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MATERNAL OCCUPATIONAL EXPOSURE TO ORGANIC SOLVENTS AND INTRAUTERINE GROWTH IN THE ELFE COHORT

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Highlights:

- Petroleum and oxygenated solvents were associated with a higher risk of SGA.
- Oxygenated and chlorinated solvents were linked to a smaller head circumference.
- Third trimester solvent exposure seemed to affect fetal growth most.

ABSTRACT

Background: In developed countries, about 15% of women are occupationally exposed to solvents. Associations between this maternal occupational exposure and intrauterine fetal growth are inconsistent, but almost no existing study has investigated this relation by solvent family (oxygenated, petroleum, and chlorinated), although they may affect fetal growth differently.

Objectives: To investigate the relations between maternal occupational solvent exposure, by solvent family, and the risk of neonates born small for gestational age (SGA), or with low birthweight, or with small head circumference (HC).

Methods: Among the 18,040 women included in the Elfe birth cohort, we included 13026 women who worked during pregnancy (72% of the cohort). Information about maternal occupations and industrial activities during pregnancy was collected by questionnaire at the maternity ward, and completed at 2-month when necessary. Using Matg  n   job-exposure matrices, we assessed maternal occupational exposure to solvents. Logistic and multiple linear regressions were used to assess the association between maternal occupational solvent exposure and SGA status, birth weight, and HC. Analyses were conducted for exposure during pregnancy and also stratified by the trimester that pregnancy leave began.

Results: We observed a higher risk of SGA newborns among mothers occupationally exposed during pregnancy to petroleum solvents ($OR_{adjusted} = 1.26$; 95%CI: 1.01 to 1.57). Among women working until the third trimester of pregnancy, we observed a higher risk of SGA newborns to those occupationally exposed to oxygenated solvents ($OR_{adjusted} = 1.75$; 95%CI: 1.11 to 2.75), a significantly lower birthweight for infants of mothers exposed to petroleum solvents ($\beta_{adjusted} = -47.37$ g; -89.33 to -5.42), and a lower HC among newborns of those occupationally exposed to oxygenated solvents ($\beta_{adjusted} = -0.28$; -0.49 to -0.07) and to chlorinated solvents ($\beta_{adjusted} = -0.29$; -0.53 to -0.05).

Discussion: Our results suggest that maternal occupational solvent exposure may influence fetal growth, especially exposure into the third trimester of pregnancy.

Keywords: fetal growth retardation, head circumference, solvents, occupational exposure, pregnancy

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1. INTRODUCTION

In developed countries, most women work during pregnancy (Casas et al., 2015; “Enquête nationale périnatale,” 2016; “Maternity Leave and Employment Patterns of First-Time Mothers: 1961-2008,” 2011). For example in France, 70.8% of women included in the 2016 French perinatal survey did (“Enquête nationale périnatale,” 2016), as well as 65.6% of those included in the 2008 Panel of the U.S. Census Bureau’s Survey of Income and Program Participation (“Maternity Leave and Employment Patterns of First-Time Mothers: 1961-2008”). During the first decade of this century, 14.7% of women workers were occupationally exposed to solvents (Pilorget et al., 2017), defined as liquids with the property of dissolving, diluting, or extracting other substances without causing chemical modification of either those substances or themselves. These chemicals are present in a wide range of products, such as adhesives, paints, dyes, inks, cleaning products, and cosmetics. Solvents are classified into 3 major chemical families: oxygenated solvents (e.g., alcohols, esters, and ketones), petroleum solvents (e.g., benzene, aliphatic solvents, and aromatic solvents), and chlorinated solvents (e.g., perchloroethylene and trichloroethylene). Many of these can cross the placental barrier (Donald et al., 1991; Elkin et al., 2020; Loch-Caruso et al., 2019; Ungváry and Tátrai, 1985).

