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► To cite this version:

Vicente Mustieles, Matthieu Rolland, Isabelle Pin, Cathrine Thomsen, Amrit K Sakhi, et al.. Early-Life Exposure to a Mixture of Phenols and Phthalates in Relation to Child Social Behavior: Applying an Evidence-Based Prioritization to a Cohort with Improved Exposure Assessment. *Environmental Health Perspectives*, 2023, 131 (8), pp.240 - 244. 10.1289/EHP11798). . hal-04650466

HAL Id: hal-04650466

<https://hal.science/hal-04650466v1>

Submitted on 16 Jul 2024

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Early-Life Exposure to a Mixture of Phenols and Phthalates in Relation to Child Social Behavior: Applying an Evidence-Based Prioritization to a Cohort with Improved Exposure Assessment

Vicente Mustieles,¹ Matthieu Rolland,¹ Isabelle Pin,² Cathrine Thomsen,³ Amrit K. Sakhi,³ Azemira Sabaredzovic,³ Gina Muckle,⁴ Karine Guichardet,² Rémy Slama,¹ and Claire Philippat¹

¹University Grenoble Alpes, Inserm U 1209, CNRS UMR 5309, Team of Environmental Epidemiology Applied to Development and Respiratory Health, Institute for Advanced Biosciences, Grenoble, France

²Pediatric Department, Grenoble Alpes University Hospital, La Tronche, France

³Norwegian Institute of Public Health, Oslo, Norway

⁴Centre Hospitalier Universitaire de Québec - Université Laval Research Center, Québec City, Canada

BACKGROUND: Previous studies aiming at relating exposure to phenols and phthalates with child social behavior characterized exposure using one or a few spot urine samples, resulting in substantial exposure misclassification. Moreover, early infancy exposure was rarely studied.

OBJECTIVES: We aimed to examine the associations of phthalates and phenols with child social behavior in a cohort with improved exposure assessment and to *a priori* identify the chemicals supported by a higher weight of evidence.

METHODS: Among 406 mother–child pairs from the French Assessment of Air Pollution exposure during Pregnancy and Effect on Health (SEPAGES) cohort, 25 phenols/phthalate metabolites were measured in within-subject pools of repeated urine samples collected at the second and third pregnancy trimesters (~21 samples/trimester) and at 2 months and 1-year of age (~7 samples/period). Social behavior was parent-reported at 3 years of age of the child using the Social Responsiveness Scale (SRS). A structured literature review of the animal and human evidence was performed to prioritize the measured phthalates/phenols based on their likelihood to affect social behavior. Both adjusted linear regression and Bayesian Weighted Quantile Sum (BWQS) regression models were fitted. False discovery rate (FDR) correction was applied only to nonprioritized chemicals.

RESULTS: Prioritized compounds included bisphenol A, bisphenol S, triclosan (TCS), diethyl-hexyl phthalate (ΣDEHP), mono-ethyl phthalate (MEP), mono-*n*-butyl phthalate (MnBP), and mono-benzyl phthalate (MBzP). With the exception of bisphenols, which showed a mixed pattern of positive and negative associations in pregnant mothers and neonates, few prenatal associations were observed. Most associations were observed with prioritized chemicals measured in 1-y-old infants: Each doubling in urinary TCS ($\beta = 0.78$; 95% CI: 0.00, 1.55) and MEP ($\beta = 0.92$; 95% CI: -0.11, 1.96) concentrations were associated with worse total SRS scores, whereas MnBP and ΣDEHP were associated with worse Social Awareness ($\beta = 0.25$; 95% CI: 0.01, 0.50) and Social Communication ($\beta = 0.43$; 95% CI: -0.02, 0.89) scores, respectively. BWQS also suggested worse total SRS [Beta 1 = 1.38; 95% credible interval (CrI): -0.18, 2.97], Social Awareness (Beta 1 = 0.37; 95% CrI: 0.06, 0.70), and Social Communication (Beta 1 = 0.91; 95% CrI: 0.31, 1.53) scores per quartile increase in the mixture of prioritized compounds assessed in 1-y-old infants. The few associations observed with nonprioritized chemicals did not remain after FDR correction, with the exception of benzophenone-3 exposure in 1-y-old infants, which was suggestively associated with worse Social Communication scores (corrected $p = 0.07$).

DISCUSSION: The literature search allowed us to adapt our statistical analysis according to the weight of evidence and create a corpus of experimental and epidemiological knowledge to better interpret our findings. Early infancy appears to be a sensitive exposure window that should be further investigated. <https://doi.org/10.1289/EHP11798>

Introduction

Neurobehavioral impairments, including autism spectrum disorders (ASDs), affect millions of children worldwide, are very costly,¹ and seem to be increasing in prevalence.² Subclinical symptoms are more frequent and also affect quality of life. Exposure to endocrine disrupting chemicals (EDCs) is among the suspected risk factors.³

Phthalates and phenols are chemical families used as plasticizers, antimicrobials, and ultraviolet blockers in many everyday consumer products (e.g., plastic bottles, food containers, canned foods, personal care products, cosmetics, textiles), resulting in ubiquitous population exposure.^{4–6} Some of them are recognized EDCs, capable of disrupting hormonal signaling (including estrogenic,

anti-androgenic, and thyroid pathways among others) during critical periods, such as pregnancy and infancy.^{7,8} Among other adverse outcomes, these EDCs can impact brain development and behavior in experimental animals,^{9–12} and epidemiological evidence has begun to mount.^{13,14} Although studies have investigated exposure to phenols and phthalates during pregnancy in relation to child autistic traits,^{15–19} no study evaluated exposure during so-called mini-puberty. In humans, mini-puberty spans from birth to 6 months in males and until 2 years of age in females and has been recently identified as an important but understudied critical period for brain development.^{20,21}

Given the large within-day and within-week variability of phenol and phthalate urinary concentrations, accurate exposure characterization remains a major challenge.²² Notably, exposure characterization using one spot urine sample leads to exposure misclassification and attenuation bias, that is, a bias toward null findings.^{23,24}

Another poorly addressed limitation is the management of the multiple comparison issue that often arises when investigating associations between multiple exposures and outcomes. Post hoc multiple-testing correction techniques are not always indicated and can even be counterproductive (especially for chemical compounds supported by experimental data) because they reduce type I error at the expense of increasing type II error. Therefore, some authors suggest to adapt the choice of adjusting or not for multiple comparisons to each exposure–outcome pair investigated.^{25,26} In addition, a related concern is that mixture analyses frequently

Address correspondence to Vicente Mustieles, Institute for Advanced Biosciences, Grenoble Alpes University – INSERM U1209 – CNRS UMR5309, Site Santé – Allée des Alpes, 38700 La Tronche, France. Telephone: 33 476 54 94 66. Email: vmustieles@ugr.es

Supplemental Material is available online (<https://doi.org/10.1289/EHP11798>).

The authors declare they have nothing to disclose.

Received 30 June 2022; Revised 10 May 2023; Accepted 26 June 2023; Published 9 August 2023.

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consider all chemicals measured in biospecimens, assuming a similar biological relevance; however, this may not be the case. Although this may constitute a good strategy when scarce toxicological/epidemiological evidence is available, using such an approximation could also increase noise or even lead to noncausal cancel-out effects.²⁷

The aims of this work were, first, to perform a structured comprehensive review of the *in vivo* toxicological and epidemiological literature to prioritize, among the phthalates and phenols assessed in our study, those with a higher weight of evidence (WoE) for an effect on social behavior. The second aim of this work was to rely on this prioritization to *a*) identify the associations that should be corrected or not for multiple comparisons in single-pollutant models and *b*) identify the most toxicologically relevant chemicals to be considered in a mixture model.

Methods

Literature Search and Chemical Prioritization

We relied on previous toxicological and epidemiological studies to determine *a priori* whether adjustment for multiple comparisons was appropriate or not. Our underlying logic was that the need for multiple-testing correction is inversely proportional to the existing WoE for a given chemical–outcome pair.²⁵ Therefore, we performed a structured and comprehensive literature search in PubMed/MEDLINE, adapting the main points of the Navigation Guide systematic review methodology for environmental health studies.^{28,29}

First, the study question was defined: “Among the phenols and phthalates assessed in our study, what are those showing the highest strength of evidence regarding alterations in social behaviors?” Second, the participants, exposures, comparators, and outcomes (the PECO) were identified as follows:

- Participants: humans or animals, prioritizing exposure during preconception, pregnancy and infancy. Urine was prioritized as the exposure matrix.
- Exposures: phenols and phthalates frequently detected in mother’s and infant’s urine from the current Assessment of Air Pollution exposure during Pregnancy and Effect on Health Study (SEPAGES).
- Comparators: comparable groups of dosed animals or their tissues vs. those exposed to vehicle-only treatment. Comparable groups of human subjects exposed to higher vs. lower phenol/phthalate concentrations.
- Outcomes: neurodevelopmental outcomes, especially those closely related to the regulation of social, communicative, and repetitive behaviors.

Third, the evidence was selected executing the following search algorithm on 15 August 2021 and using the filters “Full-text” and “Abstract” availability:

(phthalate OR phthalic acid OR “Phthalic Acids”[nm] OR 1,2-Cyclohexane dicarboxylic acid diisononyl ester OR DINCH OR benzophenone-3 OR oxybenzone OR 2-Hydroxy-4-methoxybenzophenone OR triclosan OR methylparaben OR ethylparaben OR propylparaben OR butylparaben OR bisphenol A OR bisphenol S) AND (social OR social behavior OR repetitive behavior OR communication OR social responsiveness scale OR SRS OR autism OR autistic OR autistic traits OR asperger OR autism spectrum disorder OR neurodevelopment).

The bibliographic lists of the most recent reviews identified were hand-searched for additional studies. All titles and abstracts retrieved were screened by one author (V.M.) to determine eligibility based on inclusion criteria. A second author (C.P.) screened

25% of titles/abstracts for quality assurance. Studies were excluded if *a*) they were not related to the prespecified phenols/phthalates, *b*) they were not related to social behavior, *c*) there was no control group in animal studies, or *d*) they were not published in English. The selected studies were subjected to a study quality assessment and tabulated in an Excel database (see Supplemental Excel File), reporting study quality parameters, such as the following: study design; characteristics of the population, including sample or litter size; exposure assessment (biological matrix, number of biospecimens analyzed, timing of collection, chromatographic method, and quality assurance and quality control measures) or dose/route of administration; neuropsychological or behavioral test evaluated; statistical analysis and adjustment for confounders; and main results/effect estimates. Strengths and limitations of each study were also included.

A summary table was created (Table 1), classifying the overall body of evidence for each chemical exposure as “limited,” “moderate,” or “supportive” evidence. Such classification was justified for each compound in the table considering *a*) the quantity and quality of *in vivo* and epidemiological evidence, and *b*) additional judgment and agreement between V.M. and C.P., including mechanistic evidence from previous reviews, evidence on other related neurobehavioral end points, consistency across species, and structural and toxicological analogy in the case of substitutes. This classification was then used to prioritize the chemicals for which a confirmatory or exploratory analysis would be performed. Associations for chemicals in the supportive evidence category were considered as confirmatory analyses and will not be corrected for multiple comparisons. In the case of “moderate” evidence, we justified the specific chemicals that were upgraded to confirmatory or downgraded to exploratory analyses. Associations for chemicals in the limited evidence category were considered as exploratory and will be corrected for multiple comparisons. Nevertheless, the “limited” category could be exceptionally upgraded to a confirmatory analysis if a high degree of consistency was observed across the limited evidence available together with other relevant criteria, such as structural and toxicological analogy to a chemical classified in the “supportive” category.

Study Population

The SEPAGES cohort consists of 484 pregnant French women and their corresponding families recruited between 2014 and 2017 at eight obstetrical ultrasonography practices in the Grenoble metropolitan area.³⁰ Eligibility criteria included singleton pregnancies up to gestational week 19, being >18 years of age and affiliated to the French national security system, and planning to deliver in one of the four Grenoble maternity clinics. The present analysis included children with child social behavior assessed at 3 years of age and exposure biomarkers assessed in at least one of the following time windows (Figure S1): early pregnancy ($N = 406$), late pregnancy ($N = 399$), neonates ($N = 380$), and infants ($N = 358$). The SEPAGES cohort received approvals from the Ethics Committee (CPP) Sud-Est V and the National Commission on Informatics and Liberty (CNIL). Trained staff explained the study details to participants, and both prospective parents signed the written informed consent prior to inclusion.

