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Occupational exposure to organic solvents during pregnancy and child behavior from early childhood to adolescence

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Abstract

Background Organic solvents are used in formulating an extensive range of products for professional use. Animal and human studies suggest that in utero solvent exposure may affect neurodevelopment. Our objective was to assess the association between occupational exposure to solvents during pregnancy and child behavior aged 2–12 years.

Methods The French mother-child cohort PELAGIE (2002–2006) included 3,421 women recruited in early pregnancy. Occupational exposure to solvents was self-reported. For 459 children, parents used a questionnaire derived from the Child Behavior Checklist and the Preschool Social Behavior Questionnaire to assess their child's behavior, at age 2, and the Strengths and Difficulties Questionnaire at ages 6 and 12. A cross-lagged structural equation modeling approach was used to assess direct and indirect associations between exposure and child behavior.

Results At age 2, an increased externalizing behavior score was suggested with prenatal exposure to solvents (mean change in standardized score (95%CI): 0.28 (-0.01, 0.57) for occasional exposure and 0.23 (-0.05, 0.51) for regular exposure). At ages 6 and 12, distinct sex-specific patterns were observed: among boys, no association with externalizing behavior was observed, while among girls, an association was seen for both occasional and regular exposure (total effect at age 12: 0.45 (0.06,0.83) and 0.40 (0.03, 0.76), respectively). For both sexes, occasional exposure may be associated with internalizing behavior at ages 6 and 12 (total effect at age 6: 0.37 (0.06, 0.68) and at age 12: 0.27 (-0.08, 0.62)).

Conclusions Occupational exposure to solvents during pregnancy may impact child behavior through either direct or cumulative effects during childhood; these associations may persist until early adolescence, especially among girls.

Keywords Solvents, Prenatal exposure, Occupational exposure, Behavior, Neurodevelopment

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Introduction

Organic solvents are substances used to dissolve, dilute or disperse other substances across many industries – in paints, varnishes, lacquers, adhesives and glues, as well as in degreasing and cleaning agents and in the production of dyes, polymers, plastics, textiles, printing inks, agricultural products, and pharmaceuticals [1]. Since 70% of pregnant women in France reported working during pregnancy in 2010 [2], the issue of occupational exposure to organic solvents during pregnancy is certainly a salient one.

Organic solvents fall into nine groups, according to their chemical structure and properties: alcohols, ketones, esters, ethers and glycol ethers, aromatic hydrocarbons (such as toluene or benzene), petroleum solvents (aliphatic, such as cyclohexane, paraffinic or complex mixture such as white spirit), halogenated compounds (most of which are chlorinated) and other solvents that do not pertain to the previous categories [3]. Solvents such as toluene, benzene, xylene [4], and tetrachloroethylene [5] have been shown, due to their lipophilic characteristics, to cross the placental barrier. Organic solvents have been identified as potential developmental neurotoxicants [6] with neurobehavioral effects [7]. Since the 1980s, animal data have suggested the possible neurodevelopmental toxicity of certain solvents, such as some glycol ethers [8, 9], toluene [10, 11], white spirit [12–14] and trichloroethylene [15]. The relationships between prenatal occupational exposure to organic solvents and neurodevelopment [16] have been explored in a few epidemiological studies. Because of the heterogeneity of the studies identified (different outcomes: behavior, cognitive, language and neuromotor functioning, vision; different age of children and measure of exposure), and in some, modest sample sizes, the results remain inconsistent [17–23].

Previous studies in the PELAGIE (*Perturbateurs Endocriniens: Étude Longitudinale sur les Anomalies de la Grossesse, l'Infertilité et l'Enfance*) mother-child cohort have highlighted neurodevelopmental issues in children born to mothers exposed to organic solvents during pregnancy. Results have shown that occupational exposure to solvents during pregnancy was associated with a higher incidence of externalizing behaviors at age 2 [24], although this association was attenuated at age 6 [25]. Prenatal exposure to solvents, especially glycol ethers, has been also associated with lower cognitive abilities [26] and inhibitory capacity [27, 28] in children aged 6.

Benefiting from the longitudinal design of the PELAGIE cohort and its consistent behavioral assessments, the study had two main objectives. First, we aimed to determine whether the behavioral associations observed at ages 2 and 6 persisted through to pre-adolescence, specifically at age 12. Second, we examined the internalizing behaviors, which have been relatively under-studied, and their potential interactions with externalizing behaviors throughout childhood.

Methods

Study population

The PELAGIE mother-child cohort included 3,421 pregnant women from Brittany, France in 2002–2006. Women were recruited at their first prenatal visit (before the 19th week of gestation), by gynecologists, obstetricians, or ultra sonographers of 3 departments (Ille-et-Vilaine, Côtes d'Armor and Finistère) who agreed to participate in the study [29]. Mothers who gave birth to singletons (N=3,323) were then included in the follow-up. At age 2, 1,506 (45.3%) families participated in the 2-year follow-up; of these, 947 (28.5%) and 625 (18.8%) participated in the 6-year and 12-year follow-up, respectively. 50 of these 625 women had declared that they did not work during pregnancy and were thus excluded from the present study.

At inclusion and at the 2, 6 and 12-year follow-ups, were asked about their family, social and demographic characteristics and child's health using a self-reported questionnaire. At birth, information about the pregnancy and pregnancy outcome was reported by hospitals. For our study, children born before the 35th week of gestation (n=4) or with a genetic or chromosomic disease (n=1) or who had suffered severe head trauma during childhood (n=1) were excluded. Another eight children treated on a regular or prolonged basis with tranquilizers, anti-depressant or psychostimulant neuroleptic drugs were also excluded. Ultimately, 561 children were eligible. The sample selection flow chart is shown in Figure S1 in the Supplemental Material.

Individuals participating in this study provided their written informed consent. The Advisory Committee on Information Processing in Health Research (CCTIRS 2015: No. 15.326bis), the Committee for the Protection of Persons (CPP 2015: No. 15/23–985) and the French data protection authority (CNIL 2002 and 2007: No. 902076, 2015: No. 915420) approved this study.

Child behavior assessment

Child behavior was reported by parents using standardized psychometric questionnaires. At age 2, items derived from the Child Behavior Checklist (CBCL) [30, 31] and the Preschool Social Behavior Questionnaire (PSBQ) [32] were used and broken down into four different subscales: attention deficit/hyperactivity (6 items), aggression, opposition, and emotionality (3 items each). See Table S1 in the Supplemental Material for details.

