	409	409 (100%)	2.86	12.24
Propylparaben	523	467 (89%)	<LOD	0.69	149	409	328 (80%)	<LOD	0.56
Triclosan	523	467 (89%)	<LOD	0.71	110	409	401 (98%)	0.19	0.86

Biomarkers detected in less than 2% of samples (ie, fewer than 21 of 1024 women; bisphenols AF, B, F, and triclosan) were excluded. Denominators correspond to the number of participants with available exposure measurements for each trimester. The total sample size (N=1024) includes all participants with at least one measurement across either trimester. BiSC=Barcelona Life Study Cohort. LOD=limit of detection. p5=5th percentile. p50=50th percentile. p95=95th percentile. SEPAGES=Suivi de l'Exposition à la Pollution Atmosphérique durant la Grossesse et Effets sur la Santé. * Concentrations were standardised for protocol-related factors, such as analytical batch and/or sampling conditions; for further details, see Methods.³

Table 2: Detection rates and phenol urinary concentrations stratified by cohort and trimester (N=1024)

Adjustment factors

All models were adjusted for cohort and key confounders or outcome predictors: maternal age, maternal education level (below university, university [below master's degree]; or university [master's degree or higher]), maternal ethnicity (European, Latin American, or other), parity, maternal BMI (pre-pregnancy for SEPAGES and at inclusion for BiSC), active smoking, alcohol use during pregnancy, maternal anxiety (normalised and presented as Z scores; for BiSC, scores were derived from the Perceived Stress Scale, the Edinburgh Postnatal Depression Scale, and the Symptom Checklist-90-Revised anxiety subscale; for SEPAGES, scores were based on the Hospital Anxiety and Depression Scale, which includes separate subscales for anxiety and depression), sex of the child, birth season (winter [December–February] vs other), breastfeeding duration, and child day care attendance at age 12 months. For the first mediation models (hormones regressed on phenols), breastfeeding duration and day care attendance were not included. Covariate selection was informed by directed acyclic graphs (appendix pp 34–35). Because we relied on pooled urine samples, urine dilution was not accounted for in our main model.²⁰ Age at CBCL assessment was not included because it was strongly collinear with cohort; including both would have introduced multicollinearity. However, this covariate was added in the cohort stratified analysis.

Sensitivity analyses

Analyses were repeated for participants with complete covariate data (N=567–581) as a covariate, using raw instead of standardised phenol concentrations, and applying win-sorisation (capping the top and bottom 1% of CBCL scores and phenol concentrations at the 1st and 99th percentiles, corresponding to 12 or 13 participants depending on the phenol). To compare effects across trimesters, models were re-run for participants with both second-trimester and third-trimester urine samples (N=794–795). Finally, analyses were run in the two cohorts separately, then a meta-analysis was conducted on the results of each cohort.

We used R version 4.4.2 for analysis.

Role of the funding source

The funders of the study had no role in study design, data collection, data analysis, data interpretation, or writing of the report.

Results

1024 mother–child pairs were included in the study: 607 from BiSC and 417 from SEPAGES. Participant characteristics and CBCL raw scores are presented in table 1. Notable differences between cohorts included older maternal age, a lower proportion of mothers with BMI 18.5–24.9 kg/m², shorter breastfeeding duration, and higher total cortisol concentrations in BiSC than in SEPAGES. Children were also younger at CBCL

assessment and had lower CBCL scores in BiSC than in SEPAGES.

For each of the second and third trimesters, respectively, pooled samples were available for 455 and 523 women from BiSC and for 415 and 409 women from SEPAGES, corresponding to a total of 1024 participants with at least one available measure. Most phenols were detected in more than 80% of samples (table 2). Median standardised concentrations of parabens and benzophenone-3 were higher in BiSC, whereas bisphenol A and triclosan concentrations were higher in SEPAGES. Bisphenol S was more frequently detected, and at higher concentrations, in BiSC than in SEPAGES. The highest within-sample correlations were observed between parabens (Spearman's $r=0.27-0.64$); correlation coefficients for other phenols were less than 0.25 (appendix p 9).

Single-pollutant analyses revealed associations between third-trimester methylparaben concentration and increased behavioural problems. For a ten-fold increase in urinary concentrations, the estimated increase in CBCL score was 0.44 points (95% CI 0.10–0.79; $p=0.011$) for internalising behaviours and 0.67 points (0.12–1.24; $p=0.017$) for externalising behaviours (figure 1, appendix p 10). These associations were consistent across both cohorts (appendix p 12).