Repeated Urine Collection and Exposure Assessment

Pregnant women were asked to collect three urine samples per day (morning, midday, and evening), for 7 consecutive d, twice during pregnancy: at the second trimester [median (25th percentile, 75th percentile) gestational age = 17 (16–18) wk] and during the third trimester [33 (31–34) wk]. After birth, parents collected

Table 1. Evidence summary and decision for the prioritization of each compound (extended data available in Supplemental Excel File).

Rank	MoA/Pathways ^d	<i>In vivo</i> Toxicology ^b	Epidemiology ^b	Prioritization based on evidence and justification ^c
BPA	Estrogenic and anti-androgenic (ER α , ER β , ERR γ , GPER, aromatase, AR) ^{30,31} Anti-thyroid (NIS) and glutamatergic (NMDA receptors) ³² Oxytocin/vasopressin pathways in hypothalamus and related neuro-structures ^{10,33} Microbiome–brain axis ³⁴	Twenty-two BPA–social behavior <i>in vivo</i> studies, most testing low doses and reporting alterations in social interaction, recognition and explorations, ^{34–36} and 4 reported improved social investigation. ^{37–40} Perinatal BPA reduced offspring social interactions in mice, ^{41–49} prairie vole, ⁵⁰ and nonhuman primates. ^{51,52} Three studies reported altered pup vocalizations. ^{42,43,53} In some cases, effects varied by sex, and BPA often increased or decreased normal differences between sexes.	Six prenatal cohorts investigated BPA–social behavior (primary outcome). Three mid-to-high-sample-sized studies ^{19,54,55} and 1 small-sized study ¹⁸ found increased social problems in children. The remaining 2 small-sized studies reported null findings. ^{16,56} Six of 9 studies investigating social or adaptive subscales (secondary outcome) reported associations with poorer behavior. ^{57,58,59,60–62}	Supportive evidence—confirmatory analysis Early-life low-dose BPA exposure alters social behaviors in different rodent strains (mice, rats, and voles) and even nonhuman primates, showing a high degree of interspecies consistency. The human observational evidence, although more limited, is also supportive. Existing MoAs may account for this altered phenotype. Expert reviews and panels support BPA's neurotoxicity at low doses. ^{10,31,63}
BPS	Estrogenic and anti-androgenic ⁶⁴	One BPS–social behavior study in mice showing that a moderate oral dose during pregnancy/lactation increased male offspring anxiety and decreased interest in social interaction. ⁶⁵	Only 1 study with BPS detected in 58% of prenatal urine samples. In the whole population, BPS showed a null association with poorer socioemotional symptoms. ⁵⁷ Effect–measure modification by child sex was marginally significant ($p=0.09$) for child socioemotional scores. However, BPS was not separately investigated in boys and girls.	Limited but concerning evidence—upgraded to confirmatory analysis The limited number of studies would not allow per se to achieve a conclusion. However, we upgraded BPS based on a) high similarity to BPA in chemical structure and <i>in vitro</i> mechanisms, ⁶⁴ and b) emerging <i>in vivo</i> evidence including anxiety and aggressive behaviors. ^{30,66}
DEHP—MEHP, MEHHP, MEOHP, and MEOPP	Anti-androgenic ⁶⁷ Thyroid disruption ⁶⁸ Oxytocin/vasopressin Brain aromatase disruption ⁶⁹	Four DEHP–social behavior studies. Two studies in mice showed that perinatal DEHP exposure at both low ⁷⁰ and high ⁷¹ doses caused decreased offspring social investigation. Two studies in rats investigated perinatal exposure to phthalate mixtures containing DEHP, reporting decreased social play, increased time alone, and decreased socio-cohesive interactions. ^{72,73} Sex-dependent associations were observed. Another mice study tested complex mixtures containing DEHP, other phthalates, and chemical families. Offspring showed alterations in social behavior. ⁴¹	Nine cohorts investigated DEHP–social behavior, mostly using the SRS test. Three well-sized cohorts supported associations with poorer social development, ^{74–76} whereas the remaining studies, mostly using small samples, did not. ^{17,56,74,77,78} Although two small-sized high-risk cohorts reported null associations between DEHP and ASD risk, ^{79,80} a cohort found positive associations with ASD risk. ⁸¹ Six of 10 studies investigating social or adaptive subscales (secondary outcome) reported associations toward poorer behavior; ^{58,82–86} and 2 studies reported altered social sex-typed play behavior. ^{87,88}	Supportive evidence—confirmatory analysis Early-life DEHP exposure even at low doses has been shown to alter social behaviors in both mice and rats. The human evidence overall supports an effect not only on social behavior, but also on diverse cognitive and behavioral end points. ^{14,89,90} Existing MoAs for DEHP can account for the altered social phenotype. Expert panels and reviews support the neurotoxicity potential of DEHP. ^{91,92}
DEP–MEP	Androgen-independent reproductive and developmental toxicity in rodents ^{93,94} Reduced neural cell migration and proliferation ⁹⁵ Indirect estrogen receptor modulation ⁹⁶	One DEP–social behavior study in rats investigated perinatal exposure to a phthalate mixture that predominantly contained DEP (35% of the mixture), reporting decreased social play and increased time spent alone. ⁷⁵ Another study in mice tested complex mixtures containing MEP, other phthalates, and chemical families. Offspring showed alterations in social behavior. ⁴¹	Of 7 studies investigating MEP–social problems, 5 reported positive associations. ^{17,18,56,74,77} In high-risk ASD cohorts, 1 study reported positive associations between MEP and risk of atypical development, but not ASD, ⁸⁰ whereas another found more communication problems in response to indoor dust DEP concentrations among typically developing children. ⁷⁹ A prospective cohort found that higher prenatal DEP was associated with increased ASD risk. ⁸¹	Moderate evidence—upgraded to confirmatory analysis Prenatal exposure to MEP has been linked to child social problems in several human cohorts. Although the animal evidence is limited for social behavior, and MEP does not seem to be anti-androgenic as other phthalates, it has been shown to interfere with neural cell migration and proliferation and to modulate estrogen responses, thus supporting a possible link with neurodevelopment.

Table 1. (Continued.)

Rank	MoA/Pathways ^a	<i>In vivo</i> Toxicology ^b	Epidemiology ^b	Prioritization based on evidence and justification ^c
DBP–MnBP	Anti-androgenic ⁶⁷ Reduced neural cell migration and proliferation ⁹⁵	Two social behavior studies in rats investigating mixtures of phthalates including DBP. Both studies reported decreased socio-cohesive interactions, decreased social play, and increased time spent alone. ^{72,73} Two additional studies, 1 in rats and another in mice tested complex mixtures containing phthalates and other chemical families. The two mixtures included DBP or MBP in their composition, and offspring showed alterations in social behavior. ^{41,97}	Of 8 cohorts investigating MBP–social behavior, 2 mid-to-large cohorts found increased problems ^{15,74} and 2 additional cohorts with either small and large samples sizes showed suggestive associations toward increased social problems. ^{17,18} A large study found that early postnatal, but not prenatal MBP exposure was associated with social problems. ⁷⁵ The remaining three studies found null associations, but analyzed sample sizes of <150 subjects. ^{56,74,77} Two small high-risk ASD cohorts found null results. ^{79,80} A prospective cohort reported higher ASD risk for DBP intake estimated from both MiBP and MBP. ⁸¹ Eight of 10 secondary studies reported associations between prenatal MBP and altered social/adaptive, ^{58,82,85,98} externalizing/conduct, ^{84,99} and play behaviors. ^{87,88}	Moderate evidence—upgraded to confirmatory analysis Prenatal exposure to MBP is linked to child social problems in human cohorts. Although the animal evidence is limited for social behavior, MBP has a well-known anti-androgenic MoA ⁶⁷ and has been shown <i>in vitro</i> to reduce neural cell migration and proliferation, supporting the link with altered neurodevelopment.
DiBP–MiBP	Lower anti-androgenic potential than MBP ⁶⁷	One DiBP–social behavior study in rats investigated perinatal exposure to a phthalate mixture that contained 8% DiBP, reporting decreased social play and increased time spent alone. ⁷³	Five cohorts studied MiBP–social problem associations. One mid-sized cohort reported a positive association, ⁷⁴ 1 large cohort did not report a positive association with SRS scores, but, rather, with externalizing problems. ¹⁷ Three small cohorts found null associations. ^{56,74,77} One small ASD cohort reported null findings, ⁸⁰ whereas a large cohort estimated DBP intake from both MiBP and MBP, reporting a higher risk of both ASD/ASD traits. ⁸¹	Limited evidence—exploratory analysis DiBP has not been investigated alone in rodents for social behavior. The information provided by epidemiological studies is still limited and mixed, precluding the achievement of a conclusion regarding social behavior.
BBzP–MBzP	Anti-androgenic ⁶⁷ Reduced neural cell migration but not proliferation ⁹⁵	One BBzP–social behavior study in rats investigated perinatal exposure to a phthalate mixture that contained 5% BBzP, reporting decreased social play and increased time spent alone. ⁷³ Another study in mice tested complex mixtures containing phthalates and other chemical families. The mixture included BBzP in its composition, and offspring showed alterations in social behavior. ⁴¹	Four cohorts investigated MBzP–social problem associations. A large cohort identified MBzP as the primary driver of positive associations of a phthalate mixture. ¹⁷ Mid- and small-sized cohorts showed associations in the same direction, being significant for the middle one. ⁷⁴ Another large cohort showed a nonsignificant but suggestive association with repetitive behaviors. ¹⁵ Two modest-sized ASD cohorts reported null findings. ^{79,80} Seven of 8 secondary studies reported associations with poorer behavior, including social/adaptive alterations. ^{58,82,85,99,100} A study reported social problems in response to early childhood but not prenatal MBzP exposure. ⁸⁴ Another reported altered sex-typed play behavior. ⁸⁸	Moderate evidence—upgraded to confirmatory analysis Limited <i>in vivo</i> evidence: no animal study has evaluated BBzP in isolation. The human evidence is supportive of an association although more studies assessing social behavior are needed. General behavior tests in humans show that MBzP is linked to poorer socioemotional performance, and the evidence in relation to motor effects was judged as moderate in a meta-analysis. ¹⁴ Together with its known anti-androgenic action, ⁶⁷ <i>in vitro</i> reduction of neural migration, and animal studies showing altered neurodevelopment, ¹⁰¹ we upgraded MBzP.
DiNP–MiNP, MCOP	Anti-androgenic ⁶⁷	Two phthalate-mixture studies containing DiNP reported decreased socio-cohesive interactions, decreased social play and increased time spent alone in offspring rats. ^{72,73} Another mixture study containing DiNP, other phthalates, and flame retardants reported decreased social interaction in the offspring. ⁹⁷	Only 1 modest-sized cohort measured MiNP and it reported null results with ASD risk. ⁸⁰ A limited number of secondary studies looking at behavioral subscales reported null associations for MCOP. ^{58,80,78}	Limited evidence—exploratory analysis Limited <i>in vivo</i> evidence, no animal study has evaluated DiNP in isolation. Limited number of human studies, with no clear link with social behavior.

Table 1. (Continued.)