Small for gestational age (SGA) newborns are an important public health concern, because they are at higher risk of various immediate-, mid-, and long-term postnatal complications, including metabolic, immune, neurologic, respiratory, and endocrine adverse outcomes (Kesavan and Devaskar, 2019; Mayer and Joseph, 2013). The relation of maternal occupational solvent exposure to SGA status has thus far been explored in 6 studies (Ahmed and Jaakkola, 2007; Lipscomb et al., 1991; Desrosiers et al., 2015; Seidler et al., 1999; Shirangi et al., 2020; Zhu et al., 2006) and that to birthweight in 10 studies (Ish et al., 2022; Desrosiers et al., 2015; Burdorf et al., 2011; Snijder et al., 2012; Ahmed and Jaakkola, 2007; Ronda et al., 2010; Axelsson et al., 1984; Khattak et al., 1999; Ha et al., 2002; Vaktskjold et al., 2014). Two of these studies reported a significantly higher risk of SGA status (Ahmed and Jaakkola, 2007; Lipscomb et al., 1991), and three observed a significantly lower birth weight (Khattak et al., 1999; Vaktskjold et al., 2014; Ha et al., 2002), but the others did not report significant associations. Among the reasons that may explain these inconsistent results, we note the lack of power in some studies, their different assessment methods (job-exposure matrices, expertise, or self-report), and the heterogeneous definitions of solvents in most studies, without any investigation of these potential associations by solvent family, although these families may have different effects on fetal growth. Accordingly, among the 10 studies that investigated the impact of maternal occupational exposure to solvents in the general population (Ahmed and Jaakkola, 2007; Burdorf et al., 2011; Ish et al., 2022; Khattak et al., 1999; Seidler et al., 1999; Shirangi et al., 2020; Snijder et al., 2012; Vaktskjold et al., 2014; Zhu et al., 2006; Desrosiers et al., 2015), nine explored the relation with solvents as a single group. Only the study by Desrosiers et al. investigated these relations separately

for petroleum and chlorinated solvents (Desrosiers et al., 2015). It found a higher — but not statistically significant — risk of SGA status. Unfortunately, this study did not consider oxygenated solvents, although it is the most frequent family (Pilorget et al., 2017).

In addition to SGA status and birthweight, measurement of head circumference (HC) at birth is another fetal growth parameter of particular interest as it is regularly used as a proxy for brain volume and intrauterine brain development (Barbier et al., 2013). In addition, several publications have shown positive associations between HC and cognitive function, long-term memory storage and retrieval, and visuospatial ability (Gale et al., 2006; Veena et al., 2010). To the best of our knowledge, only one study (Snijder et al., 2012) has investigated the relation between HC and maternal occupational exposure to solvents; it did not distinguish solvent families and did not report any associations.

While pregnant women remain frequently exposed to organic solvents at work, the question concerning their impact on fetal growth is still debated, especially in view of the lack of data by solvent family, as these different families may have different effects. Using data from a large sample of newborns from the French ELFE cohort, we aimed to assess the influence of occupational exposure to oxygenated, petroleum, and chlorinated solvents on SGA status, birthweight, and HC.

2. MATERIALS AND METHODS

2.1 Study design

ELFE (*“Etude Longitudinale Française depuis l’Enfance”*) is a French nationwide birth cohort intended to explore the influence of environmental and socioeconomic contexts on children's health and development from birth to the age of 20 years. The ELFE cohort has previously been described in detail (Charles et al., 2019).

Overall, 349 maternity departments were randomly selected among the 544 with more than one delivery per day in mainland France, and 320 of these agreed to participate in recruiting the ELFE cohort. Women aged 18 years or older who gave birth to liveborn singletons or twins after 33 weeks of gestation were included in the study. Four inclusion periods occurred in 2011: April 1–4, June 27–July 4, September 27–October 4, and November 28–December 5. Written informed consent was required to participate, and women had to state that they did not plan to leave mainland France for the next three years. Overall, 51% (18,040 women with 18,329 newborns) agreed to participate in the cohort during their stay in the maternity ward. Because 55 families subsequently requested the destruction of their data, 18,274 children were finally included in the ELFE cohort follow-up.