At 6 and 12 years old, parents assessed their children's behavior using the French version of the Strengths and Difficulties Questionnaire (SDQ) [33, 34]. The SDQ asks about 25 items (divided into five scales of five items each). In this study we used four scales, generating scores for emotional symptoms, conduct problems, hyperactivity-inattention, and peer problems. A higher score indicates a higher level of problems. The parent-reported French SDQ versions have been shown to accurately measure internalizing and, especially, externalizing symptoms in young people [35]. For all items of the CBCL, PSBQ and SDQ questionnaires, respondents use a 3-point Likert scale to indicate the extent to which each attribute applies to their child.

At age 2, no score was calculated where any item within a subscale was missing, and 40 children were then excluded from the analyses. At ages 6 and 12, no score was calculated where three (or more) SDQ items were missing within a scale, and six children were thus excluded from the analyses. Where just one or two items were missing in a subscale, the corresponding score was proportionally extrapolated from the available items ($n=45$).

Exposure assessment

Maternal occupational exposure to organic solvents was documented at inclusion, at the beginning of pregnancy. Women reported their occupational exposure, either using, producing or being exposed, on a 3-level scale (never, occasionally, regularly) to one of 11 groups of products: paints, strippers, varnishes, dyes, inks, glues, gasoline, grease remover, detergents and cleaning agents, textile treatment agents, and cosmetics. Regular exposure to at least one group of products led to categorized women as "regularly exposed"; occasional exposure to at least one group to "occasionally exposed" and no exposure to any of these groups of products to "not exposed" [29]. To verify if exposure to organic solvents remained throughout pregnancy, at the 2-year follow-up, women were asked if their occupation had changed during pregnancy. Twenty-six women were excluded because of missing data on their occupational solvent exposure status, and another 30 were excluded because they had changed jobs during pregnancy.

Potential confounding factors selection

We identify potential covariates a priori, based on existing literature on prenatal and perinatal factors capable of impacting mental health and behavior (such as current maternal stress and anxiety [36–38]; smoking, drug or alcohol consumption during pregnancy [36–41]; maternal pre-pregnancy body mass index [40]; hypertensive disorders during pregnancy; preeclampsia and other pregnancy complications [37, 40, 41]; exposure to environmental chemicals [36, 38, 39] and low birth weight and prematurity [36–38, 41]). We used a directed acyclic graph (DAG, see Figure S2 in the Supplemental Material) approach to refine our potential confounders selection. Because breastfeeding is known to influence child mental health [40, 42–44], it was considered as a covariate. When the child reached 2 years of age, mother-child interaction was assessed, using a score totaled from five items collected at the 2-year follow-up on activities shared with the child (singing, playing, reading, going for walk, playing physical games), which were coded from 1 to 5 (never or almost never, less than once a week, once or twice a week, 3–5 times a week, and every day or almost; see Table S2 in the Supplemental Material for details) [24]. Because both attachment and parental stimulation are factors associated with children's mental health and behavior [45, 46], this interaction score was also considered as a covariate. The final adjustment set included: maternal age at delivery (in years), number of years in full-time education for mother (<12 years, 12 years, > 12 years), parity (primiparous vs. multiparous), smoking status at inclusion (non-smoker, < 10 cig/day, ≥ 10 cig/day), child sex, breastfeeding duration (none, < 6 months, ≥ 6 months) and mother-child interactions score at age 2 (continuous). Selected covariates had very few missing data (<1%) and were then imputed with the mode.

Statistical analysis

The multidimensional and longitudinal features of child behavior scores were addressed using a cross-lagged panel approach [47, 48] within a structural equation modeling (SEM) framework, as had been done previously by Costet et al. [25]. In the context of repeated measurements of latent variables, the cross-lagged panel approach allows to simultaneously estimate correlations between latent variables at a single time point, as well as the autoregressive effects of each variable over time and cross-lagged paths between variables at different time points [48]. Both internalizing and externalizing behaviors, as suggested by Goodman et al. [49] for the SDQ, were defined with latent variables at ages 6 and 12: the internalizing behavior was defined by the 'emotional symptoms' and 'peer relationship problems' subscales and the externalizing behavior was defined by the 'hyperactivity/inattention' and 'conduct problems' subscales. At age 2, the internalizing behavior was defined by the 'emotional symptoms' subscale and the externalizing behavior was defined by the 'attention deficit/hyperactivity', 'aggression' and 'opposition' subscales. At each time point, covariance between these latent variables was estimated. We addressed the longitudinal feature via linear regressions of each latent variable at ages 6 and 12 on the two latent variables at the preceding age (age 2 and 6 respectively) (Fig. 1). As we had no a priori information about the stability of relationships between behavior scores over ages, we allowed the linear regression coefficients between