Interaction with the sex of the child was found for parabens and bisphenol S. In boys, detectable bisphenol S concentrations during the third trimester were associated with increased CBCL internalising scores (0.92 [95% CI 0.15 to 1.75]; $p=0.019$) and could be associated with increased externalising scores (1.14 [–0.09 to 2.44]; $p=0.070$). In girls, second-trimester butylparaben concentrations were associated with a decrease in internalising scores (–1.03 [–1.84 to –0.09]; $p=0.033$) and second-trimester propylparaben concentrations with a decrease in externalising scores (–0.68 [–1.22 to –0.11]; $p=0.019$; figure 2, appendix p 13). When further stratifying by cohort, these associations were driven by BiSC for bisphenol S and by SEPAGES for parabens, although effect directions remained consistent across cohorts (appendix p 14).

An interaction between second-trimester bisphenol S concentration and cohort was observed for internalising behaviours ($p=0.084$; appendix p 11). Stratified analyses showed a negative association for SEPAGES (–1.07 [95% CI –1.93 to –0.12]) and no clear association for BiSC (0.28 [–0.41 to 1.06]; appendix p 12).

Only propylparaben concentrations in the second trimester (internalising; $p=0.013$) and triclosan concentrations in the second and third trimesters (externalising; $p=0.032$ and $p=0.017$, respectively) showed significant evidence of deviation from linearity, but the fitted GAM curves displayed only mild curvature with wide CIs (appendix p 36). The associations remained robust across the sensitivity analyses, including complete cases, non-standardised exposures, adjustment for specific gravity, winsorisation of CBCL scores and exposure values, and the meta-analysis of the cohort-specific results. The direction of

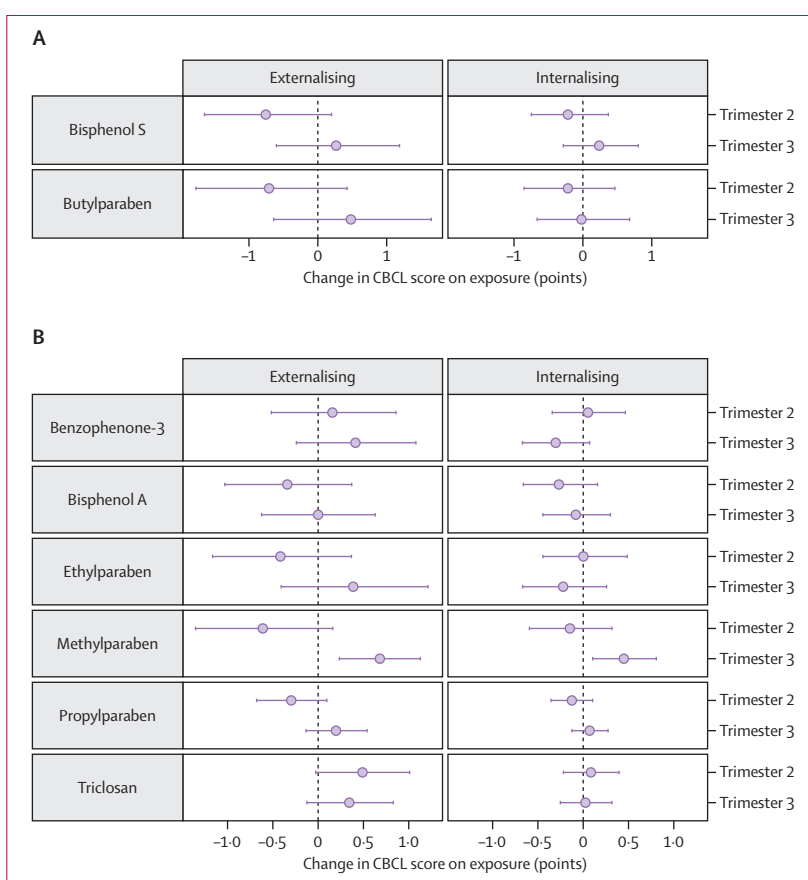


Figure 1: Single-pollutant-adjusted associations between maternal phenol concentrations during pregnancy and CBCL scores

Data are estimate (95% CI). Models were adjusted for maternal age, maternal education level, maternal BMI, active smoking status during pregnancy, alcohol consumption during pregnancy, maternal ethnicity, anxiety Z score during pregnancy, cohort, parity, sex of the child, birth season, child's attendance at day care at 12 months, and breastfeeding duration. The CBCL scores were subjected to a square-root transformation before analysis to meet the assumptions of linear regression. For each phenol, β regression estimates were back-transformed to CBCL scores using the following formula: $[\text{median}(\sqrt{\text{CBCL}} + \beta)]^2 - [\text{median}(\sqrt{\text{CBCL}})]^2$, allowing for interpretation of the results on the original CBCL scale. CBCL=Child Behavior Checklist for Ages 1–5–5.

the associations was consistent, although significance was not always maintained (appendix pp 15–27).