The population of this study excludes multiple pregnancies (n=287 twin pregnancies/574 children), major malformations as defined by the European surveillance of congenital anomalies (*“European Platform on Rare Disease Registration,”* 2014) (n=303 children), and mothers who did not work during their pregnancies (n=4159 women). The study thus finally includes 13,238 mother-child pairs (Figure 1).

2.2 Data collection

During the maternity unit stay, trained midwives collected participants' sociodemographic, socioeconomic, and medical characteristics in face-to-face interviews and data about their pregnancies, deliveries, and medical histories from their medical records. Two months after childbirth, parents were asked to complete an email questionnaire about social and medical data. More details are available at: <https://www.elfe-france.fr/en> and <https://pandora.vjf.inserm.fr/public/index.php>.

Each data collection received the necessary approvals from the French Consultative Committee for the Treatment of Information in Medical Research (n°10.623), the French National Commission for the Confidentiality of Computerized Data (n°910504), and the Committee for the Protection of Persons Participating in Biomedical Research (n°CPP-IDF IX-11-024).

2.3 Maternal occupational exposure to solvents

Information about maternal occupations and industrial activities was initially collected at the maternity ward and completed with the 2-month questionnaire when necessary. One single expert was in charge of occupational coding for all women, according the job title and the industry but also using tasks descriptions and type of contract (self-employment, employees...). The coding was made blind to the maternal and child health status, using standardized procedures (hierarchization of information used for coding and validation of homogeneity of coding with occupation and industrial activity) to limit classification bias. Maternal occupations were coded according to the International Standard Classification of Occupations from 1968 (ISCO 1968) (ISCO-International Standard Classification of Occupations, 1968) and the French classification of professions and socioprofessional categories from 1994 (French PCS 1994) ("Nomenclatures des professions et catégories socioprofessionnelles | Insee," 1994). Industry activities were coded with the International Standard Industrial Classification of All Economic Activities from 1975 (ISIC 1975 classification) ("International Standard Industrial Classification of All Economic Activities," 1975) and the French classification of economic activities from 2003 (French NAF 2003) (INSEE, 2003). French National Public Health Agency (*Santé Publique France*) conducted the Matgéné project, resulting in developing three job-exposure matrices (JEMs), focusing respectively on oxygenated, petroleum, and chlorinated solvents (Févote et al., 2011). These JEMs also assessed exposures to subgroups of solvents within each family: alcohols, ketones and esters, ethylene glycol, diethyl ether and tetrahydrofuran for oxygenated solvents; benzene, fuel oil, industrial spirit, kerosene (lighting oil), diesel and fuel oils, white spirit and other light aromatic cuts for petroleum solvents; chloroform, methylene chloride, perchloroethylene, trichloroethylene; and 1,1,1-trichloroethane for chlorinated solvents. Exposures to each family or subgroup of were defined by a probability (per class of 10% for oxygenated and chlorinated solvents; 0%, 10%, 50%, 90%, and 100% for petroleum solvents) and level of exposure (very low, low, moderate, and high for oxygenated and chlorinated solvents; low, moderate, and high for petroleum solvents). These parameters are presented in the supplemental materials (Table S1).

Due to missing or imprecise data about maternal occupation or industrial activities, exposure assessment could not be performed for 212 women; 13,026 mothers had complete assessments. When mothers reported multiple jobs during pregnancy (n=15), we consider only the job with the highest level of exposure.

Before starting the main analysis, we recoded maternal occupational exposure to solvents according to the distribution of the exposure probability of each solvent family in our study population. Maternal occupational exposure to oxygenated solvents was classified according to probability of exposure: not exposed, likely exposed (probability below 90%) and certainly exposed (probability >90%). For women certainly exposed, we differentiated those exposed at a very low level from those exposed at

least at a low level of intensity. The small numbers of combinations for maternal occupational exposures to petroleum and chlorinated solvents led us to group the JEM exposure assessments in two categories: not exposed and possibly exposed (any probability, any level) (Tables S2-S4).