Rank	MoA/Pathways ^a	<i>In vivo</i> Toxicology ^b	Epidemiology ^b	Prioritization based on evidence and justification ^c
TCS	Anti-thyroid activity ²⁸ Retinoic acid pathway ¹⁰² Gut microbiota alterations ¹⁰³ Estrogenic mechanisms ¹⁰⁴	One study tested oral exposure to a moderate dose of TCS in pregnant rats, showing reduced offspring social interaction and increased repetitive behaviors. Retinoic acid signaling and protein content in the prefrontal cortex of the offspring was altered, suggesting a potential MoA. ¹⁰² One study tested subcutaneous exposure to high TCS doses, showing a marked influence on reduced social interaction, together with altered neurogenesis and anxiety/cognitive dysfunctions. ¹⁰⁵	Three cohorts evaluated TCS—social behavior. One large French cohort reported decreased prosocial behavior in the SDQ test, ⁵⁸ whereas another large Canadian study did not find a positive association with SRS. ¹⁰⁶ A middle-sized Chinese cohort found a nonsignificant but suggestive positive prenatal association with poorer prosocial scores also using the SDQ. ¹⁰⁷ The same cohort published that early exposure at 3 years of age, but not prenatal exposure, was associated with poorer scores in the social area using the GDS test. ¹⁰⁸	Moderate evidence—upgraded to confirmatory analysis If restricted to social behavior, the evidence is rated as moderate. Notwithstanding, we decided to upgrade based on other neurobehavioral toxicities, including anxiety ¹⁰⁹ and altered hippocampal function. ¹¹⁰ Cohort studies also linked prenatal and childhood TCS to lower IQ, and externalizing behaviors. ^{111–114} Finally, diverse MoAs, including altered thyroid function and retinoic acid signaling, support potential effects on brain and behavior.
BP-3	Estrogenic and anti-androgenic pathways ¹¹⁵	No rodent data investigating effects on social behavior. One study exposed pregnant mice subcutaneously for 10 d with a moderate BP-3 dose, showing increased neural apoptosis and altered estrogenic signaling in offspring brains, including decreased gene expression and protein levels of ER α and ER β , with a simultaneous increase in GPR30 membrane receptor expression. In addition, BP-3 caused specific hypomethylation of GPR30 and hypermethylation of ER α and ER β genes. ¹¹⁶	Only 2 cohorts investigated prenatal BP-3 exposure in relation to offspring general behavior, including social subscales in the SDQ test. A mid-to-large Chinese cohort reported a prenatal association with poorer prosocial behavior, ¹⁰⁷ whereas a large French cohort found improved emotional symptoms but no association with prosocial behavior. ⁵⁸	Limited evidence—exploratory analysis BP-3 at high doses may impact rodent brain development, partly through estrogenic mechanisms. However, studies evaluating animal social behavior are needed. The epidemiological evidence is also limited (only 2 studies with mixed results).
Parabens—MEPA, ETPA, PRPA, and BUPA	Estrogenic pathways ¹¹⁷	No rodent data for MEPA, ETPA, and PRPA. One study exposed pregnant rats to a high dose of BUPA either orally or subcutaneously and studied male pups. Male offspring presented autistic-like behaviors. ¹¹⁸ In a posterior analysis, the authors showed mechanistic parallels with valproic acid, a drug used to induce an ASD-like phenotype in rodents. ¹¹⁹	Only 1 study investigated parabens in relation to general behavior, including some social subscales. Indeed, prenatal exposure to the parabens was related to improved prosocial behavior. ⁵⁸	Limited evidence—exploratory analysis The reported <i>in vivo</i> effect of BUPA should be explored at lower doses, to be comparable with human exposure. Data for the other parabens, more frequently quantified in humans, should also be generated. Additional epidemiological studies are needed.
DINCH—OH-MINCH and oxo-MINCH	Interaction with ER, AR, and PPAR receptors at high doses ¹²⁰	No rodent/animal data.	No epidemiological data on social behavior.	Limited evidence—exploratory analysis Unknown neurotoxicity potential. <i>In vitro</i> studies show endocrine disruption at high doses. ¹²⁰ <i>In vivo</i> studies show a potential effect on the thyroid gland at high oral doses. ¹²¹
DPHP—ohMPPH	Lack of data on potential MoAs	No rodent/animal data.	No epidemiological data on social behavior.	Limited evidence—exploratory analysis DPHP was linked to thyroid hypertrophy/hyperplasia in rats at high doses. ¹²² However, there is no data on neurodevelopment.

Note: The term “positive association” refers to higher neuropsychological test scores in response to higher concentrations of the exposure assessed (deleterious association), whereas the terms “negative” or “inverse association” refer to lower neuropsychological test scores in response to higher exposure concentrations (protective association). AR, androgen receptor; ASD, autism spectrum disorders; BBzP, butyl-benzyl phthalate; BP-3, benzophenone-3; BPA, bisphenol A; BPS, bisphenol S; BUPA, butylparaben; DBP, dibutyl phthalate; DEHP, di(2-ethylhexyl) phthalate; DEP, diethyl phthalate; DIBP, di(isobutyl) phthalate; DINCH, di(isononyl)cyclohexane-1,2-dicarboxylate; DiNP, di-isomonyl phthalate; DPHP, di(2-propylheptyl) phthalate; ER, estrogen receptor; ERK, estrogen related-receptor; ETPA, ethylparaben; GDS, Gessel Developmental Schedules test; GPER, G-protein-coupled estrogen receptor; GPR30, G protein-coupled receptor 30; IQ, intelligence quotient; MBP, monobutyl phthalate; MCOP, mono(carboxy-isoocetyl) phthalate; MECPP, mono(2-ethyl-5-carboxypentyl) phthalate; MEHHP, mono(2-ethyl-5-hydroxyhexyl) phthalate; MEHP, mono(2-ethylhexyl) phthalate; MEOHP, mono(2-ethyl-5-oxohexyl) phthalate; MEP, mono-ethyl phthalate; MEPA, methylparaben; MIBP, mono-isobutyl phthalate; MINP, mono-isomonyl phthalate; MnBP, mono-*n*-butyl phthalate; MoA, mode of action; NIS, sodium/iodide symporter; NMDA, *N*-methyl-D-aspartate; OH-MINCH, mono-hydroxy isomonyl cyclohexane-1,2-dicarboxylate; oxo-MINCH, mono-oxo isomonyl cyclohexane-1,2-dicarboxylate; PPAR, peroxisome-proliferator activated receptor; PRPA, propylparaben; SDQ, strengths and difficulties questionnaire; SRS, Social Responsiveness Scale; TCS, triclosan.

^aPotential MoA based on the mechanisms/pathways more frequently reported. Information retrieved from both the literature search (reviews and *in vitro* and *in vivo* mechanistic studies) and author knowledge.
^bToxicological and epidemiological studies exclusively retrieved from the literature search performed.
^cDecision taken after comparing the mainstreams of evidence (*in vitro*, *in vivo*, and epidemiology), together with previous reviews/expert panels, and also considering the ability of each compound to affect other neurodevelopmental domains. Associations for prioritized chemicals were considered as “confirmatory” and will not be corrected for multiple comparisons, in opposition to exploratory associations that will be corrected.

urine samples of their children by inserting a cotton gaze in diapers. For neonates [median (25th percentile, 75th percentile) age = 8 (7, 11) wk] and infants [13.5 (13, 14) months], one urine sample per day for a week was collected. Pregnant women and their children showed excellent compliance: The median (25th percentile, 75th percentile) number of samples collected per pregnant woman at each collection week was 21 (20, 21) and 7 (6, 7) and 6 (5, 7) for neonates and infants, respectively. The families stored the urine samples in their freezers until the SEPAGES field workers picked them up at the end of each collection week and transported them to a certified biobank (ISO 9001 standard; Grenoble University Hospital; bb-0033-00069). For each of the four windows evaluated, within-subject weekly pools were then performed by combining equal volumes of all the samples obtained over a collection week (Figure S2).

In a previous study on bisphenol A (BPA) and triclosan (TCS), we demonstrated that correlations with the volume-weighted concentrations for all urine samples collected during a week (the gold standard), were similar for both equal- and unequal-volume pooling designs, supporting that accounting for urine volume when pooling was not necessary.¹²⁴ For example, when 10 samples were used to create the pools, the correlation with the gold standard was 0.97 for TCS and 0.75 for BPA with the equal-volume pool, compared with 0.98 and 0.70 for the volume-based pool.¹²⁴

Aliquots of weekly pools were then stored at -80°C before being sent on dry ice with a temperature sensor to the Norwegian Institute of Public Health (Oslo, Norway), a certified European laboratory that has participated in recent interlaboratory comparisons.¹²⁵ The concentrations of 12 phenols and 12 phthalate and 2 nonphthalate plasticizer metabolites were measured in the urine samples (Table S1) using high-performance liquid chromatography coupled to mass spectrometry.^{126,127} The phenols measured included methyl- (MEPA), ethyl- (ETPA), propyl- (PRPA), and butylparaben (BUPA), as well as bisphenols [BPA and bisphenol S (BPS), F (BPF), B (BPB), and AF (BPAF)] and benzophenone-3 (BP-3), TCS, and triclocarban (TCB). Phthalate metabolites included mono-ethyl phthalate (MEP), mono-isobutyl phthalate (MiBP), mono-*n*-butyl phthalate (MnBP), mono-benzyl phthalate (MBzP), and 6-hydroxy-mono-propyl-heptyl phthalate (ohMHPH); four di(2-ethylhexyl) phthalate (DEHP) metabolites: mono(2-ethylhexyl) phthalate (MEHP), mono(2-ethyl-5-hydroxyhexyl) phthalate (MEHHP), mono(2-ethyl-5-oxohexyl) phthalate (MEOHP), and mono(2-ethyl-5-carboxypentyl) phthalate (MECPP); and three di-isononyl phthalate (DiNP) metabolites: mono-hydroxy-isononyl phthalate (OH-MiNP), mono-oxo-isononyl phthalate (oxo-MiNP), and mono-carboxy-isononyl phthalate (cx-MiNP). Two metabolites of the plasticizer di(isononyl)cyclohexane-1,2-dicarboxylate (DINCH) were also measured: mono-hydroxy isononyl cyclohexane-1,2-dicarboxylate (OH-MiNCH) and mono-oxo isononyl cyclohexane-1,2-dicarboxylate (oxo-MiNCH). The limits of detection (LODs) and quantification (LOQs) ranged from 0.04 to 0.7 ng/mL and from 0.10 to 2 ng/mL, respectively (Table S2). Owing to budget limitations, phthalate metabolites were assessed only in a subset of 152 neonates at 2 months of age,¹²⁸ and thus they were not considered in the present analysis.

In a previous work using data from this same cohort, total and free forms of phenol concentrations were measured to evaluate potential external contamination in a subset of 100 prenatal samples and all the neonatal and infant samples because they were at higher risk of contamination. Rolland et al. showed that no contamination was observed for prenatal samples, nor as for neonatal and infant samples, with the exception of BPA in neonates and infants, and MEPA in infants.¹²⁹ For these specific chemicals/periods, the present analysis used conjugated concentrations for associations reported in the main manuscript, whereas associations

with both total and conjugated concentrations are reported in the Supplemental Material.

Outcome Assessment

Child social behavior and autistic traits were evaluated at 3 years of age using the Social Responsiveness Scale, Second Edition (SRS-2). The SRS is a parent-reported 65-item questionnaire recognized as a valid and reliable quantitative measure of social impairment in both population and clinical settings.¹³⁰ It has good test-retest stability over time, parent-parent and parent-teacher interrater agreement, and discriminant and concurrent validity.¹³⁰ The SRS shows considerable agreement (correlation = 0.7) with the Autism Diagnostic Interview-Revised (ADI-R), a gold standard for research diagnosis of ASD.¹³¹

Each SRS item rates the frequency of a particular social behavior using a 4-point Likert scale, with higher scores indicating poorer social development. Items are grouped into five subscales: Social Awareness, Social Cognition, Social Communication, Social Motivation, and Restricted Interests and Repetitive Behaviors (RRBs). The SRS also provides a total SRS score (sum of the five subscales), which shows a good diagnostic potential for screening ASDs,¹³¹ and the Social Communication and Interaction (SCI) score (sum of four subscales), which excludes the RRB subscale. In the present study population, we included only total SRS scores in the analysis and not the SCI score based on their very high correlation (Pearson's $r > 0.98$). Continuous raw scores were used.

Statistical Analysis

A statistical plan was drafted, and submitted in advance to a registered public repository before analyses were performed (<https://osf.io/kxepb>).