No overall mixture effect was observed in the whole population in the BKMR analysis. Although not significant, a trend towards increased internalising and externalising scores with increasing exposure to the mixture of phenols in the third trimester was observed in girls (appendix pp 37–38).

None of the observed associations, in the whole population or after stratification by the sex of the child, seemed to be mediated by the hormone concentrations in maternal hair samples. The lowest p value for indirect effect was 0.49 and effect estimates were all close to zero (table 3). Similar results were seen in the mediation analyses stratified by cohort (all p values for direct effect >0.11 ; appendix pp 28–29).

Discussion

This study involved 1024 participants from two European cohorts with contrasting confounding structures and

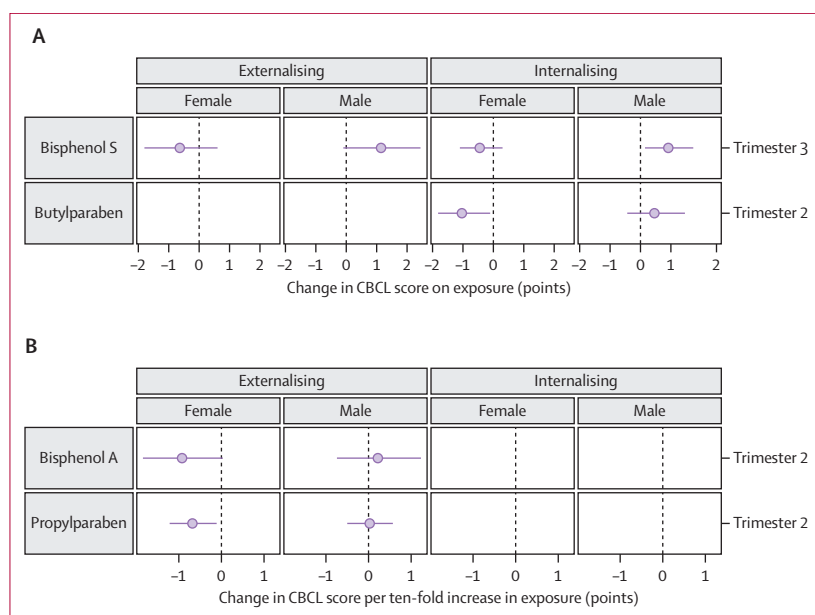


Figure 2: Single-pollutant-adjusted associations between phenol concentrations in pregnancy and CBCL scores, stratified by sex

Data are estimate (95% CI). Analyses were conducted only for exposure–outcome pairs with evidence of interaction ($p < 0.10$). Models were adjusted for maternal age, maternal education level, maternal BMI, active smoking status during pregnancy, alcohol consumption during pregnancy, maternal ethnicity, anxiety Z score during pregnancy, cohort, parity, birth season, child's attendance at day care at 12 months, and breastfeeding duration. The CBCL scores were subjected to square-root transformation before analysis to meet the assumptions of linear regression. For each phenol, β regression estimates were back-transformed to CBCL scores using the following formula: $[\text{median}(\sqrt{\text{CBCL}}) + \beta]^2 - [\text{median}(\sqrt{\text{CBCL}})]^2$, allowing for interpretation of the results on the original CBCL scale. CBCL=Child Behavior Checklist for Ages 1–5–5.

enhanced exposure assessment compared with previous studies. Exposure to individual phenols—particularly methylparaben (in boys and girls) and bisphenol S (in boys)—during the third trimester was associated with higher internalising and externalising CBCL scores, suggesting increased behavioural problems. The third trimester is a crucial window marked by heightened maternofetal exchange (eg, increased blood flow and enlarged placental surface) and rapid brain development.²¹ Key structures involved in emotional regulation, such as the prefrontal cortex and the hippocampus, undergo major maturation at this stage. Environmental contaminants could interfere with these processes, potentially resulting in lasting behavioural effects. No overall effect of the phenol mixture was observed, and none of the associations appeared to be mediated by HPA hormones.