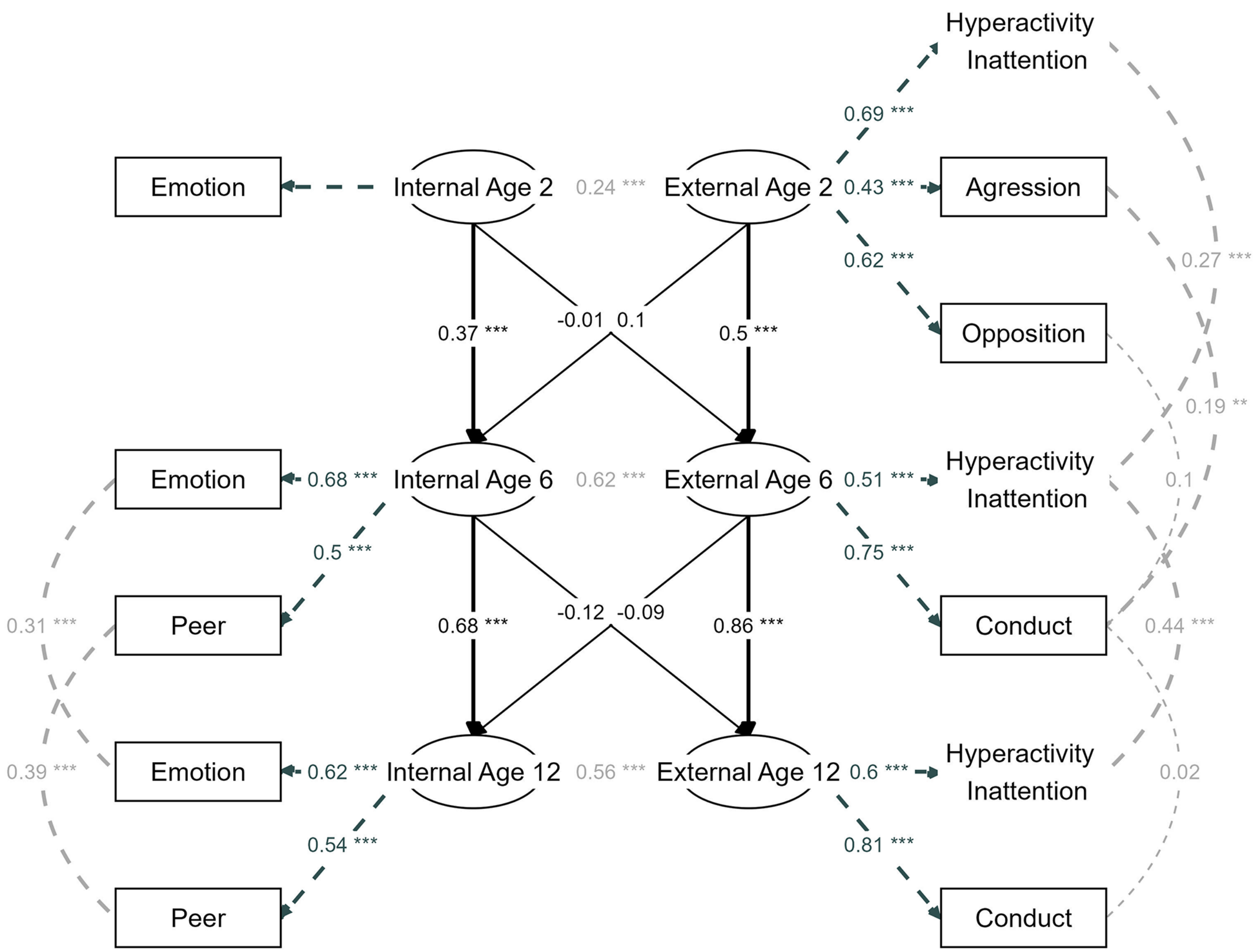

Fig. 1 Crude model of behavior latent variables at ages 2, 6 and 12 (PELAGIE mother-child cohort, France, *N* = 459). Abbreviations: Latent variables: Internal, internalizing behavior; External, externalizing behavior. Observed variables are scores from the Child Behavior Checklist (CBCL) and the Preschool Social Behavior Questionnaire (PSBQ) at age 2 and from the Strengths and Difficulties Questionnaire (SDQ) at ages 6 and 12. At age 2: Emotion, "Emotional symptoms"; Hyperactivity/Inattention, "Attention deficit/hyperactivity". At ages 6 and 12: Emotion, "Emotional symptoms", Peer, "Peer-relationship problems"; Conduct, "Conduct problems". Arrows between latent variables and observed variables represent standardized factor loadings. Gray lines represent covariances between observed variables and between latent variables at the same time point. Arrows between latent variables at different ages represent auto-regressive effect. Arrows between different latent variables at subsequent time point represent cross-lagged-effects

latent variables to vary across successive ages (between age 2 and 6 and age 6 and 12, respectively) [47]. In order to improve goodness of fit of the model, we also allowed the estimation of the residual variances of the observed variables and covariances between variables observed at different subsequent times.

A weighted least squares procedure (WLSM) was used to estimate model parameters; WLSM provides robust estimators and standard errors, as observed variables were discrete scores and did not follow a normal distribution [50].

Factor loadings, variances, covariances and regression coefficients were estimated with their 95% confidence intervals (95% CIs) and standardized. A root mean square error of approximation (RMSEA) < 0.06, a comparative fit index (CFI) > 0.9, a Goodness-of-Fit statistic (GFI) > 0.9 and a standardized root mean square residual (SRMR) < 0.05 were indices of good fit of the model [50].

First, we fitted the relations between latent behavior variables at ages 2, 6 and 12 in a crude model (Fig. 1). Second, both the exposure categorical variable and the potential confounders were included in the model. Linear regressions were used between both latent behavior variables at ages 2, 6 and age 12, and exposure variable, behavior variables at previous age and covariates. The coefficient between exposure and each latent behavioral variable represents the mean change in the latent score (expressed in number of standard deviations) for exposed (compared to unexposed) children.

We used the coefficient-product method [51] to estimate the different types of effects of exposure at each point in time: both the direct effect of the exposure on