Exposure biomarkers. TCB, BPAF, BPB, and BPF were quantified in <5% of the urine samples and were therefore excluded from further analyses. BUPA, quantified in 11%–25% of the samples, depending on the period, was also excluded. BPS was dichotomized as detected/quantified vs. nondetected. The remaining exposure biomarkers were detected in ~70% or more of the urine samples. In this later case, concentrations below the LOD and between the LOD and the LOQ were singly imputed by values randomly selected between 0 and the LOD and between the LOD and the LOQ, respectively, following the underlying distribution of concentrations.^{132,133} This method has shown good performance when <30% of the data are below quantification limits.¹³³

When needed, the measured biomarker concentrations were standardized using a two-step approach to account for between-sample variations related to urine processing and chemical assay.^{134,135} Three conditions were considered: *a*) time of sample transport from the participant's home to the biobank, *b*) the time individual samples were kept at 4°C during the pooling procedure, and *c*) the analytical batches. Details can be consulted elsewhere.¹¹¹ Descriptive statistics were determined for both standardized and nonstandardized concentrations, comparing them using Spearman's correlation coefficients. Standardized urinary biomarker concentrations were used in all exposure-outcome analyses.

For metabolites belonging to the same parent compound, molar sums (in micromoles per liter) were computed [i.e., ΣDEHP (sum of MEHP, MEHHP, MEOHP, and MECPP), ΣDiNP (sum of OH-MiNP, oxo-MiNP, and cx-MiNP), and ΣDINCH (sum of OH-MiNCH and oxo-MiNCH)]. We also computed the molar sum of parabens [$\Sigma\text{Parabens}$ (sum of MEPA, ETPA, and PRPA)] to limit the number of statistical tests.

For statistical analyses, exposure biomarkers were \log_2 -transformed to reduce the skewness of distributions and the influence of extreme values.

Covariates and confounding factors. Directed acyclic graphs (DAGs) were used to select adjustment variables based on *a priori* causal knowledge.¹³⁶ Models were controlled for covariates that may be a cause of the outcome without being a consequence of the exposure or a cause of both the outcome and exposure.¹³⁷ The main prenatal models were adjusted for maternal age (continuous), prepregnancy body mass index (BMI, continuous), education (below vs. master's degree or above), anxiety/depression score at the third trimester (continuous, assessed using the Hospital Anxiety and Depression scale),¹³⁸ active smoking (smoker vs. non-smoker), passive tobacco exposure (exposed vs. nonexposed), parity (nulliparous vs. uniparous/multiparous), mode of child care up to 1 year of age (day care vs. at home/others), family environment [continuous score, assessed using the Home Observation Measurement of the Environment (HOME)],¹³⁹ child sex (male/female), and child age (continuous) at SRS evaluation (Figure S3). Infant main models (Figure S4) were additionally adjusted for breast-feeding (lower vs. higher than a month). Regarding tobacco, neonatal models were adjusted for both maternal active and passive smoking, whereas 1-y-old–infant models were adjusted for maternal active smoking (as outcome predictor), and child passive smoking at 1 year of age (as potential confounder). Data on covariates were collected by self-administered questionnaires and questionnaires administered by a fieldworker during study visits.

Study participant covariates were described using measures of central tendency and dispersion for numerical variables and frequencies for categorical variables. Covariates between included and excluded participants were compared using the two-sample proportion test and the two-sample *t*-test for categorical and continuous variables, respectively.

Missing covariate values were multiple imputed using chained equations (StataCorp).¹⁴⁰ Imputed data sets ($N = 20$) were generated using linear and logistic regression methods for continuous and dichotomized variables, respectively (percentage of missing data was <15%). All variables considered in the final analyses (exposures, outcomes, and central covariates), as well as additional covariates included in sensitivity analyses, were included in the imputation model.

Associations between phenols, phthalates, and child social behavior. Linear regression models were separately fit for each exposure biomarker at each of the four time windows and each raw SRS score (the five subscales and the total score). Because coherence was observed between unadjusted and adjusted models, all subsequent analyses were run with covariate adjustment. For single-pollutant models, effect estimates (β) represented the adjusted mean difference for each doubling in standardized urinary exposure biomarkers. In the case of BPS (dichotomized), we report the β of the upper category compared with the lowest exposure category taken as reference.

Potential sex-specific associations were evaluated by including a product interaction term between child sex and exposure biomarker concentrations. A $p_{\text{Interaction}} < 0.10$ was considered as evidence of effect modification,¹⁴¹ in which case, models were sex-stratified.

Phenols and phthalate metabolite concentrations were also categorized in quartiles and entered in the regression model as an ordinal level indicator in relation to total SRS scores. Effect estimates and p_{Trend} across quartiles were checked for linearity.

False discovery rate (FDR) correction was applied only to exploratory associations, that is, associations with the nonprioritized compounds (those showing a limited WoE based on the *a priori* literature search).

Bayesian Weighted Quantile Sum regression. We used adjusted Bayesian Weighted Quantile Sum (BWQS) regression to

assess the association between phenols and phthalate metabolites, treated as a mixture, and social behavior. BWQS is a quantile-based approach that combines multiple independent variables additively into a weighted index, with weights estimating the contribution of each component to the mixture. Based on quantile transformations of the independent variables, it provides results that are insensitive to exposures outliers and skewed distributions.¹⁴² This method constitutes a Bayesian extension of the WQS regression,¹⁴³ counteracting its main drawbacks, including higher stability of estimates, higher statistical power (no data splitting into training and validation sets), and avoiding the need to *a priori* select the directionality of the mixture association.

Exposure variables were modeled in quartiles. BWQS effect estimates (Beta1) are interpreted as the mean change in social behavior scores for each quartile increase in the mixture. We observed potential scale-reduction statistic (R-hat) values of ~ 1 , indicating optimal convergence of the Hamiltonian–Monte Carlo chain. BWQS models were performed running the 20 imputations for each mixture–outcome association, and regression estimates were pooled following Rubin's rules.¹⁴⁴ We estimated the overall mixture association under two scenarios: *a*) considering only the prioritized chemicals with a higher WoE (main model), and *b*) all phenols and phthalate metabolites analyzed in single-pollutant models (secondary model). The relative weights of the components were shown only for the most relevant mixture associations.

Sensitivity analyses. The robustness of the main models was tested with additional covariates. Maternal and infant models were further adjusted for urine specific gravity (continuous, log-transformed; assessed in each weekly pool using a handheld Atago PAL 10-S refractometer) to rule out any potential influence of urine dilution¹⁴⁵; multivitamin intake at first trimester (yes/no), which may constitute both a source of MnBP/MEP and of beneficial nutrients for brain development¹⁴⁶; maternal employment at first trimester (yes/no) as a proxy for socioeconomic status; and breast-feeding (<1 vs. >1 month), which was not included in the main prenatal models because it could behave as a mediator.¹⁴⁷

For the main associations observed with molar sums (Σ Parabens, Σ DEHP, Σ DiNP, and Σ DINCH), a sensitivity analysis was performed to assess the individual effect of each paraben or phthalate metabolite contained in the sum.

Interpretation criteria and software. All tests were two-tailed and statistical significance was set as $p < 0.05$. A *p*-value between 0.05 and 0.10 was considered as suggestive of an association. Nevertheless, results were interpreted considering patterns of associations, confidence intervals (CIs) and the prioritization of chemicals performed altogether, rather than considering solely statistical significance.¹⁴⁸ Regression analyses and multiple imputation were carried out with Stata (version 14.2; Stata Corp). BWQS was performed using the rstan package (bwqs function) in RStudio (version 4.0.3; RStudio Team).

Results

Evidence from the Literature and Prioritization

Of the 821 publications identified, 34 *in vivo* toxicological and 37 epidemiological studies were selected (Figure S5) and tabulated in detail (Supplemental Excel File). Table 1 provides an evidence-based summary of the animal and human studies retrieved for each chemical, together with additional *in vitro*, *in vivo*, or review works that contributed to formulate the WoE (limited, moderate, or supportive), its gradings (i.e., upgrade/downgrade decisions), and the justification of decisions. The search prioritized BPA, BPS, TCS, Σ DEHP, MEP, MnBP, and

MBzP. For these prioritized compounds, associations will not be corrected for multiple comparisons, in contrast to the remaining chemicals (BP-3, Σ Parabens, MiBP, ohMPHP, Σ DiNP, and Σ DINCH; Table 1).

Characteristics of the Study Population

SEPAGES mothers were highly educated (58% reached a master's degree or higher), presented an overall healthy BMI (mean \pm SD = 22.3 \pm 3.8 kg/m²), and conceived at a mean \pm SD age of 32.6 (3.9) y (Table 2). Approximately half (46%) of the mothers were nulliparous at the time of conception, most of them (91%) breast-fed their infant for >1 month, and there was a greater number of boys (54%) born in the cohort. Maternal active smoking at pregnancy was infrequent (7%) compared with data from France,¹²³ whereas approximately one of five pregnant mothers and infants were exposed to secondhand tobacco smoke.

Children were on average 3 years of age (mean \pm SD = 37.1 \pm 1.1 months) at completion of the SRS questionnaire. Total SRS scores ranged between 4 and 100, with a mean \pm SD of 28.9 (13.5) points, and only three children (0.74%) had a score \geq 70 raw points, the cutoff for a higher risk of ASD over childhood.¹³⁰ Mothers excluded from the present analysis were slightly younger, less educated, more likely to breast-feed their infants for <1 month, and presented higher anxiety and depression scores (Table 2).

With the exception of BPS (detected in between 26% and 70% of the samples, according to the exposure window) and BUPA (quantified in 9% and 25% of samples), the remaining phenols, phthalates, and DINCH metabolites were detected and quantified in most samples (Table S2). MEPA showed the highest median urinary concentration at all windows of exposure, whereas among phthalate metabolites, the highest median concentrations were observed for the sum of DEHP metabolites and

Table 2. Characteristics of included and excluded participants in the SEPAGES cohort (France, 2014–2017).

Characteristics	Included (N = 406 mother–child pairs)		Excluded (N = 78)		p-Value ^a
	N (%) or mean \pm SD	Missing N (%) ^c	N (%) or mean \pm SD	Missing N (%)	
Mother's age at conception of index pregnancy (y)	32.6 \pm 3.90	0 (0)	31.7 \pm 3.59	0 (0)	0.046
Mother's prepregnancy BMI (kg/m ²)	22.3 \pm 3.8	3 (0.7)	22.9 \pm 4.0	1 (1.3)	0.161
Mother's anxiety/depression symptoms at the third trimester ^b	10.2 \pm 4.9	14 (3.45)	13.6 \pm 5.0	29 (37.2)	<0.001
Mother's education	—	2 (0.5)	—	1 (1.3)	0.064
<Master's degree	169 (41.8)	—	41 (53.2)	—	—
\geq Master's degree	235 (58.2)	—	36 (46.8)	—	—
Mother's tobacco consumption during pregnancy	—	33 (8.1)	—	21 (26.9)	0.632
Yes (\geq 1 cigarette/d)	26 (7.0)	—	3 (5.3)	—	—
No	347 (93.0)	—	54 (94.7)	—	—
Mother's passive tobacco exposure	—	23 (5.7)	—	21 (26.9)	0.201
Exposed	73 (19.1)	—	15 (26.3)	—	—
Unexposed	310 (81.9)	—	42 (73.7)	—	—
Children's passive tobacco exposure	—	26 (6.4)	—	43 (55.1)	0.585
Exposed	80 (21.1)	—	6 (17.1)	—	—
Unexposed	300 (78.9)	—	29 (82.9)	—	—
HOME inventory score (family environment)	24.6 \pm 2.8	43 (10.6)	24.1 \pm 2.8	64 (82.1)	0.530
Parity	—	0 (0)	—	0 (0)	0.956
Nulliparous	186 (45.8)	—	36 (46.1)	—	—
Uniparous/Multiparous	220 (54.2)	—	42 (53.9)	—	—
Breast-feeding	—	8 (2.0)	—	35 (44.9)	<0.001
<1 month	36 (9.1)	—	12 (27.9)	—	—
>1 month	362 (90.9)	—	31 (72.1)	—	—
Child sex	—	0 (0)	—	4 (5.1)	0.955
Boys	218 (53.7)	—	40 (54.1)	—	—
Girls	188 (46.3)	—	34 (45.9)	—	—
Child attending day care by 1 year of age	—	32 (7.9)	—	50 (64.1)	0.393
Yes	93 (24.9)	—	9 (32.1)	—	—
No	281 (75.1)	—	19 (67.9)	—	—
Mother's multivitamin intake at first trimester	—	61 (15.0)	—	26 (33.3)	0.681
Yes	270 (78.3)	—	42 (80.8)	—	—
No	75 (21.7)	—	10 (19.2)	—	—
Mother's employment at first trimester	—	21 (5.2)	—	19 (24.4)	0.675
Yes	334 (86.8)	—	50 (84.8)	—	—
No	51 (13.2)	—	9 (15.2)	—	—
Child age at SRS assessment (months)	37.1 \pm 1.1	0 (0)	—	—	—
Total SRS raw score ^d	28.9 \pm 13.5	0 (0)	—	—	—
Social Awareness raw score ^d	5.6 \pm 2.7	0 (0)	—	—	—
Social Cognition raw score ^d	5.2 \pm 3.3	0 (0)	—	—	—
Social Communication raw score ^d	8.6 \pm 5.0	0 (0)	—	—	—
Social Motivation raw score ^d	5.8 \pm 3.7	0 (0)	—	—	—
Restricted Interests and Repetitive Behaviors (RRB) raw score ^d	3.6 \pm 2.9	0 (0)	—	—	—

Note: Additional covariates considered but that were excluded from analyses due to low variability or no relation with the outcome (total SRS score): maternal ethnicity (95.5% Caucasian), marital status (98.8% living with partner at enrolment), maternal alcohol (very low intake), canned food (not related to bisphenols or outcome), sampling date (not related to outcome), season of sample collection (not related to outcome), season of birth (not related to outcome). —, not applicable; BMI, body mass index; HOME, Home Observation Measurement of the Environment; SD, standard deviation; SEPAGES, Assessment of Air Pollution exposure during Pregnancy and Effect on Health; SRS, Social Responsiveness Scale.