Methylparaben was detected in 100% of the samples and had the highest median concentrations of all compounds assessed, which is consistent with findings from other cohorts. We found that third-trimester methylparaben concentration was associated with increased internalising and externalising behaviours. Only a few epidemiological studies have examined the associations between prenatal methylparaben or paraben (molar sum) concentrations and child behaviour. Most reported null associations;^{2,22–24} one study reported detrimental associations but with paternal rather than maternal exposure.²⁴ However, these studies

had smaller sample sizes ($N \leq 708$) than ours and a smaller number of urine samples (three or fewer, compared with at least 12 in our study), which would affect their statistical power. Consistent with our study, although measuring another aspect of neurodevelopment, Jiang and colleagues²⁵ found that higher prenatal methylparaben concentrations were associated with lower mental developmental index.

Our study also revealed unexpected protective associations of second-trimester exposures in girls: between propylparaben and externalising behaviours and between butylparaben and internalising behaviours, both driven by the SEPAGES cohort. We do not have a biological explanation for these findings. One hypothesis is that they could result from an artefact related to the relatively low concentrations of these compounds, which could, in the presence of non-linear relationships, artificially lead to the observation of protective associations.²⁶

The adverse associations between third-trimester bisphenol S and externalising and internalising problems in boys were driven by BiSC. These findings could be explained by the lower detection rates of bisphenol S in SEPAGES (<30% vs around 60% for BiSC), probably resulting from the earlier recruitment period of this cohort (2014–17 vs 2018–21 for BiSC). Bisphenol S has been used as a replacement for bisphenol A following regulatory restrictions. Like bisphenol A, bisphenol S has endocrine-disrupting properties and might therefore affect neurodevelopment. Previous studies have found associations between bisphenol S and neurodevelopmental outcomes, such as decreased psychomotor development index²⁶ and reduced cognitive function in children;²⁷ however, behavioural outcomes have not been studied, with the exception of one previous paper restricted to the SEPAGES cohort.³

Brain development is sexually dimorphic and sensitive to hormonal cues. Sex steroids such as testosterone and oestradiol have key roles in shaping brain structure and function. Disruption of these pathways could affect males and females differently owing to variations in hormone concentrations and receptor distribution. Such differential effects could explain the sex-specific associations we observed for butylparaben and bisphenol S, as both interfere with oestrogen signalling. Notably, effect modification by sex has previously been described for bisphenol A and behavioural problems, in which effects were more often seen in males in both human children^{2,28,29} and young animals,³⁰ suggesting that a similar pattern could occur with bisphenol S. However, because the sex-specific effects we observed tended to be driven by one cohort (BiSC for bisphenol S and SEPAGES for butylparaben), our findings should be interpreted with caution.

Both animal and human studies have suggested that synthetic phenols can interact with the HPA axis and influence, among others, cortisol homeostasis,⁷ which has an essential role in neurodevelopment.⁶ Furthermore, in a separate analysis using the same dataset,³¹ we observed modified cortisol concentrations associated with second-trimester exposure to methylparaben, propylparaben, and

	Boys and girls		Girls		Boys	
	Estimate (95% CI)*	p value	Estimate (95% CI)*	p value	Estimate (95% CI)*	p value
Methylparaben: trimester 3, internalising						
Total cortisol	0.000 (−0.002 to 0.002)	0.89	—	—	—	—
Total cortisone	0.000 (−0.002 to 0.002)	0.82	—	—	—	—
11-Dehydrocorticosterone	0.000 (−0.002 to 0.002)	0.74	—	—	—	—
Methylparaben: trimester 3, externalising						
Total cortisol	0.000 (−0.002 to 0.002)	0.99	—	—	—	—
Total cortisone	0.000 (−0.002 to 0.002)	0.88	—	—	—	—
11-Dehydrocorticosterone	0.000 (−0.002 to 0.002)	0.97	—	—	—	—
Propylparaben: trimester 2, externalising						
Total cortisol	—	—	−0.001 (−0.007 to 0.004)	0.61	0.000 (−0.003 to 0.003)	0.92
Total cortisone	—	—	−0.002 (−0.009 to 0.004)	0.49	0.000 (−0.003 to 0.003)	0.89
11-Dehydrocorticosterone	—	—	0.000 (−0.003 to 0.002)	0.76	0.001 (−0.003 to 0.005)	0.68
Butylparaben: trimester 2, internalising						
Total cortisol	—	—	−0.011 (−0.044 to 0.023)	0.53	0.000 (−0.014 to 0.014)	0.99
Total cortisone	—	—	−0.005 (−0.034 to 0.024)	0.73	0.000 (−0.018 to 0.017)	0.96
11-Dehydrocorticosterone	—	—	−0.002 (−0.021 to 0.017)	0.85	0.001 (−0.016 to 0.018)	0.91
Bisphenol S: trimester 3, internalising						
Total cortisol	—	—	0.003 (−0.014 to 0.021)	0.71	0.000 (−0.013 to 0.013)	0.98
Total cortisone	—	—	0.002 (−0.014 to 0.018)	0.84	0.000 (−0.011 to 0.011)	0.99
11-Dehydrocorticosterone	—	—	0.000 (−0.013 to 0.013)	0.97	0.000 (−0.010 to 0.011)	0.94