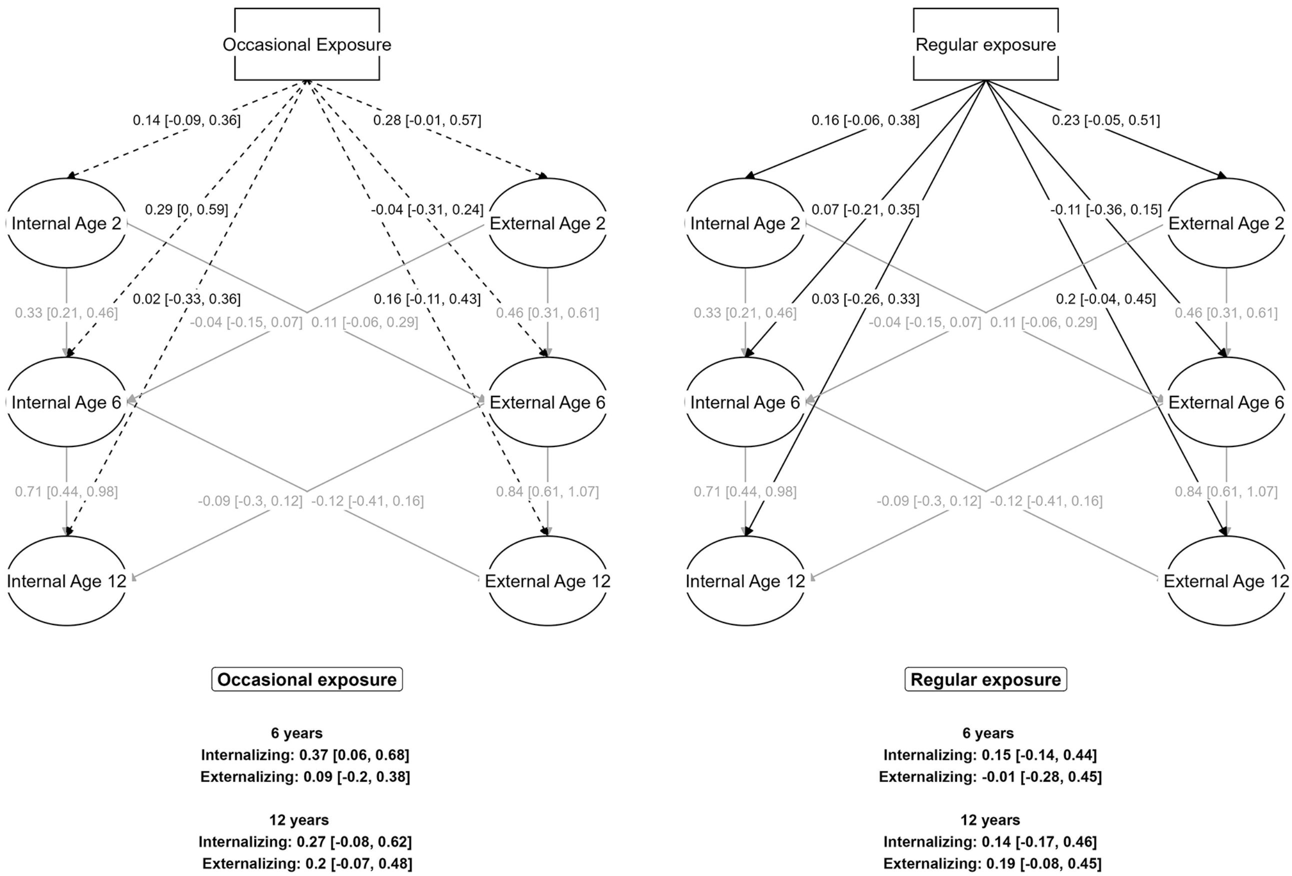

Fig. 2 Associations of occasional and regular self-reported occupational exposure to solvents during pregnancy with behavior at ages 2, 6 and 12 (PELAGIE mother-child cohort, France, *N* = 459) compared to non-exposure. Latent variables: Internal, internalizing behavior; External, externalizing behavior. All regression coefficients were adjusted for sex, maternal education level, maternal age, breastfeeding duration, smoking during pregnancy, parity and mother-child interaction score at age 2. The direct effect of latent variables at a given age with prenatal exposure can be directly read for occasional exposure on the left and regular exposure on the right. The indirect associations of each latent variable at age 6 and 12 were derived by summing the associations along the two effects pointing to it via internal and external variables at age 2 and 6 (gray arrows). Each of these effects generates an association with exposure. The intensity of the association is given by multiplying all the regression coefficients along the respective effect. The total association, indicated under each latent variable at age 12, was obtained by summing the direct and indirect associations with exposure. Example of decomposition of the total association of occasional exposure to solvents with internalizing behavior at age 12: Direct association = 0.02; Indirect association via internalizing behavior variable at age 2 and 6 = (0.14*0.33*0.71); via internalizing behavior variable at age 2 and externalizing at age 6 = (0.14*-0.04*-0.12); via externalizing behavior variable at age 2 and 6 = (0.28*0.46*-0.12) and via externalizing behavior variable at age 2 and internalizing at age 6 = (0.28*0.11*0.71); via internalizing behavior variable at age 6 = (0.29*0.71);.via externalizing behavior variable at age 6 = (-0.04*-0.12);. Indirect association = (0.14*0.33*0.71) + (0.14*-0.04*-0.12) + (0.28*0.46*-0.12) + (0.28*0.11*0.71) + (0.29*0.71) + (-0.04*-0.12) = 0.25. Total association = 0.02 + 0.25 = 0.27

each latent variable and its overall total effect – which is the sum of coefficient-products through every possible pathway. The associations between exposure and behavior latent variables at ages 6 and 12 (total effects) were broken down into direct and indirect effects. The direct effect corresponds to the regression coefficient of the association, at ages 6 and 12, between exposure and behavior, after adjusting for the associations at ages 2 and 6, and the covariates. The indirect effect at age 12 represents associations observed at age 12 that are due to the effect of exposure on behavior variables at previous ages (age 2 and 6) and associations between behavior variables at ages 2 and 6, and ages 6 and 12, respectively.

To identify potential heterogenous associations between boys and girls, measurement invariance was tested by comparing a model constrained to estimate equal factor loadings in boys and girls (restricted model) with the unrestricted model. The measurement invariance between boys and girls was not rejected (Chi²: p=0.3 in the crude and p=0.18 in the adjusted models). We then computed a model by constraining factor loadings, covariances between latent variables and between those variables observed equally among boys and girls at each time point. Direct and total associations between exposure and behavior were then reported by sex. In the models exploring sex specific associations, the child sex was removed from the covariates.

Analyses were performed using R-4.0.2 software [52]. The lavaan package was used for SEM analyses [53].

Results

The characteristics of the 459 mother-child pairs included in the analysis are shown in Table 1, and mothers' jobs during pregnancy are described in Table 2. Teachers represented the highest proportion (17%) in the study population, followed by healthcare workers (nurses, midwives and medical x-ray technicians) (12%) and clerical and related workers (10%). Occupational exposure to solvents during pregnancy was declared by 229 women (49.9%). Of these, 88 (38.4%) reported occasional exposure and 141 (61.6%) reported regular exposure. Nurses and midwives represented the highest proportion of women regularly exposed to solvents (27%), followed by teachers (13%) and cleaners and helpers (11%). Teachers represented the highest proportion of occasionally exposed women (25%), see Table 2 for details. In terms of types of solvent products, women declared being exposed to cleaning products, with detergents most often observed (36.5% of women). This was followed by glues, mastics, resins and adhesives (19.2%) for occasional and regular use (see details in Table S4 in the Supplemental Materials).

Table 1 Characteristics of the study population (PELAGIE mother-child cohort, France, $N = 459$)

	N	Mean (SD) or *N* (%)
Mother's characteristics at inclusion		
Age (years)	459	31.1 (3.9)
Education (years)	458	
< 12		41 (9.0)
12		64 (14.0)
≥ 12		353 (77.1)
BMI (kg/m²)	458	
<18.5		27 (5.9)
18.5 - < 25		363 (79.3)
25 - < 30		50 (10.9)
30 or more		18 (3.9)
Tobacco status	456	
Non or former smoker		367 (80.5)
< 10 cig/day		70 (15.4)
≥ 10 cig/day		19 (4.2)
Parity	459	
Primiparous		186 (40.5)
Multiparous		273 (59.5)
Geographic origin of mother's parents	459	
European		454 (98.9)
Non european		5 (1.1)
Marital status at inclusion	459	
In couple		457 (99.6)
Live alone		2 (0.4)
Exposure to solvents	459	
None		230 (50.1)
Occasional		88 (19.2)
Regular		141 (30.7)
Child's characteristics		
Birth weight (grams)	458	3449.6 (458.2)
Gestational age (weeks)	458	39.6 (1.2)
Sex at birth	459	
Boys		236 (51.4)
Girls		223 (48.6)
Breastfeeding	459	
None		125 (27.2)
< 6 months		221 (48.1)
≥ 6 months		113 (24.6)

Table 3 presents the results for parent-reported outcomes both for the sample population as a whole, and for boys and girls separately. At each age, boys had higher median scores than girls on both the externalizing subscale ($p<0.001$) and the hyperactivity/inattention subscale ($p<0.001$). In terms of internalizing scores, no differences were seen between boys and girls. For externalizing scores at ages 2, 6 and 12, Cronbach's alpha (polychoric) was >0.8. For internalizing scores, Cronbach's alpha (polychoric) was 0.61 at age 2, and 0.78 and 0.85 at ages 6 and 12 respectively (see Table S3 in the Supplemental Material for the coefficients for each subscale).