^aCategorical variables compared using the two-sample proportion test and continuous variables compared using the two-sample *t*-test.

^bHospital Anxiety and Depression scale score on a scale of 21. Anxiety and depression symptoms were summed, so the scores should be interpreted on a scale of 42.

^cNumber and percentage of missing values for variables considered in the analysis.

^dSRS score ranges were: total SRS (4–100 points), Social Awareness (0–15 points), Social Cognition (0–15 points), Social Communication (0–39 points), Social Motivation (0–19 points), and RRB (0–18 points).

the low-molecular-weight metabolites MEP, MiBP, and MnBP (Table S2). Extended data on exposure levels and their predictors can be consulted elsewhere.^{128,129}

Spearman correlations between standardized and measured concentrations were >0.80 for all compounds considered in the analysis (Table S3), indicating a limited influence of urine processing and assay batch conditions. Phenols presented low correlations ($r < 0.4$) among them at all windows examined (Figures S6 and S7). Phthalate metabolites, especially MEP, MnBP, MiBP, MBzP, Σ DEHP, Σ DiNP, and ohMPHP showed moderate correlations ($r = 0.4$ – 0.6) at all windows, being strongest (>0.6) in infancy (Figure S7).

Associations with Child Social Behavior

The most relevant adjusted associations are reported based on patterns of associations by chemical or SRS scales. Results are organized by window of exposure and distinguishing prioritized and nonprioritized chemicals. Effect estimates represent the adjusted mean difference for each doubling in urinary exposure biomarkers.

Prenatal second and third trimester associations. Prenatal unadjusted and adjusted associations are shown in Tables S4 and S5, respectively. Few associations with prenatal exposure were observed in the main adjusted models (Figure 1A,B).

Regarding prioritized compounds, several associations were observed for bisphenols. At the prenatal third trimester (T3), children born to mothers with detected/quantified BPS presented higher (i.e., worse) SRS total scores compared with mothers with nondetected concentrations ($\beta = 3.09$; 95% CI: 0.27, 5.90; Figure 1B). This association was driven by the Social Awareness, Social Cognition, and Social Communication subscales (Table S5).

A suggestive inverse (i.e., “protective”) association with total SRS scores was observed for BPA at the prenatal second trimester (T2) ($\beta = -0.98$; 95% CI: $-2.01, 0.05$, Figure 1A), but not at T3. This association was driven by the Social Awareness and Social Cognition subscales (Table S5). At T3, a sex-specific pattern was found, with girls showing more social communication problems in response to higher BPA ($\beta = 0.41$; 95% CI: $-0.04, 0.85$), MEP ($\beta = 0.48$; 95% CI: 0.01, 0.95), and MnBP ($\beta = 0.72$; 95% CI: 0.02, 1.42) concentrations than boys (Figure 2A; Table S6).

No other relevant patterns of linear associations with total or subscale scores were found at either T2 or T3 for the remaining prioritized chemicals (Table S5 and S6), whereas a few isolated nonlinear associations peaking at the second quartile were observed (Table S7).

For the nonprioritized chemicals, with the exception of an inverse association between Σ DINCH and Social Awareness in boys at both T2 and T3 (Figure 2A; Table S6), few borderline, isolated, or nonlinear associations were observed (Tables S5–S7).

Neonatal associations at 2 months of age. Unadjusted and adjusted associations with neonatal exposure to phenols [phthalates were not assessed at 2 months (M2)] are shown in Tables S8 and S9, respectively. Among prioritized phenols, in adjusted models, BPA ($\beta = -0.68$; 95% CI: $-1.27, -0.09$) and BPS ($\beta = -2.19$; 95% CI: $-4.74, 0.35$) were both inversely associated with total SRS scores (Figure 1C; Table S9). The negative association with BPA was driven by the Social Awareness, Social Cognition, and Social Motivation subscales, whereas the BPS association was driven by the Social Motivation subscale (Table S9).

The only other association observed at M2 was between TCS and worse Social Awareness scores in boys ($\beta = 0.26$; 95% CI: $-0.00, 0.52$; Figure 2B and Table S10).

Infant associations at 1 year of age. Unadjusted and adjusted associations with infant exposures are shown in Tables S8 and S9, respectively. At 1 year of age (Y1), with the exception of BPS, all the prioritized compounds showed associations toward worse social behavior in at least one SRS scale (Figures 1D and 3A–E; Table S9). TCS and MEP were associated with higher total SRS scores ($\beta = 0.78$; 95% CI: 0.00, 1.55 and $\beta = 0.92$; 95% CI: $-0.11, 1.96$, respectively; Figure 1D; Table S9), whereas other prioritized compounds were associated only with subscales, mainly the Social Awareness (BPA, MnBP, and MBzP; Figure 3A) and the Social Communication subscales (TCS, MEP, MBzP, and Σ DEHP; Figure 3C).

Regarding nonprioritized chemicals, BP-3, and Σ Parabens were also associated with higher total scores ($\beta = 1.14$; 95% CI: 0.17, 2.12 and $\beta = 0.36$; 95% CI: $-0.04, 0.76$, respectively), whereas several compounds were inversely associated with the Social Cognition subscale (Figure 3B), mainly MiBP ($\beta = -0.29$; 95% CI: $-0.57, -0.02$), ohMPHP ($\beta = -0.36$; 95% CI: $-0.72, 0.00$), and Σ DiNP ($\beta = -0.45$; 95% CI: $-0.81, -0.09$) (Table S9).

The observed associations at Y1 generally followed a dose–response pattern, peaking at the fourth quartile (Table S11).

Some isolated sex-specific associations were also observed at Y1 (Figure 2B), including a positive association between TCS and Social Awareness in boys ($\beta = 0.28$; 95% CI: 0.03, 0.52; Table S10).

Multiple comparisons correction (restricted to nonprioritized compounds). Nonprioritized compounds showed only significant linear associations at the Y1 window. The positive associations observed with total SRS and subscale scores for BP-3 and Σ Parabens at Y1, as well as the negative associations observed with MiBP, ohMPHP, and Σ DiNP did not remain after FDR correction (Table S12).

Among all the linear associations observed for nonprioritized chemicals, the unique suggestive association remaining after FDR correction was the positive association between BP-3 and the Social Communication subscale (corrected $p = 0.07$).

Sensitivity Analyses of Single-Pollutant Models

Overall, the main associations were not materially changed after additional simultaneous adjustment for urine specific gravity, maternal employment, and maternal multivitamin intake (Tables S13 and S14). At Y1, the strength of the positive associations for MEP and Σ Parabens was attenuated (Table S14), whereas a not-previously observed inverse association was identified between Σ DiNP and total SRS scores ($\beta = -1.67$; 95% CI: $-3.22, -0.11$).

MEPA, especially the conjugated form, drove the suggestive positive association observed between Σ Parabens at Y1 with total SRS scores ($\beta = 0.40$; 95% CI: 0.01, 0.78; Table S15).

Mixture Associations

No evident mixture associations were observed during pregnancy and neonatal windows in relation to total SRS scores (Table 3). The mixture of prioritized chemicals at Y1 tended to be associated with higher total SRS scores (beta 1 = 1.38; 95% CrI: $-0.18, 2.94$). This association was driven by the Social Awareness (beta 1 = 0.37; 95% CrI: 0.04, 0.69) and Social Communication (beta 1 = 0.91; 95% CrI: 0.31, 1.50) subscales. Components contributed approximately equally to the mixture, although TCS and MEP contributed more to the total and communication scales, whereas the contribution of BPA was higher for the Social Awareness subscale (Figure S8).

When the overall mixture was considered (both prioritized and nonprioritized chemicals), similar effect estimates were observed at Y1 in relation to Social Awareness (beta 1 = 0.36;