Analyses were conducted only for exposure–outcome pairs for which a direct effect was observed ($p < 0.05$; figures 1, 2). For the model for which $\sqrt{\text{CBCL}}$ is the outcome, we adjusted for maternal age, maternal education level, maternal BMI, active smoking status during pregnancy, alcohol consumption during pregnancy, maternal ethnicity, anxiety Z score during pregnancy, cohort, parity, birth season, child's attendance at day care at 12 months, breastfeeding duration, maternal cortisol concentrations, and sex of the child for the non-stratified models. For the model for which cortisol is the outcome, we adjusted for cohort, birth season, maternal BMI, maternal age, maternal education level, maternal ethnicity, anxiety Z score during pregnancy, parity, passive and active smoking during pregnancy, and sex of the child for the non-stratified models. CBCL=Child Behavior Checklist for Ages 1–5. HPA=hypothalamic–pituitary–adrenal. *The indirect effect corresponds to the portion of the association between $\log_{10}$ -transformed exposure and square-root-transformed CBCL score that is mediated by $\log_{10}$ -transformed hormone concentrations. Estimates represent the change in $\sqrt{\text{CBCL}}$ per ten-fold increase in exposure mediated through the hormone.

Table 3: Assessing the potential indirect effect of HPA hormones in the association between prenatal phenol exposure and CBCL score

bisphenol S—the three chemicals also associated with child behaviour in our study. Bisphenol S was additionally associated with 11-dehydrocorticosterone concentrations whereas propylparaben was also associated with lower concentrations of cortisone and 11-dehydrocorticosterone, highlighting the ability of these chemicals to affect HPA regulation.³¹ However, despite these previous findings, our current analysis did not reveal significant mediating effects of cortisol in the observed associations of phenol exposure with behavioural outcomes. Several biological and methodological factors could explain this absence of mediation. Our design was not optimal to assess the mediation of third-trimester exposures: in BiSC, hair samples used for hormone measurements were collected concurrently with third-trimester urine samples. This sampling schedule limited our ability to establish the temporal ordering required for mediation (ie, exposure preceding mediator). Moreover, the use of 3 cm of maternal scalp hair reflects average hormone production over the previous 3 months, which might not be the window in which mediation effects occur. Although hair concentration offers a valuable measure of cumulative cortisol production, it does not capture diurnal variation related to alterations of the circadian rhythm, which could also influence behavioural

outcomes. In addition, cortisol concentrations in our cohorts were relatively low (study population median 3.39 pg/mg [IQR 1.92–5.53])—falling within, but on the lower side of, the expected range during pregnancy reported in a systematic review (2.1–290 pg/mg in 70% of pregnant women³²). Low concentrations could reduce the signal-to-noise ratio and the ability to detect subtle mediation effects. Additionally, the total effects observed between phenols and CBCL scores were moderate, making indirect effects statistically harder to detect. Finally, phenols might act through other hormonal pathways: thyroid and oestrogen signalling, in particular, are both crucial for neurodevelopment, and are biologically plausible alternative mediators that should be explored in future research.

Pooling two cohorts with distinct populations and settings strengthened the robustness and generalisability of our findings, particularly for methylparaben, for which consistent associations were observed in both cohorts. This strategy aligns with recommendations for enhancing statistical power and helps to avoid spurious conclusions in causal inference.³³ Pooling data increased our sample size ($N=1024$) compared with previous studies ($N=140$ – 708) and, combined with intensive urine sampling protocols (up to 24 samples in BiSC and 42 in SEPAGES), reduced

exposure misclassification and improved statistical power. The use of two different cohorts also enabled us to capture greater heterogeneity in exposure and population characteristics. Several aspects of the protocol were harmonised across cohorts, including urine collection (collected during the same trimesters and analysed in the same laboratory), hormone concentrations (assessed in the same laboratory), and behaviour evaluation (using the same questionnaire), even though the age at assessment differed (median age 18.8 months in BiSC and 24.7 months in SEPAGES). This harmonisation improved consistency and comparability across cohorts and facilitated reliable data pooling. Pooling measurements from different laboratories would have required some calibration, which can introduce uncertainties.