Compared to the women that were not included ($n=2{,}962$, see Table S5 in Supplemental Material), women included in this study ($n=459$) had higher education level (77% with >12 years of schooling, vs. 60% for those not included ($n=2962$), $p<0.001$), and were older (mean age (SD) 31.1 (3.9) vs. 29.9 (4.3), $p<0.001$). The externalizing behavior scores of the children at age 2 tended to be lower among the included than the non-included population (see Table S6 in the Supplemental Material). The distribution of prenatal occupational exposure to solvents across the included and non-included population was similar ($p=0.9$) although we observed more nurses, midwifes and x-ray technicians and teachers, and fewer cleaners and helpers in the study sample, compared to the non-included (see Table S5 in the Supplemental Material).

The crude structural equation model of relationships between behavior subscales and latent behavior variables (factor loadings λ) is shown in Fig. 1. At age 2, externalizing behavior was determined mainly by the attention deficit/hyperactivity score (factor loadings $\lambda=0.69$). At ages 6 and 12, externalizing behavior was determined mainly by conduct problems ($\lambda=0.75$ and 0.81, respectively) and then by the hyperactivity score ($\lambda=0.51$ and 0.60). The internalizing behavior latent variable, at ages 6 and 12, was determined by both emotional ($\lambda=0.68$ and 0.62, respectively) and peer problems ($\lambda=0.50$ and 0.54, respectively).

Table 2 Distribution of maternal occupations during pregnancy in the PELAGIE mother-child cohort

Job titles	Exposure to solvents		N (%)	
	None N=230	Occasional N=88	Regular N=141	Total N=459
Scientific, technical workers				
Medical, dental, veterinarians, pharmacists	18 (9.3)	5 (6.8)	8 (5.8)	31 (7.7)
Nurses, midwives, medical x-ray technicians	4 (2.1)	7 (9.6)	37 (26.6)	48 (11.9)
Architects, engineers and related technicians	12 (6.2)	4 (5.5)	1 (0.7)	17 (4.2)
Statisticians, mathematicians, system analysts	11 (5.7)	1 (1.4)	0 (0.0)	12 (3.0)
Teachers	33 (17.1)	18 (24.7)	18 (12.9)	69 (17.0)
Social workers	4 (2.1)	5 (6.8)	1 (0.7)	10 (2.5)
Chemists, biologists and related workers	4 (2.1)	3 (4.1)	10 (7.2)	17 (4.2)
Jurists, journalists and related workers	29 (15.0)	2 (2.7)	0 (0.0)	31 (7.7)
Other professional and technical workers	6 (3.1)	0 (0.0)	3 (2.2)	9 (2.2)
Managerial workers	5 (2.6)	1 (1.4)	0 (0.0)	6 (1.5)
Clerical and related workers	31 (16.1)	3 (4.1)	6 (4.3)	40 (9.9)
Sales workers and commercial				
Technical saleswomen, commercial travelers	6 (3.1)	1 (1.4)	0 (0.0)	7 (1.7)
Saleswomen, shop assistants	10 (5.2)	6 (8.2)	10 (7.2)	26 (6.4)
Other sales workers	6 (3.1)	1 (1.4)	4 (2.9)	11 (2.7)
Service workers				
Cleaners and helpers	2 (1.0)	1 (1.4)	15 (10.8)	18 (4.4)
Hairdressers, beauticians	0 (0.0)	0 (0.0)	5 (3.6)	5 (1.2)
Nurses' aides	2 (1.0)	4 (5.5)	10 (7.2)	16 (4.0)
Other service workers	3 (1.6)	2 (2.7)	4 (2.9)	9 (2.2)
Agricultural workers	2 (1.0)	2 (2.7)	3 (2.2)	7 (1.7)
Industrial workers				
Textile workers	0 (0.0)	1 (1.4)	0 (0.0)	1 (0.2)
Food and beverage processors	0 (0.0)	1 (1.4)	0 (0.0)	1 (0.2)
Electronic or metal processors	2 (1.0)	1 (1.4)	3 (2.2)	6 (1.5)
Material handlers and related equipment operators	1 (0.5)	2 (2.7)	0 (0.0)	3 (0.7)
Other production workers	2 (1.0)	2 (2.7)	1 (0.7)	5 (1.2)
N-Miss	37	15	2	54

For each behavior type, the latent variables were strongly associated between the ages 6 and 12 (mean change in standardized regression coefficients: 0.68 (95% CI=0.46, 0.90) for internalizing behavior, and 0.86 (95% CI=0.68, 1.05) for externalizing behavior) and between the ages 2 and 6, though with a lower magnitude (0.37 (95% CI=0.24, 0.50) for internalizing behavior and 0.50 (95% CI=0.36, 0.63) for externalizing behavior). These structural relations and the factor loadings were not modified after adjustment for the exposure variable and covariates. Associations between behavioral latent variables at ages 2, 6 and 12 are provided in Table S7 and S8 in the Supplemental Material, respectively).

At age 2, externalizing behavior scores were slightly higher for children whose mothers declared occasional and regular occupational exposure to organic solvents exposure during pregnancy (mean change in standardized score respectively, 0.28 (95% CI = -0.01, 0.57) and 0.23 (95% CI = -0.05, 0.51)) compared to unexposed mothers (Table 4; Fig. 2). No association was observed between exposure and the internalizing behavior score at age 2.

At age 6, an association between occasional prenatal exposure and higher internalizing behavior appeared (0.37, 95% CI=0.06, 0.68); this was due mainly to marginal association, i.e. the direct effect (0.29, 95% CI=0.00, 0.58). Association between regular exposure and internalizing behavior was also positive, though weaker (Table 4; Fig. 2). No association was observed between prenatal exposure and externalizing behavior at age 6.

At age 12, externalizing behavior scores were slightly higher among children whose mothers declared being occasionally and regularly exposed to organic solvents during pregnancy, compared to those of non-exposed mothers (respectively, 0.20 (95% CI = -0.07, 0.48) and 0.19 (95% CI = -0.08, 0.45)), with evidence of a possible direct effect between exposure and behavior at 12 years of age (respectively, 0.16 (95% CI = -0.11, 0.43) and 0.20 (95% CI = -0.04, 0.45), Table 4; Fig. 2). A slight association between occasional prenatal exposure and internalizing behavior at age 12 was observed (0.27 (95% CI = -0.08, 0.62)) though without any evidence of direct effect. The indices of model quality were satisfactory (RMSEA=0.017, GFI=0.999, CFI=0.99, SRMR=0.03).