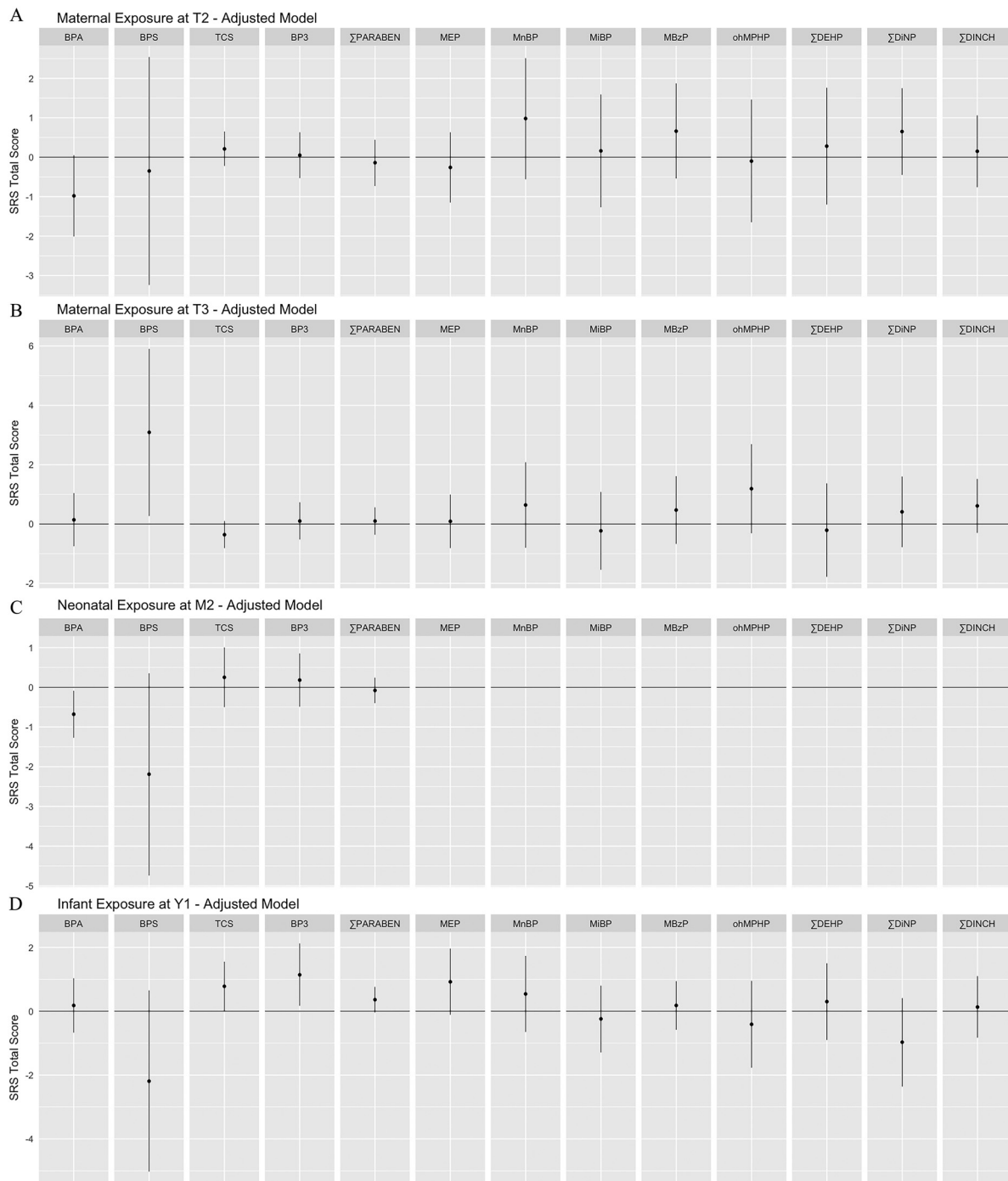


Figure 1. Associations between urinary phenol and phthalate metabolite concentrations measured at the (A) second trimester (T2) and (B) third trimester (T3) and in (C) 2-month-old neonates (M2) and (D) 1-year-old infants (Y1) in relation to child total SRS scores evaluated at 3 years of age in the SEPAGES cohort (France, 2014–2017). Owing to budget limitations, phthalate metabolites were only assessed in a subset of 152 neonates at 2 months of age and were not included in the present analysis. Circles and error bars represent linear regression effect estimates with their corresponding 95% CIs for each doubling in urinary exposure biomarkers except BPS (detected/quantified vs. nondetected). Higher SRS raw scores indicate more social problems. Prenatal models were adjusted for maternal age, prepregnancy body mass index, education, anxiety/depression, active and passive smoking, parity, mode of child care, family environment, child age at SRS evaluation, and child sex. Infant models were adjusted for the same prenatal covariates together with breast-feeding. Sample size was 406 (T2) and 399 (T3) mother–child pairs, 380 neonates (M2), and 358 infants (Y1). Numeric data corresponding to this figure can be found in Tables S5 and S9. Note: BP3, benzophenone-3; BPA, bisphenol A; BPS, bisphenol S; CI, confidence interval; M2, at 2 months of age; MBP, monobutyl phthalate; MBzP, mono-benzyl phthalate; MEP, mono-ethyl phthalate; MnBP, mono-*n*-butyl phthalate; ohMPPH, mono-hydroxy-isononyl phthalate; Σ DEHP, sum of mono(2-ethylhexyl) phthalate (MEHP), mono(2-ethyl-5-hydroxyhexyl) phthalate (MEHHP), mono(2-ethyl-5-oxohexyl) phthalate (MEOHP), and mono(2-ethyl-5-carboxypentyl) phthalate (MECPP); Σ DINCH, sum of mono-hydroxy isononyl cyclohexane-1,2-dicarboxylate (OH-MiNCH) and mono-oxo isononyl cyclohexane-1,2-dicarboxylate (oxo-MiNCH); Σ DiNP, sum of mono-hydroxy-isononyl phthalate (OH-MiNP), mono-oxo-isononyl phthalate (oxo-MiNP), and mono-carboxy-isononyl phthalate (cx-MiNP); Σ Parabens, sum of, methyl-, ethyl-, and propyl-parabens (MEPA, ETPA, and PRPA); SEPAGES, Assessment of Air Pollution exposure during Pregnancy and Effect on Health; SRS, Social Responsiveness Scale; T2, prenatal second trimester; T3, prenatal third trimester; TCS, triclosan; Y1, at 1 year of age.

95% CrI: -0.02, 0.75) and Social Communication (beta 1 = 0.84; 95% CrI: 0.14, 1.53) scores, although the association with total scores was attenuated (beta 1 = 1.16; 95% CrI: -0.73, 3.05; Table 3).

Discussion

In this cohort relying on within-subject pools of multiple urine biospecimens to improve exposure characterization during pregnancy, neonatal, and infancy periods, we observed several associations between specific phenols and phthalates and worse social behavior scores at 3 years of age, with most of these associations corresponding to an increased population risk of ASD in children.

Infancy as a Sensitive Exposure Window

Results of both single- and multipollutant models highlight early infancy as the most sensitive window of exposure for altered social behavior, although some associations were also observed at other time windows in single-pollutant models. Social awareness and communication were the skills most clearly affected by infant exposure to phenols and phthalates. The following factors could explain the heightened susceptibility observed for infants. First, infant exposure patterns may differ from those of pregnant women, with dust and toys constituting differential exposure sources coupled to frequent hand-to-mouth behaviors.¹⁴⁹⁻¹⁵² Second, detoxification pathways are immature in neonates and infants, possibly leading to increased EDC blood levels for longer periods.¹⁵³ Finally, the transition from crawling to walking at ~1 year of age is linked to important advances in social and language development.¹⁵⁴ At the public health level, our results showed that infants in the highest quartile of the prioritized mixture showed an average increase of ~4 points in the total SRS scale, which is substantial, knowing that exposure to these chemicals is widespread and that even slight shifts in the population distribution of social symptoms could result in a non-negligible excess of children entering borderline or clinical ASD diagnoses.^{155,156} Future studies investigating EDC exposure at early infancy are needed to confirm our results.

The toxicological evidence retrieved from our literature search identified several modes of action through which phenols and phthalates may alter social behavior including estrogenic (BPA, BPS, TCS, MEP, BP-3, and parabens), anti-androgenic (BPA, MnBP, MBzP, DEHP, DiNP, and MiBP), thyroid (TCS, DEHP, and BPA), retinoic acid (TCS), gut microbiota (TCS and BPA), and vasopressin/oxytocin pathways (BPA and DEHP), among others (Table 1; Supplemental Excel File). Consequently, the infant mixture association observed could be the result of additive effects resulting from both similar and dissimilar modes of action. This mixture effect is supported by rodent studies demonstrating impairments in social behavior after gestational/lactational exposure to mixtures of phthalates containing between 3 and 6 of the phthalates investigated,^{41,72,73} and particularly by Repouskou et al.⁴¹ and Caporale et al.,¹⁵⁷ who followed a human-to-laboratory approach, testing doses of phthalates and BPA found in humans on social behavior in rodents and in ASD-related pathways in human brain organoids, respectively. Although the need to evaluate the risk of co-occurring chemical families, such as phenols and phthalates is clear, regulation of chemical mixtures is still lagging.¹⁵⁸

Associations between Prioritized Compounds and SRS Scores

Most single-pollutant linear associations were observed for prioritized compounds (~68% of associations with $p < 0.05$ and

~71% of associations with $p < 0.10$ in the whole population; Tables S5 and S9). Similarly, most patterns of associations were also observed for prioritized chemicals.

Regarding bisphenols, neonatal exposure to both BPA and BPS showed protective associations with social behavior. These results were in line with the suggestive protective association observed for BPA at T2, but not with the deleterious association observed at T3 for BPA in girls and BPS in the whole sample. Although there is strong toxicological evidence for the effects of BPA on social behavior (Table 1), our results suggest a complex interplay for bisphenols depending on the window of exposure and sex. Sex-specific associations have been previously reported for BPA, with two epidemiological studies showing poorer social performance among girls,^{54,55} although another reported such an association in boys.¹⁹ Prenatal BPA levels in our cohort ranged from 1.8 to 2.6 ng/mL, not differing from previous prenatal cohorts reporting associations with child SRS scores (range: 0.8–2 ng/mL).^{18,19,54,55}

The only other epidemiological study that assessed BPS reported, like us, a moderate frequency of detection: 58% in Liu et al.,⁵⁷ vs. 26%–70% in our study, depending on the exposure window. The study by Liu et al., reported no clear association between second trimester urinary BPS concentrations and socio-emotional scores at 2 years of age.⁵⁷ Although a suggestive interaction ($p = 0.09$) between BPS and sex was observed for this subscale, the authors did not stratify the models.⁵⁷ Thus, the deleterious association observed at T3 in our study needs further investigation because rodent studies have suggested poorer social interaction, along with increased anxiety and aggressive behavior,^{30,65,66} after prenatal and lactational exposure to BPS.

TCS exposure can trigger autism-like phenotypes in rodents,^{102,105,159} through different modes of action, including altered retinoic acid signaling and changes in gut microbiota (Table 1). Our study suggested that infant TCS exposure predicted poorer social behavior in general, including repetitive behaviors, a cornerstone of autistic traits. In addition, both neonates and infant TCS exposure was associated with more social awareness problems in boys, whereas no clear pattern of association was observed during pregnancy for this compound. Although a large Canadian study did not find prenatal associations with child autistic traits,¹⁰⁶ a French cohort reported decreased prosocial behavior in boys.⁵⁸ Regarding postnatal exposure, a Chinese cohort reported that TCS exposure at 3 years of age—but not at pregnancy—was cross-sectionally associated with poorer social scores at 3 years of age.¹⁰⁸ When these children were 10 y old, a suggestive prenatal association between TCS and poorer prosocial scores was also observed.¹⁰⁷ Altogether, TCS exposure may be a risk factor contributing to child autistic traits that should be further investigated.

Regarding prioritized phthalates, MEP at T2 showed a nonlinear positive association with total SRS scores peaking at the second quartile. At T3, higher MEP concentrations were associated with social communication problems but only among girls. At Y1, MEP was associated with higher total SRS scores. These results for the prenatal windows are, overall, consistent with the available toxicological and epidemiological evidence (Table 1). Thus, prenatal exposure to MEP has been associated with worse social behavior or ASD-spectrum in several studies,^{17,18,74,77,79-81} although others reported null¹⁶ or inverse associations.¹⁵ Even though the human evidence converges in a similar direction, additional toxicological studies are needed to support the association between MEP and worse child social performance.

MnBP is a known anti-androgenic chemical (Table 1). Although no association was seen for this compound at T2, MnBP at T3 showed a nonlinear association with higher total