For mediation analyses, one key assumption—that exposure temporally precedes the mediator—was not fully met in BiSC, in which third-trimester urine and hair samples were both collected at around 32 weeks' gestation. Given that 3 cm of hair reflects the preceding 3 months, this overlap limits causal interpretation. By contrast, temporal ordering was clearer in SEPAGES: urine was collected at around 36 weeks' gestation and hair was collected at delivery. Although multiple imputation was used for the single-pollutant and mediation models, BKMR analyses were limited to single imputation owing to computational constraints. As no mixture effects were observed, and multiple imputation would primarily increase uncertainty, this limitation probably had minimal effect on our results. No formal correction for multiple testing was applied, which was justified by the relatively low number of tests run and some biological plausibility for an effect of the studied phenols on child behaviour. However, we acknowledge that some associations could reflect chance findings, and we therefore gave more weight to associations observed in both cohorts. Eligibility criteria (eg, language fluency) could have excluded some potential participants, including some from more disadvantaged populations, potentially limiting generalisability.

With a large sample size and improved exposure assessment, our study identified associations between third-trimester exposure to methylparaben and bisphenol S and increased behavioural problems in young children, with sex-specific patterns observed for bisphenol S. Further research is needed to support these associations. The absence of observed mediation by HPA hormones could reflect the timing of hormone measurements in late pregnancy or suggest that other mechanisms are involved. Continued investigation of these underlying mechanisms is crucial to better understand the health effect of these chemicals.

Contributors

CP, RS, JS, and PD conceived the study. PJ and AM curated the data. MR and PJ conducted the formal analyses. MV, JS, RS, PD, and CP acquired funding. MB, CT, AKS, MFo, MG, MDG-R, EL, IR, MFe, OJP, and SL-C conducted the investigation. CP was responsible for project administration. SC, SB, and SL-C contributed resources. MR and CP wrote the original draft of the manuscript, which was reviewed and edited by all other authors. The

phenol exposure data were originally accessed and validated by AKS and the steroid hormone data by OJP; all data were then also validated by PJ and MR. All authors had full access to all the data in the study and had final responsibility for the decision to submit for publication.

Declaration of interests

We declare no competing interests.

Data sharing

Participant data used in this study and the data dictionary are available on reasonable request to the cohort steering committees (contact-sepages@inserm.fr; <https://projectebisc.org/en/contact/>). Data can only be shared for research projects in line with the objectives of the cohorts and after approval of the research proposal by the cohort steering committees. A signed data transfer agreement (one for each cohort) is also mandatory. The statistical analysis plan¹⁴ and the cohort protocols^{15,16} have been previously published.

Acknowledgments

This study was funded by the French National Research Program for Environmental and Occupational Health of the French Agency for Food, Environmental and Occupational Health & Safety (ANSES; 2019/1/039) and the EU's Horizon 2020 research and innovation programme (874583 - ATHLETE project). MR's salary was funded by the French Fund – Fondation de France (ELEMENTUM - 00124527). The SEPAGES cohort was supported by the European Research Council (ERC; 311765-E-DOHAD), the European Community's Seventh Framework Programme (FP7/2007-206 - 308333-892 HELIX), the EU's Horizon 2020 research and innovation programme (874583 - ATHLETE project and 825712 - OBERON project), the French Research Agency (ANR; PAPER project ANR-12-PDOC-0029-01; SHALCOH project ANR-14-CE21-0007, ANR-15-IDEX-002, and ANR-15-IDEX5; GUMME project ANR-17-CE34-0013; ETAPE project ANR-18-CE36-0005; EDeN project ANR-19-CE36-0003-01; MEMORI project ANR 21-CE34-0022; and ORANDANI project ANR-22-CE36-0018), ANSES (CNAP project EST-2016-121, PENDORE project EST-2018-1-264, HyPAXE project EST-2019/1/039, and PENDALIRE project EST-2022-169), the Plan Cancer (Canc'Air project), the French Cancer Research Foundation Association de Recherche sur le Cancer, the French Endowment Fund AGIR for chronic diseases (APMC; projects PRENAPAR, LCI-FOT, and DysCard), the French Endowment Fund for Respiratory Health, and the French Fund – Fondation de France (CLIMATHES - 00081169, SEPAGES 5 - 00099903, and ELEMENTUM - 00124527). SEPAGES biospecimens are stored at Grenoble University Hospital biobank (bb-0033-00069); we thank the whole Biological Resources Centre team, in particular the technicians, for the huge work involved in the processing and pooling of biospecimens. We thank the SEPAGES study group—clinical research assistants, nurses, midwives, field workers, neuropsychologists, and data managers—along with the staff from the Grenoble Center for Clinical Investigation; the sonographers, medical doctors, and clinicians from Grenoble University Hospital for their support in the recruitment of the study volunteers; and all midwives from the four maternity wards of Grenoble urban areas. SEPAGES data are stored thanks to Inserm RE-CO-NAI platform funded by Commissariat Général à l'Investissement. Finally, and importantly, we express our sincere thanks to participants of the SEPAGES study. The BiSC cohort has received funding from the ERC under the EU's Horizon 2020 research and innovation programme (785994 - AirNB project), the Health Effects Institute (4959-RFA17-1/18-1 - FRONTIER project), the EU's Horizon 2020 research and innovation programme EU.3.1.2 (874583 - ATHLETE project) and EU.3.1.1 (GA964827 - AURORA project), the AXA Research Fund (MOOD-COVID project), ANSES (2019/01/039 - HyPAXE project), the Agència de Gestió d'Ajuts Universitaris de Recerca (2017 SGR 826 - Population Neuroscience group), the Centro de Investigación Biomédica en Red de Epidemiología y Salud Pública (CB06/02/0041), the Instituto de Salud Carlos III (ISCIII) and the European Regional Development Fund - Maternal and Child Health and Development Network (RD16/0022/0014 and RD16/0022/0015), and the ISCIII and the EU Next Generation EU - Primary Care Interventions to Prevent Maternal and Child Chronic Diseases of Perinatal and Developmental Origin Network (RD21/0012/0001 and RD21/0012/0003). We thank all the participants and their families