Table 3 Behavior scores at ages 2, 6 and 12 years (PELAGIE mother-child cohort, France, N=459)

Subscale	Total (*N*=459)	2 years (CBCL / PSBQ) median (Q1, Q3)			Total (*N*=459)	6 years (SDQ) median (Q1, Q3)			Total (*N*=459)	12 years (SDQ) median (Q1, Q3)		
		Girls (*N*=223)	Boys (*N*=236)	*p* value[a]		Girls (*N*=223)	Boys (*N*=236)	*p* value[a]		Girls (*N*=223)	Boys (*N*=236)	*p* value[a]
Emotion[b, c]	1 (0, 2)	1 (0, 2)	1 (1, 2)	0.7	2 (1, 3)	2 (1, 3)	2 (1, 4)	0.9	2 (1, 4)	3 (1, 4)	2 (1, 4)	0.1
Peer relationships[c]					1 (0, 2)	1 (0, 2)	1 (0, 2)	0.9	1 (0, 2)	1 (0, 2)	1 (0, 2)	0.2
Internalizing[b, d]	1 (0, 2)	1 (0, 2)	1 (1, 2)	0.7	3 (1, 5)	3 (1, 5)	3 (1, 5)	0.9	3 (2, 6)	3 (2, 5)	3 (1, 6)	0.6
Hyperactivity/inattention[c, e]	5 (3, 6)	4 (3, 6)	5 (3, 7)	0.02	2 (1, 4)	2 (0, 3)	3 (1, 5)	< 0.001	2 (0, 4)	1 (0, 3)	3 (1, 5)	< 0.001
Aggression[b]	1 (0, 3)	1 (0, 3)	1 (0, 3)	0.02								
Opposition[b]	3 (2, 3)	3 (2, 3)	3 (2, 4)	0.7								
Conduct[c]					2 (1, 3)	1 (1, 2)	2 (1, 3)	< 0.001	1 (0, 2)	1 (0, 2)	1 (0, 2)	0.005
Externalizing[d, f]	8 (6, 11)	8 (6, 11)	9 (6, 12)	0.03	4 (2, 6)	3 (2, 5)	5 (3, 7)	< 0.001	3 (1, 6)	2 (1, 4)	4 (2, 7)	< 0.001

CBCL: Child behavior checklist, PSBQ: Preschool Social Behavior Questionnaire, SDQ: Strengths and Difficulties Questionnaire

[a] *p* value of the Wilcoxon test comparing boys and girls; [b] CBCL/PSBQ: 3 items; [c] SDQ: 5 items; [d] SDQ: 10 items; [e] CBCL/PSBQ: 6 items; [f] CBCL/PSBQ: 12 items

The results for the model with factor loadings and covariances constrained to equality between boys and girls (Table 5) suggested that the associations between regular and occasional exposure to solvents during pregnancy and externalizing behavior was observed only at age 2 for boys, and at every time point for girls, with stronger magnitude at ages 6 and 12 (total pathway for occasional and regular exposure respectively: at age 2, 0.26 (95%CI= -0.16, 0.68) and 0.18 (95%CI= -0.25, 0.60), at age 6, 0.23 (95%CI= -0.21, 0.68) and 0.44 (95%CI=0.00, 0.88) and at age 12, 0.45 (95%CI= 0.06, 0.83) and 0.40 (95%CI= 0.03, 0.76)). Moreover, the association between occasional exposure to solvents during pregnancy and internalizing behavior was observed only among girls at age 6 (total pathway: for boys, 0.11 (95%CI= -0.27,0.49) and for girls, 0.56 (95%CI= 0.06, 1.06)), and was weak and similar at age 12 for both boys and girls.

Discussion

Our study aimed to assess the association between maternal occupational exposure to solvents during pregnancy, and child behavior throughout childhood (from 2 to 12 years). The results suggested a higher level of externalizing behavior at age 2 that was associated with both occasional and regular exposure to solvents during pregnancy. At ages 6 and 12, distinct patterns were observed for boys and girls. Among boys, this association disappeared, while among girls it was reinforced for both occasional and regular exposure. We observed a higher level of internalizing behavior in girls at age 6, associated with occasional exposure to solvents during pregnancy, for both direct and total (direct and indirect) pathways. At age 12, this was attenuated and seemed driven mostly by indirect pathways, suggesting a possible long-lasting impact of prenatal exposure to solvents on the child's internalizing behavior.

The fact that the association with externalizing behavior was not observed at ages 6 and 12 among boys may be explained by possible compensatory mechanisms and/or sociocultural experiences that may have reduced externalized behavioral disorders across childhood among boys specifically. Research on attention deficit hyperactivity disorder (ADHD) has until recently focused on boys and men [54]. Presentations in females are still underrepresented, and therefore less well-known. The list of symptoms associated with ADHD is biased toward male behaviors such as physical hyperactivity and risk-taking, whereas symptoms more associated with girls are excessive verbalization and subtle signs of impulsivity [54]. Girls are also less likely than boys to display disruptive behaviors, or at least, they do so later on – which delays detection of their disorder. Screening tools are mainly completed by parents and teachers, both of whom tend to systematically underreport symptoms presented

Table 4 Associations between occupational solvent exposure during pregnancy and child behavior at ages 2, 6 and 12 (PELAGIE mother-child cohort, France, $N=459$)

Behavior score	Self-reported exposure	N	2 years	6 years		12 years	
				Direct effect	Total (direct + indirect effect)	Direct effect	Total (direct + indirect effect)
			Stand.coeff. [a] (95%CI)	Stand.coeff. [a] (95%CI)	Stand.coeff. [a] (95%CI)	Stand.coeff. [a] (95%CI)	Stand.coeff. [a] (95%CI)
Internalizing	**None**	230	ref.	ref.	ref.	ref.	ref.
	Occasional	88	0.14 (-0.09, 0.36)	0.29 (0.00, 0.59)	0.37 (0.06, 0.68)	0.02 (-0.33, 0.36)	0.27 (-0.08, 0.62)
	Regular	141	0.16 (-0.06, 0.38)	0.07 (-0.21, 0.35)	0.15 (-0.14, 0.44)	0.03 (-0.26, 0.33)	0.14 (-0.17, 0.46)
Externalizing	**None**	230	ref.	ref.	ref.	ref.	ref.
	Occasional	88	0.28 (-0.01, 0.57)	-0.04 (-0.31, 0.24)	0.09 (-0.20, 0.38)	0.16 (-0.11, 0.43)	0.20 (-0.07, 0.48)
	Regular	141	0.23 (-0.05, 0.51)	-0.11 (-0.36, 0.15)	-0.01 (-0.28, 0.26)	0.20 (-0.04, 0.45)	0.19 (-0.08, 0.45)