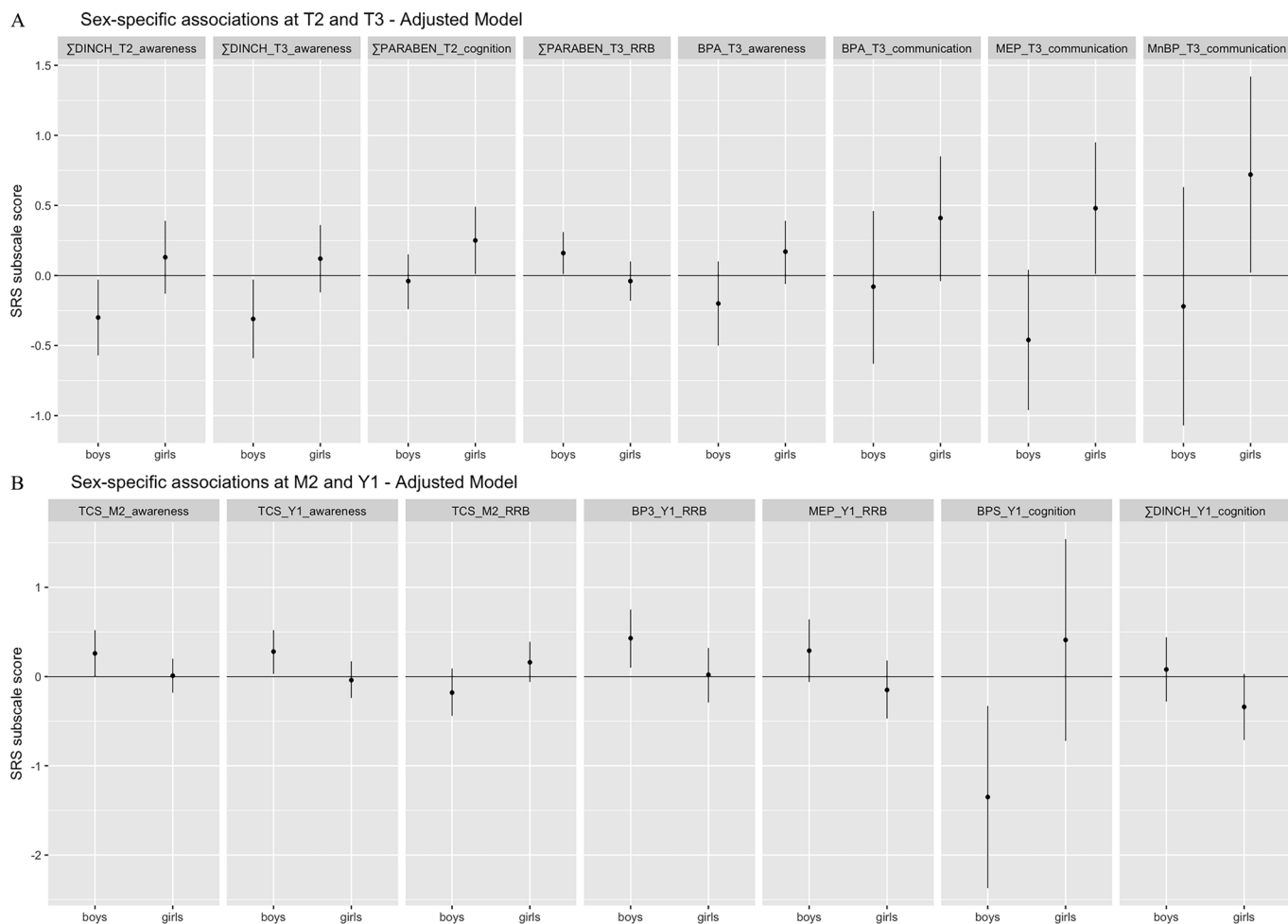


Figure 2. Sex-stratified associations between phenols and phthalate metabolite concentrations at the (A) second (T2) and third trimesters (T3) and at (B) 2 months (M2) and 1 year of age (Y1) in relation to child SRS subscale scores evaluated at 3 years of age in the SEPAGES cohort (France, 2014–2017). Only associations showing a sex-interaction $p < 0.10$ were sex-stratified and displayed (Tables S6 and S10). SRS subscales: Social Awareness, Social Cognition, Social Communication, Social Motivation, and Restricted Interests and Repetitive Behaviors (RRB). Circles and error bars represent linear regression effect estimates with their corresponding 95% CIs for each doubling in urinary exposure biomarkers except BPS (detected/quantified vs. nondetected). Higher SRS raw scores indicate more social problems. Sex-stratified models were adjusted for the same set of covariates included in the main models. Sample size was 406 (T2) and 399 (T3) mother–child pairs, 380 neonates (M2), and 358 infants (Y1). Numeric data corresponding to this figure can be found in Tables S6 and S10. Note: BPA, bisphenol A; BPS, bisphenol S; CI, confidence interval; DINCH, di(isononyl)cyclohexane-1,2-dicarboxylate; M2, at 2 months of age; MEP, mono-ethyl phthalate; Σ DEHP, sum of mono(2-ethylhexyl) phthalate (MEHP), mono(2-ethyl-5-hydroxyhexyl) phthalate (MEHHP), mono(2-ethyl-5-oxohexyl) phthalate (MEOHP), and mono(2-ethyl-5-carboxypentyl) phthalate (MECPP); Σ DINCH, sum of mono-hydroxy isononyl cyclohexane-1,2-dicarboxylate (OH-MiNCH) and mono-oxo isononyl cyclohexane-1,2-dicarboxylate (oxo-MiNCH); Σ Parabens, sum of methyl-, ethyl-, and propyl-parabens (MEPA, ETPA, and PRPA); SEPAGES, Assessment of Air Pollution exposure during Pregnancy and Effect on Health; SRS, Social Responsiveness Scale; T2, prenatal second trimester; T3, prenatal third trimester; TCS, triclosan; Y1, at 1 year of age.

SRS scores, together with an association with higher social communication problems in girls. At Y1, the fourth quartile of MnBP was associated with higher total SRS scores, in addition to a linear association with more social awareness problems. Pregnancy MnBP exposure has been linked to child social problems in several studies, supporting the associations observed in this work for the prenatal window,^{15,17,18,74,79,81} although three small cohorts reported null results.^{56,74,77} Kim et al. reported a positive association between MnBP exposure at 4 years of age—but not at pregnancy—and social problems in late childhood.⁷⁵

We observed few deleterious associations with MBzP. These associations were observed at the 1-y window, limiting comparisons with previous studies that assessed only prenatal exposure. That being said, of the cohorts that investigated prenatal MBzP exposure in relation to SRS scores, a large cohort identified MBzP as the primary driver of an association with a mixture of phthalates.¹⁷

Another three cohorts showed significant or suggestive associations in the same direction,^{15,74} suggesting overall that MBzP may be a contributor to child autistic traits, although additional toxicological and epidemiological data are needed to achieve a higher degree of confidence.

DEHP has been shown to affect social behavior in rodents, as well as in some epidemiological studies (Table 1). Notwithstanding, we observed a few associations that were either nonlinear (association with total score at T2) or borderline significant (association with social communication problems at Y1). Although *in vivo* toxicological studies support an effect of DEHP on social behavior,^{70,71} the epidemiological literature has shown mixed results, with some prenatal cohorts reporting positive,^{74–76} null,^{17,56,77,78} or negative⁷⁴ associations with SRS scores. Because prenatal DEHP concentrations in our study (range: 32.8–33.6 ng/mL) were similar and higher to other cohorts reporting associations between prenatal

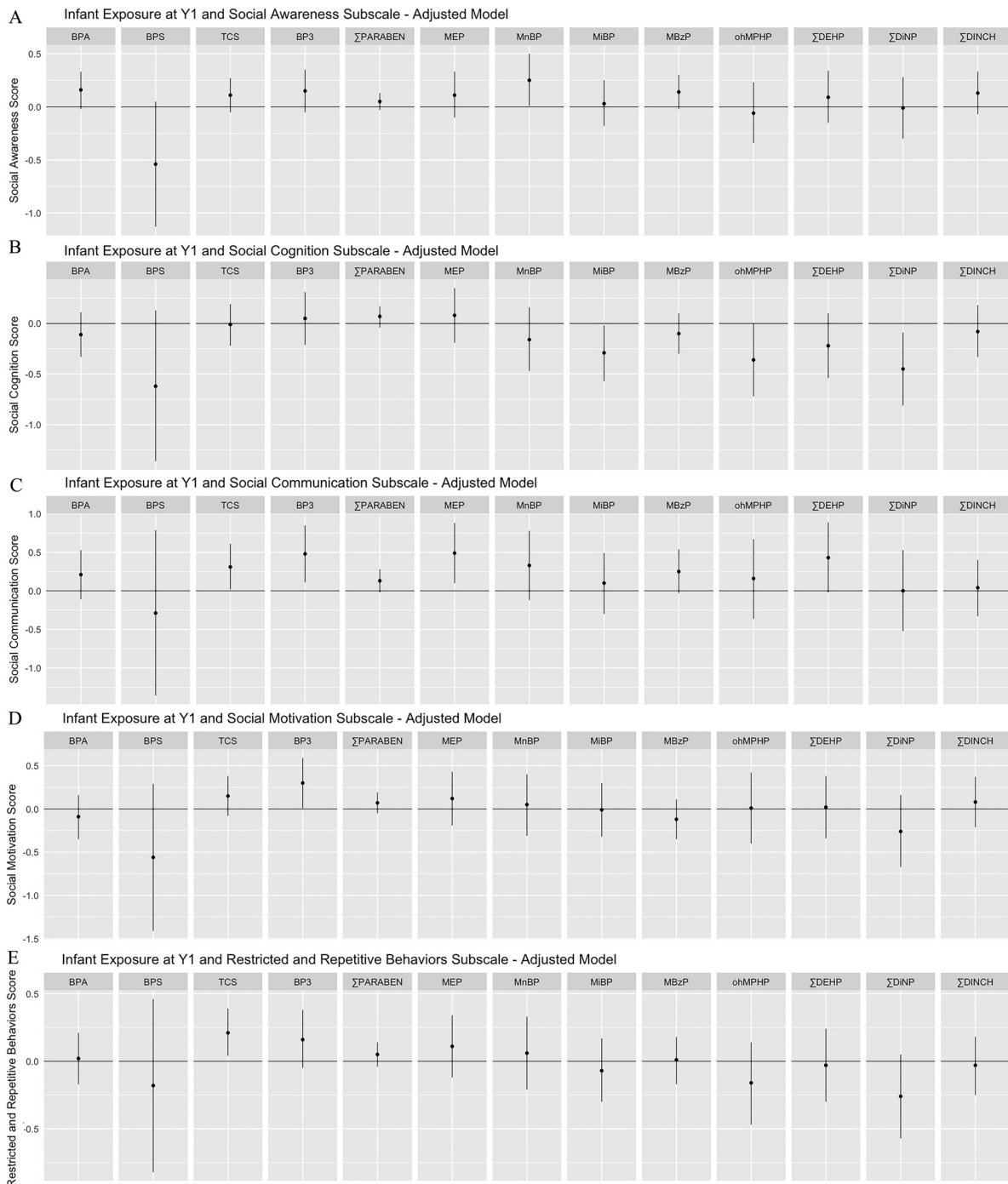


Figure 3. Associations between phenol and phthalate metabolite concentrations measured in the urine of 1-y-old infants (Y1) in relation to child SRS subscale scores evaluated at 3 years of age ($N = 358$) in the SEPAGES cohort (France, 2014–2017). Adjusted models for the five subscales: (A) Social Awareness, (B) Social Cognition; (C) Social Communication, (D) Social Motivation; and (E) Restricted Interests and Repetitive Behaviors. Circles and error bars represent linear regression effect estimates with their corresponding 95% CIs for each doubling in urinary exposure biomarkers except BPS (detected/quantified vs. nondetected). Higher SRS raw scores indicate more social problems. Infant models were adjusted for maternal age, prepregnancy body mass index, education, anxiety/depression, active smoking, parity, breast-feeding, mode of child care, family environment, child passive smoking at 1 year of age, child age at SRS evaluation, and child sex. Numeric data corresponding to this figure can be found in Table S9. Note: BP3, benzophenone-3; BPA, bisphenol A; BPS, bisphenol S; CI, confidence interval; MBP, monobutyl phthalate; MBzP, mono-benzyl phthalate; MEP, mono-ethyl phthalate; MnBP, mono-*n*-butyl phthalate; ohMPHP, mono-hydroxy-isononyl phthalate; Σ DEHP, sum of mono(2-ethylhexyl) phthalate (MEHP), mono(2-ethyl-5-hydroxyhexyl) phthalate (MEHHP), mono(2-ethyl-5-oxohexyl) phthalate (MEOHP), and mono(2-ethyl-5-carboxypentyl) phthalate (MECPP); Σ DiNCH, sum of mono-hydroxy isononyl cyclohexane-1,2-dicarboxylate (OH-MiNCH) and mono-oxo isononyl cyclohexane-1,2-dicarboxylate (oxo-MiNCH); Σ DiNP, sum of mono-hydroxy-isononyl phthalate (OH-MiNP), mono-oxo-isononyl phthalate (oxo-MiNP), and mono-carboxy-isononyl phthalate (cx-MiNP); Σ Parabens, sum of methyl-, ethyl-, and propyl-parabens (MEPA, ETPA, and PRPA); SEPAGES, Assessment of Air Pollution exposure during Pregnancy and Effect on Health; SRS, Social Responsiveness Scale; TCS, triclosan; Y1, at 1 year of age.

Table 3. Mixture associations in Bayesian Weighted Quantile Sum (BWQS) regression models in the SEPAGES cohort (France, 2014–2017).