for their generous collaboration. A full list of BiSC researchers can be found at <https://projectebisc.org/en/team/>. During the preparation of this work the authors used ChatGPT in order to improve grammar and readability. After using this tool, the authors reviewed and edited the content as needed and take full responsibility for the content of the publication.

References

- Mustieles V, Pérez-Lobato R, Olea N, Fernández MF. Bisphenol A: human exposure and neurobehavior. *Neurotoxicology* 2015; **49**: 174–84.
- Philippat C, Nakiwala D, Calafat AM, et al. Prenatal exposure to nonpersistent endocrine disruptors and behavior in boys at 3 and 5 years. *Environ Health Perspect* 2017; **125**: 097014.
- Guilbert A, Rolland M, Pin I, et al. Associations between a mixture of phenols and phthalates and child behaviour in a French mother–child cohort with repeated assessment of exposure. *Environ Int* 2021; **156**: 106697.
- European Commission. Commission delegated regulation (EU) 2023/707 amending regulation (EC) no 1272/2008 as regards hazard classes and criteria for the classification, labelling and packaging of substances and mixtures. Dec 19, 2022. <https://eur-lex.europa.eu/legal-content/EN/TXT/PDF/?uri=CELEX:32023R0707&from=EN> (accessed May 1, 2025).
- Zheng J, Reynolds JE, Long M, et al. The effects of prenatal bisphenol A exposure on brain volume of children and young mice. *Environ Res* 2022; **214**: 114040.
- Davis EP, Head K, Buss C, Sandman CA. Prenatal maternal cortisol concentrations predict neurodevelopment in middle childhood. *Psychoneuroendocrinology* 2017; **75**: 56–63.
- Crowther CA, Doyle LW, Haslam RR, Hiller JE, Harding JE, Robinson JS. Outcomes at 2 years of age after repeat doses of antenatal corticosteroids. *N Engl J Med* 2007; **357**: 1179–89.
- Tung I, Hipwell AE, Grosse P, et al. Prenatal stress and externalizing behaviors in childhood and adolescence: a systematic review and meta-analysis. *Psychol Bull* 2024; **150**: 107–31.
- Prasanth GK, Divya LM, Sadasivan C. Bisphenol-A can bind to human glucocorticoid receptor as an agonist: an in silico study. *J Appl Toxicol* 2010; **30**: 769–74.
- Panagiotidou E, Zerva S, Mitsiou DJ, Alexis MN, Kitraki E. Perinatal exposure to low-dose bisphenol A affects the neuroendocrine stress response in rats. *J Endocrinol* 2014; **220**: 207–18.
- Giesbrecht GF, Liu J, Ejaredar M, et al. Urinary bisphenol A is associated with dysregulation of HPA-axis function in pregnant women: findings from the APrON cohort study. *Environ Res* 2016; **151**: 689–97.
- Giesbrecht GF, Ejaredar M, Liu J, et al. Prenatal bisphenol A exposure and dysregulation of infant hypothalamic–pituitary–adrenal axis function: findings from the APrON cohort study. *Environ Health* 2017; **16**: 47.
- Verma G, Khan MF, Akhtar W, Alam MM, Akhter M, Shaquiquzzaman M. Molecular interactions of bisphenols and analogs with glucocorticoid biosynthetic pathway enzymes: an in silico approach. *Toxicol Mech Methods* 2018; **28**: 45–54.
- Philippat C, Rolland M. Associations of phenol exposure with child behavior checklist: direct effects and mediation through cortisol levels—a pooled study of BiSC and SEPAGES. Oct 23, 2024. <https://osf.io/38pg2/> (accessed Nov 10, 2025).
- Dadvand P, Gascon M, Bustamante M, et al. Cohort profile: Barcelona Life Study Cohort (BiSC). *Int J Epidemiol* 2024; **53**: dyae063.