95% CI, 95% Confidence Interval; SEM: structural equation model; SD: standard deviation

[a]SEM standardized regression coefficients, expressed in number of SD of the latent variable. Models were adjusted for child sex, maternal education level, maternal age, breastfeeding duration, smoking during pregnancy, parity, and mother-child interaction score. Fit indices: Chi Square = 122.885, df = 109, $p=0.17$; RMSEA = 0.034; GFI = 0.999; CFI = 0.990; SRMR = 0.030

Table 5 Associations between occupational solvent exposure during pregnancy and child behavior at ages 2, 6 and 12 for boys ($N=236$) and girls ($N=223$) (PELAGIE mother-child cohort, France)

Behavior score	Self-reported exposure	N	2 years	6 years		12 years	
				Direct effect	Total (direct + indirect) effect	Direct effect	Total (direct + indirect) effect
			Stand.coeff. [a] (95%CI)	Stand.coeff. [a] (95%CI)	Stand.coeff. [a] (95%CI)	Stand.coeff. [a] (95%CI)	Stand.coeff. [a] (95%CI)
				Boys			
Internalizing	**None**	121	ref.	ref.	ref.	ref.	ref.
	Occasional	37	0.06 (-0.26, 0.38)	0.05 (-0.34, 0.43)	0.11 (-0.27, 0.49)	0.19 (-0.27, 0.65)	0.26 (-0.22, 0.73)
	Regular	78	0.26 (-0.03, 0.56)	0.04 (-0.34, 0.42)	0.16 (-0.23, 0.54)	-0.05 (-0.43, 0.33)	0.05 (-0.36, 0.46)
Externalizing	**None**	121	ref.	ref.	ref.	ref.	ref.
	Occasional	37	0.31 (-0.09, 0.72)	-0.20 (-0.59, 0.19)	-0.05 (-0.45, 0.36)	0.04 (-0.38, 0.46)	-0.01 (-0.43, 0.41)
	Regular	78	0.28 (-0.09, 0.65)	-0.36 (-0.70, -0.03)	-0.22 (-0.56, 0.12)	0.29 (-0.07, 0.66)	0.08 (-0.31, 0.47)
				Girls			
Internalizing	**None**	109	ref.	ref.	ref.	ref.	ref.
	Occasional	51	0.21 (-0.09, 0.51)	0.47 (-0.01, 0.94)	0.56 (0.06, 1.06)	-0.11 (-0.63, 0.41)	0.29 (-0.21, 0.80)
	Regular	63	0.02 (-0.31, 0.36)	-0.07 (-0.52, 0.38)	-0.04 (-0.50, 0.41)	0.35 (-0.12, 0.83)	0.21 (-0.23, 0.65)
Externalizing	**None**	109	ref.	ref.	ref.	ref.	ref.
	Occasional	51	0.26 (-0.16, 0.68)	0.13 (-0.32, 0.58)	0.23 (-0.21, 0.68)	0.20 (-0.17, 0.56)	0.45 (0.06, 0.83)
	Regular	63	0.18 (-0.25, 0.60)	0.35 (-0.05, 0.74)	0.44 (0.00, 0.88)	0.20 (-0.18, 0.58)	0.40 (0.03, 0.76)

95% CI, 95% Confidence Interval; SEM: structural equation model; SD: standard deviation

[a]SEM standardized regression coefficients, expressed in number of SD of the latent variable

Factor loadings, covariances between latent variables and between subscales at subsequent time point were constrained to equality between boys and girls

Models were adjusted for maternal education level, maternal age, breastfeeding duration, smoking during pregnancy, parity, and mother-child interaction score. Fit indices: Chi Square = 205.525, df = 222, $p=0.78$; RMSEA = 0.035; GFI = 0.999; CFI = 1.0; SRMR = 0.039

by girls [55]. These differences in behavior measurement may have impacted the association between prenatal exposure and externalizing behavior.

The current study serves to extend previous findings from the PELAGIE mother-child cohort. The first study, conducted on the sample of the 1,278 mother-child pairs followed up at age 2, identified that children exposed prenatally presented with higher scores for attention deficit/hyperactivity and aggression at age 2 [24]. It identified an increase in scores for each level of occupational exposure (occasional and regular). The second study, conducted among the families at ages 2 and 6 (N=715), confirmed the earlier findings and also suggested a possible impact on behavior at age 6, though at a lower magnitude than at age 2 – and more pronounced among girls [25]. This second study also suggested an association between occasional exposure and internalizing behavior at age 6.

Few epidemiological studies have examined the association between maternal occupational exposure to organic solvents during pregnancy and child behavior. The earliest of these (1988) was performed in the USA on 82 mother-child pairs, and did not identify any association between occupational solvent exposure (measured by hygienist) and child behavior at age 4, assessed by the Conners Parent Hyperactivity Rating Scale or Childhood Personality Scale-Revised [17]. In this study, women were mostly lab-workers, artists or art teachers, and were mostly exposed to hydrocarbons (41.5%) and halogenated (31.7%) solvents. Two Canadian case-control studies were performed on 61 [18] and 64 [21] mother-child pairs respectively. For both, higher internalizing and externalizing behavior scores were suggested among children aged 3 to 9 whose mothers had been occupationally exposed to solvents [18, 21]. In the first Canadian study by Till et al. [18], child behavior was measured using the Child Behavior Checklist (CBCL), while the second, by Laslo-Baker et al., also used CBCL as well as Conner's Rating Scale-Revised and the Behavioral Style Questionnaire, completed by the mother [21]. None of these studies explored a possible sex-specific effect (perhaps because of limited sample sizes). In both studies, occupational exposure to solvents was assessed through mother interview by physicians. In the study by Till et al. [18], women were mostly lab (27%) or factory (18%) workers, or graphic designers (18%), and were mostly exposed to hydrocarbons (48%), halogenated (39%), alcohol (30%) or glycol (27%) solvents.

In our study sample, women reporting occasional occupational exposure were mostly teachers (25%) and those reporting regular exposure were mostly nurses, midwifes and x-ray technicians (27%). Cleaning products and detergents were most often cited as product categories (36.5% of women – 16.3% and 20.2% for occasional and regular use, respectively) followed by glues, mastics, resins and adhesives (19.2% −11.7% and 7.5% for occasional and regular use, respectively). This reflects exposure mainly to oxygenated solvents, an aspect in which we differ from the previous studies cited above [18, 21].

In our study, child behavior assessment at age 2 was performed using a hybrid questionnaire adapted from two different scales (CBCL and PSBQ) used in several Canadian studies [56, 57]. While internal consistency measured using Cronbach's alpha was fairly satisfactory for the hyperactivity / inattention and aggression subscales in our study, this was much less true of other subscales – especially the 'emotionality' subscale, built on just three items. This lack of consistency might have prevented us from identifying associations between prenatal exposure and internalizing behavior at age 2.