Exposure window	N	Social Responsiveness (SRS) Scale	Overall mixture	Mixture restricted to prioritized chemicals
			Beta1 (95% CrI)	Beta1 (95% CrI)
Second trimester (T2)	406	Total	0.87 (−1.27, 3.01)	0.71 (−1.14, 2.56)
Third trimester (T3)	399	Total	1.00 (−1.00, 3.00)	0.59 (−1.17, 2.35)
Neonates (M2)	380	Total	−0.47 (−2.29, 1.36)	−0.63 (−2.15, 0.89)
Infants (Y1)	358	Total	1.16 (−0.73, 3.05)	1.38 (−0.18, 2.94)
		Social Awareness	0.36 (−0.02, 0.75)	0.37 (0.04, 0.69)
		Social Cognition	−0.19 (−0.67, 0.30)	−0.07 (−0.48, 0.34)
		Social Communication	0.84 (0.14, 1.53)	0.91 (0.31, 1.50)
		Social Motivation	0.04 (−0.52, 0.59)	0.03 (−0.46, 0.52)
		Restricted Interests and Repetitive Behaviors (RRB)	0.07 (−0.35, 0.48)	0.19 (−0.17, 0.55)

Note: Beta1 represents the mean change in SRS scores per quartile increase of the mixture, with its related 95% CrI. Because single-pollutant models showed many associations for SRS subscales at the infant window, we also estimated mixture associations for subscales in this particular period. The weight contributed by each chemical compound to the most relevant mixture associations can be consulted in Figure S8. The prioritized mixture included BPA, TCS, Σ DEHP, MEP, MnBP, and MBzP. BPS (dichotomized) was not considered in mixture models. Mixture models were adjusted for the same set of covariates considered in single-pollutant analyses. BPA, bisphenol A; BPS, bisphenol S; CrI, credible interval; M2, at 2 months of age; MBzP, mono-benzyl phthalate; MEP, mono-ethyl phthalate; MnBP, mono-*n*-butyl phthalate; Σ DEHP, sum of mono(2-ethylhexyl) phthalate (MEHP), mono(2-ethyl-5-hydroxyhexyl) phthalate (MEHHP), mono(2-ethyl-5-oxohexyl) phthalate (MEOHP), and mono(2-ethyl-5-carboxypentyl) phthalate (MECPP); SEPAGES, Assessment of Air Pollution exposure during Pregnancy and Effect on Health; SRS, Social Responsiveness Scale; T2, prenatal second trimester; T3, prenatal third trimester; TCS, triclosan; Y1, at 1 year of age.

DEHP exposure and child SRS scores (range: 15–32 ng/mL),^{74–76} the differences in results are not explained by differences in exposure levels.

Associations between Nonprioritized Compounds and SRS Scores

The single-pollutant associations observed with nonprioritized chemicals should be interpreted with caution, given that for these chemicals the WoE was quite limited, and most associations did not remain after correction for multiple comparisons.

BP-3 was the unique nonprioritized chemical that still showed a suggestive association with social problems after FDR correction. Some consistency across windows was also observed: BP-3 concentrations at Y1 were associated with higher total SRS scores, together with nonlinear positive associations observed at both T2 and T3 windows. BP-3 is estrogenic and anti-androgenic at relatively low doses and has been linked to altered expression of estrogenic receptors in the rodent brain at moderate doses.¹¹⁶ This chemical was not prioritized because of the lack of animal studies investigating effects on social behavior and the limited number of human studies—only two studies—and those showed mixed findings.^{58,107} Additional toxicological and epidemiological studies are needed to confirm our results.

Sex-Specific Associations

Exposure to phenols and phthalates has been linked to sex-specific neurodevelopmental effects in both experimental animals and humans.^{14,160} The prevalence of ASD is about four times higher in boys than girls worldwide, linked to sex-differential genetic and hormonal factors.^{161,162} In the present work, a clear sex-specific pattern of associations emerged at T3, with girls showing more social communication problems in response to the prioritized chemicals BPA, MEP, and MnBP. Interestingly, this pattern is coherent with a previous SEPAGES analysis reporting that prenatal exposure to a mixture of phenols and phthalates led by BPA, MEP, MnBP, and MBzP was associated with poorer externalizing and internalizing behaviors among girls at 2 years of age.¹¹¹ Other studies also reported an association between prenatal and childhood exposure to BPA and more social problems among girls,^{54,55,59} and between prenatal MEP exposure and more social symptoms in girls.⁵⁶ The fact that some studies tended to observe more associations in girls, whereas other studies tended to observe more associations in boys may be the result of how chemicals and their mixtures interfere with hormonal

regulation (especially estrogen-to-androgen balance) at specific periods of brain development.^{20,160}

We observed few other sex-specific associations, but in most cases, they were isolated and only for SRS subscales.

Strengths, Limitations, and Conclusions

Among the strengths of this work is the within-subject pooling of multiple repeated urine samples, which was designed to reduce exposure misclassification and attenuation bias.²⁴ Previous risk assessment panels excluded observational exposure–outcome studies based on exposure misclassification concerns for nonpersistent chemicals, such as BPA.¹³ Our work counteracted this limitation, presenting a higher potential for regulatory uptake. The SEPAGES design allowed us to investigate exposure not only during pregnancy but also in neonates and infants, producing new and relevant data during this understudied period. Another strength was the implementation of a novel mixture model (namely, BWQS), that counteracted some of the WQS limitations, providing higher power and stability of estimates, and avoiding the need to *a priori* assume the directionality of the mixture.¹⁴²

Based on the Navigation Guide systematic review methodology,²⁹ we were able to prioritize the phenols and phthalates with the highest WoE for an effect on social behavior before executing the statistical analyses. This allowed us to decide whether a multiple comparisons correction was indicated or not for each exposure–outcome pair examined. Interestingly, in single-pollutant models, most patterns of associations were observed for the prioritized compounds. Although mixture approaches help to counteract the multiple comparison issue,¹⁶³ risk assessment continues to mostly rely on single chemicals, and therefore both single-pollutant and mixture models are needed and complementary. Moreover, the application of our evidence-based prioritization to the mixture analysis also revealed that the mixture effect seemed to be driven by prioritized chemicals, given that the prioritized model provided similar and even strengthened estimates compared with the overall mixture. Because the inclusion of chemicals with uncertain or limited weights of evidence may increase noise or even lead to noncausal cancel-out effects,²⁷ the need for prioritization in mixture analyses may be directly proportional to the number of chemicals investigated. The literature search also resulted in a comprehensive corpus of mechanistic, *in vivo*, and observational evidence specifically related to social behavior that helped to interpret our findings and identify data gaps. Indeed, the knowledge and prioritization generated may be useful for future studies in the

field, and researchers should consider the need to prioritize their analyses based on study design, the number of comparisons made, and the WoE available for the chemical families under study. Admittedly, the implementation of an evidence-based prioritization is not applicable to all contexts, requiring: *a*) a sufficient quantity and quality of evidence on the exposures investigated, and *b*) a reproducible and valid prioritization given that this step will partly determine the interpretation of results. A shortcoming of our prioritization strategy is that novel chemicals are more likely to be classified as nonprioritized compounds just due to limited data availability. This aspect should be considered when judging the evidence, as was exemplified with BPS (limited evidence, but prioritized based on structural, *in vitro*, and *in vivo* analogy with BPA). Further, the main limitation of our evidence-based prioritization (possible underestimation of true associations for novel chemicals) will tend to self-correct over time in parallel to the generation of new evidence.

Other limitations include the medium size of our cohort, particularly when facing sex-stratified analyses. However, our improved exposure assessment is anticipated to substantially increase the statistical power compared with similar-sized cohorts collecting few urine samples.²³ Owing to budget limitations, phthalate metabolites could not be assessed in all neonatal urine samples, resulting in an incomplete comparison with the remaining windows. Although not a limitation because representativeness is not an essential element in etiologic studies,¹⁶⁴ it should be kept in mind that SEPAGES mothers were highly educated and healthy, meaning that the observed associations could differ (possibly being stronger)¹⁶⁵ in populations with a lower socioeconomic status. On the other hand, the homogeneity of our population limited the potential for confounding bias.

In conclusion, the present work developed a prioritization strategy based on previous toxicological and epidemiological studies, which helped to manage the issue of multiple comparisons, as well as to define a toxicologically relevant mixture. Infant exposure to a mixture of the prioritized endocrine disruptors BPA, TCS, MEP, MnBP, MBzP, and DEHP was associated with worse social behavior at 3 years of age. The novel associations observed suggest that early infancy—the period at which children begin to communicate and interact with peers—represents a critical window of vulnerability for child social development that should be further investigated.

Acknowledgments

We thank the Assessment of Air Pollution exposure during Pregnancy and Effect on Health (SEPAGES) study group: E. Eyrie, A. Licinia, A. Vellement (Groupe Hospitalier Mutualiste, Grenoble), I. Pin, S. Bayat, P. Hoffmann, E. Hullo, C. Llerena (Grenoble Alpes University Hospital, La Tronche), X. Morin (Clinique des Cèdres, Echirolles), A. Morlot (Clinique Belledonne, Saint-Martin d'Hères), J. Lepeule, S. Lyon-Caen, C. Philippat, I. Pin, J. Quentin, V. Siroux, R. Slama (Grenoble Alpes University, Inserm, French National Centre for Scientific Research, Institute for Advanced Biosciences).

We are grateful to the whole Centre de Ressources Biologiques (CRB) team, led by P. Mossuz and P. Lorimier, and, in particular, the technicians, for the huge work of biospecimens processing and pooling: W. Jayar and L. Than, as well as G. Schummer. We also acknowledge the data management assistance provided by K. Supernant and A. Boudier.

We thank A. Benlakhryfa, L. Borges, Y. Gioria, clinical research assistants; J. Giraud, M. Marceau, and M.-P. Martin, nurses; E. Charvet and A. Putod, midwives; M. Graca, K. Gridel, C. Peline, and Mailys Barbagallo, fieldworkers; A. Bossant, K. Guichardet, J.-T. Iltis, A. Levanic, C. Martel, E. Quinteiro, and S. Raffin, neuropsychologists; the staff from Grenoble Center for Clinical

Investigation: J.-L. Cracowski, C. Cracowski, E. Hodaj, D. Abry, N. Gonnet, and A. Tournier. We extend a warm thank you also to M. Althuser, S. Althuser, F. Camus-Chauvet, P. Dusonchet, S. Dusonchet, L. Emery, P. Fabbriozio, P. Hoffmann, D. Marchal André, X. Morin, E. Opoix, L. Pacteau, P. Rivoire, A. Royannais, C. Tomasella, T. Tomasella, D. Tournadre, P. Viossat, E. Volpi, S. Rey, and E. Warembourg and the clinicians from Grenoble University Hospital for their support in recruiting the study volunteers. We also thank A. Buchet, S.F. Caraby, J.-N. Canonica, J. Dujourdil, E. Eyrie, P. Hoffmann, M. Jeannin, A. Licina, X. Morin, and A. Nicolas and all the midwives from the four maternity wards of Grenoble urban areas. SEPAGES biospecimens are stored at Grenoble University Hospital (CHU-GA) biobank (bb-0033-00069). SEPAGES data are stored thanks to the Inserm RE-CO-NAI platform funded by Commissariat Général à l'Investissement, with the participation of Sophiede Visme (Inserm DSI). We extend many thanks to M.A. Charles, RE-CO-NAI coordinator, for her support. Finally, and importantly, we would like to express our sincere gratitude to the participants of the SEPAGES study.

V.M. is under postdoctoral contract with the French Research Agency (ANR) EDeN project (19-CE36-0003-01). This work was funded by the ANR EDeN project (19-CE36-0003-01, to C.P.) and the ANSES HyPaxE project (EST-2019/1/039). The SEPAGES cohort was supported by the European Research Council (No. 311765-E-DOHaD), the European Community's Seventh Framework Programme (FP7/2007-2006, No. 308333-892 HELIX), the European Union's Horizon 2020 research and innovation programme (No. 874583 ATHLETE Project, No. 825712 OBERON Project), the ANR (EDeN project ANR-19-CE36-0003-01, SHALCOH project ANR-14-CE21-0007, ANR-15-IDEX-02, and ANR-15-IDEX5, GUMME project ANR-18-CE36-005, ETAPE project ANR, PAPER project ANR-12-PDOC-0029-01), the French Agency for Food, Environmental and Occupational Health & Safety (ANSES; CNAP project EST-2016-121, PENDORE project EST-2016-121, HyPaxE project EST-2019/1/039), the Plan Cancer (Canc'Air project), the French Cancer Research Foundation Association de Recherche sur le Cancer (ARC), the French Endowment Fund (AGIR) for chronic diseases (APMC; projects PRENAPAR and LCI-FOT), the French Endowment Fund for Respiratory Health, the French Fund (Fondation de France; CLIMATH ES 00081169, and SEPAGES 5 00099903).

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