- Lyon-Caen S, Siroux C, Lepeule J, et al. Deciphering the impact of early-life exposures to highly variable environmental factors on foetal and child health: design of SEPAGES couple–child cohort. *Int J Environ Res Public Health* 2019; **16**: 3888.
- Cameron AC, Trivedi PK. *Microeconometrics: methods and applications*. Cambridge University Press, 2005.
- Bobb JF, Valeri L, Henn BC, et al. Bayesian kernel machine regression for estimating the health effects of multi-pollutant mixtures. *Biostatistics* 2015; **16**: 493–508.
- Imai K, Keele L, Tingley D. A general approach to causal mediation analysis. *Psychol Methods* 2010; **15**: 309–34.
- Philippat C, Calafat AM. Comparison of strategies to efficiently combine repeated urine samples in biomarker-based studies. *Environ Res* 2021; **192**: 110275.
- Rice D, Barone S Jr. Critical periods of vulnerability for the developing nervous system: evidence from humans and animal models. *Environ Health Perspect* 2000; **108** (suppl 3): 511–33.
- Jedynak P, Maitre L, Guxens M, et al. Prenatal exposure to a wide range of environmental chemicals and child behaviour between 3 and 7 years of age—an exposome-based approach in 5 European cohorts. *Sci Total Environ* 2021; **763**: 144115.
- Lei X, Ao J, Li J, Gao Y, Zhang J, Tian Y. Maternal concentrations of environmental phenols during early pregnancy and behavioral problems in children aged 4 years from the Shanghai Birth Cohort. *Sci Total Environ* 2024; **933**: 172985.
- Leader J, Mínguez-Alarcón L, Williams PL, et al. Paternal and maternal preconception and maternal pregnancy urinary concentrations of parabens in relation to child behavior. *Andrology* 2025; **13**: 22–33.
- Jiang Y, Zhao H, Xia W, et al. Prenatal exposure to benzophenones, parabens and triclosan and neurocognitive development at 2 years. *Environ Int* 2019; **126**: 413–21.
- Lee DH, Jacobs DR Jr. Firm human evidence on harms of endocrine-disrupting chemicals was unlikely to be obtainable for methodological reasons. *J Clin Epidemiol* 2019; **107**: 107–15.
- Bornehag CG, Engdahl E, Unenge Hallerback M, et al. Prenatal exposure to bisphenols and cognitive function in children at 7 years of age in the Swedish SELMA study. *Environ Int* 2021; **150**: 106433.
- Hansen JB, Bilenberg N, Timmermann CAG, et al. Prenatal exposure to bisphenol A and autistic- and ADHD-related symptoms in children aged 2 and 5 years from the Odense Child Cohort. *Environ Health* 2021; **20**: 24.
- Li F, Yang F, Li DK, et al. Prenatal bisphenol A exposure, fetal thyroid hormones and neurobehavioral development in children at 2 and 4 years: a prospective cohort study. *Sci Total Environ* 2020; **722**: 137887.
- Rochester JR, Bolden AL, Kwiatkowski CF. Prenatal exposure to bisphenol A and hyperactivity in children: a systematic review and meta-analysis. *Environ Int* 2018; **114**: 343–56.
- Jedynak P, Bustamante M, Rolland M, et al. Prenatal exposure to synthetic phenols assessed in multiple urine samples and dysregulation of steroid hormone homeostasis in two European cohorts. *Environ Health Perspect* 2025; **133**: 57011.
- Marceau K, Wang W, Robertson O, Shirtcliff EA. A systematic review of hair cortisol during pregnancy: reference ranges and methodological considerations. *Psychoneuroendocrinology* 2020; **122**: 104904.
- Richmond RC, Al-Amin A, Smith GD, Relton CL. Approaches for drawing causal inferences from epidemiological birth cohorts: a review. *Early Hum Dev* 2014; **90**: 769–80.