The fact that exposure was self-reported in our study is a limitation. Even though we asked about types of products rather than chemical names as a way of increasing the response rate [58–60], our assessment collected only frequency (occasional or regular) of exposure, neglecting intensity. No information was available on working conditions (e.g. whether space was ventilated) or individual behavior (e.g. protection equipment) related to the use of these products, even though such parameters could mitigate intensity of exposure. All this information as well as the brand names of products used are however not always known by the workers. To improve the self-reported occupational exposure assessment, adding some of this information might be appropriate for future research; however, when using self-reported questionnaires, excessive length and complexity should be avoided.

The way women reported their frequency of exposure might also vary across jobs, as well as across individuals [61]. For instance, we might suspect that the most anxious individuals may have overestimated their exposure frequency. And we cannot rule out the possibility that this could go some way to explaining the association observed between occupational prenatal exposure and higher internalizing behavior scores at 6 years – while this is not observed for regular exposure. One biomonitoring study is however noteworthy: performed on a subsample selected randomly (N=451) within the PELAGIE mother-child cohort, it reported statistically significant associations between the presence of some metabolites of glycol ethers (oxygenated solvents) and chlorinated solvents in maternal urine samples collected at inclusion, and the concomitant self-reported occupational use of products containing solvents [62]. In this study, women who declared regular exposure at work had significantly higher detection rate in urine samples or higher urinary concentrations, compared with unexposed women: for detection of ethoxyethoxyacetic acid (EEAA), $OR_{occasional\ exposure}$=1.16 (0.5–2.5), $OR_{regular\ exposure}$=2.12 (1.2–3.8)); for detection of ethoxyacetic acid (EAA), $OR_{occasional\ exposure}$=1.41 (0.3–5.8), $OR_{regular\ exposure}$=4.20 (1.5–11.4); for concentration of butoxyacetic acid (BAA), $\beta_{occasional\ exposure}$=-0.04 ($p$-value=0.56), $\beta_{regular\ exposure}$=0.14 ($p$-value=0.01); for detection of trichloroethanol (TCOH), $OR_{occasional\ exposure}$=0.35 (0.0-2.8), $OR_{regular\ exposure}$=2.82 (1.1–7.2) [62]. In addition, when looking at associations between these urinary monitoring data and the occupational use of the same 11 groups of products as in the present study, detection of EEAA in the urine of women was associated with the occupational exposure to multiple groups of products: paints (OR=2.7 [1.2, 6.4]), strippers (OR=4.1 [1.5, 11.4]), dyes or inks (OR=2.9 [1.3, 6.4]), cleaning agents (OR=2.2 [1.2, 4.1]) and cosmetics (OR=4.4 [1.8, 10.7]). Urinary detection rates of EAA and TCOH were associated with regular occupational exposure to cleaning agents (respectively, OR=3.3 [1.2, 8.5], OR=3.7 [1.5, 9.0]). Urinary concentrations of BAA were associated with occupational exposure to cleaning agents (β=0.12, p=0.04), and to cosmetics (β=0.21, p=0.04). According to the authors, all these associations were consistent with knowledge of glycol ethers and chlorinated solvents in composition of products likely to be used in occupations in France [62]. This suggests that the self-reported exposure assessment was of good quality and that biomonitoring study on a subsample might be encouraged for future research.

Concerning the temporal issue, the exposure assessment was conducted at the beginning of pregnancy – and women did mention at the 2-year follow-up that they had not changed occupation or activities during pregnancy. We thus believe that our assessment is likely to represent exposure during the whole pregnancy – at least up until the women went on maternity leave. Lastly, products containing solvents are likely to contain other chemicals suspected of developmental toxicity. The way our exposure categories were defined may include many job types, and thus a wide variety of chemicals to which women are exposed. Nevertheless, exposure to organic solvents remains the common factor; we cannot however rule out the possibility that the jobs accounting for the highest proportion in each exposure category may also have other chemical exposures in common that could account for the association we found. Non-occupational exposure to organic solvents is likely to occur at home as solvents are widely present in products used for cleaning, cosmetics or leisure activities such as painting. We had no sufficient data to assess the possible link between occupational and non-occupational exposures and were, therefore, unable to assess their relative contribution in the observed association of the present study.

The population sample of the present study is clearly selected towards a higher maternal age and a higher maternal level of education compared to the original cohort. To control for a potential selection bias, it is recommend to adjust models for the main determinants of participation (Rothman, Greenland, et Lash 2008; Greene et al. 2011), which was the case in our study. It is worth noting that at enrollment in the cohort, women were already more educated than the general population. Conclusion of these findings may, then, primarily be more relevant to highly educated populations. Finally, because the education level of our study population is both high and fairly homogenous, confounding linked to socioeconomic status is unlikely to occur.

Conclusion

In conclusion, occupational exposure to solvents during pregnancy could impact externalizing and internalizing behavior in children from infancy to early adolescence, via either direct or mediated effects during childhood. These effects may persist until early adolescence, especially for girls. These findings are in accordance with the sparse literature available on younger children. Further studies, using biomarkers of exposure to solvents, and/or considering older children and adolescents, are needed to confirm those results.

Supplementary Information

The online version contains supplementary material available at https://doi.org/10.1186/s12940-024-01120-z.

Supplementary Material 1

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Author contributions

HT, NC, DSA, CC: Conceptualization. HT, NC, CM, RB: Data curation. HT, NC: Formal analysis. HT, DSA, CC: Writing - original draft. CM, RB, RG, FR: Investigation. SC, DSA, CC: Supervision. All authors reviewed and approved the final manuscript.

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Data availability

Availability of data and materials: The PELAGIE cohort data comply with European regulation on the protection of personal data (25/05/2018). This regulation is based on a logic of compliance and increased responsibility of actors accessing the data. In addition, the cohort study complies with the French "Informatique et liberté" law (Law No. 78-17, January 1978, 2018). Access to data is thus possible with the agreement of the cohort principal investigators (Cécile Chevrier, Charline Warembourg) and on condition that the actors demonstrate respect for these European and French principles of personal data protection, to strengthen the rights of individuals. Further inquiries can be directed to the corresponding author.

Declarations

Ethics approval and consent to participate

Individuals participating in this study provided their written informed consent. The Advisory Committee on Information Processing in Health Research (CCTIRS 2015: No. 15.326bis), the Committee for the Protection of Persons (CPP 2015: No. 15/23–985) and the French data protection authority (CNIL 2002 and 2007: No. 902076, 2015: No. 915420) approved this study.

Consent for publication
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Competing interests
The authors declare no competing interests.

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