2.4 Anthropometric parameters and small-for-gestational-age assessment

Birthweight and head circumference at birth were recorded in the medical files. SGA was defined as a birthweight under the 10th percentile for gestational age and sex in France, by using the EPOPé charts (Ego et al., 2016). Among the 13,026 children for whom occupational exposure was assessed, SGA status was assessed for 12,676 (97.3%), while 12,756 newborns had information available for birthweight (97.9%) and 11,676 for head circumference (89.6%) (Figure 1).

2.5 Statistical analysis

We reviewed the relevant literature to develop a directed acyclic graph (DAG) (Shrier and Platt, 2008), which was used to determine the minimally sufficient adjustment sets of variables for regression models to prevent for confounding and estimate the total effects of the studied exposure on the outcome (Figure S1). Based on this DAG, our models were systematically adjusted for maternal education level (primary and secondary education, passing baccalaureate, university level), smoking status (nonsmoker, stopped smoking during pregnancy, smoker), alcohol consumption during pregnancy (no, yes), and maternal body mass index ($BMI < 18.5 \text{ kg/m}^2$, $18.5 \text{ kg/m}^2 \leq BMI < 25 \text{ kg/m}^2$, $25 \text{ kg/m}^2 \leq BMI < 30 \text{ kg/m}^2$, $BMI \geq 30 \text{ kg/m}^2$). Statistical models for birthweight and head circumference were additionally adjusted for gestational age (in weeks of gestation; linear and quadratic form) and the newborn's sex.

Due to the small numbers of missing values for covariables, we imputed missing values by the mode: maternal education level (baccalaureate; $n=43$, 0.3%), smoking status (nonsmoker; $n=141$, 1.1%), alcohol consumption during pregnancy (none; $n=60$, 0.5%), and maternal body mass index ($18.5 \text{ kg/m}^2 \leq BMI < 25 \text{ kg/m}^2$; $n=179$, 1.4%).

We first studied the relation between each outcome and each maternal occupational exposure to each solvent family (oxygenated, petroleum, and chlorinated solvents) individually. In addition, if several exposures were significantly associated with the same outcome, mutual adjustments were performed in a subsequent analysis. We also performed analyses stratified by when mothers stopped working: in the first, second, or third trimester of pregnancy.

We used logistic regression to study associations with SGA status and multiple linear regression to study association with birthweight and HC. Results are presented as odds ratios (ORs) and beta coefficients with their 95% confidence intervals (95% CI).

Three sensitivity analyses were performed to test the robustness of our results: 1) we changed the threshold for considering women to be certainly exposed to oxygenated solvents (probability of exposure above 50% rather than the 90% applied in the main analyses); 2) we aggregated women certainly exposed to oxygenated solvents at very low level and at a low level; and 3) we further adjusted the models studying HC for mode of delivery.

A p -value <0.05 was defined as statistically significant. SAS 9.4 and R version 3.6.2 were used for statistical analyses.

3. RESULTS

3.1 Population characteristics

Table 1 describes the study population. The participants' mean age was 31 ± 5.0 years. Almost two-thirds of them had attended at least some university (65.6%), 16.9% were overweight, and 8.2% obese; 16.9% smoked, and 19.6% had drunk alcohol during their pregnancy. Boys accounted for 51% of the newborns. On average, children were born at 39 weeks of gestation, weighed $3340 \text{ g} \pm 469 \text{ g}$ and had a HC of $34.4 \text{ cm} \pm 1.4 \text{ cm}$ at birth. Overall, 9.7% of newborns were SGA and 4% preterm. Half the women stopped working during their third trimester of pregnancy ($n=6968$, 52.6%), 28.9% ($n=3825$) during the second trimester, and 8.1% ($n=1071$) during the first. This information was unavailable for 10.4% of our population ($n=1374$).

3.2 Maternal occupational exposure to solvents

The mothers of children included in this analysis were employed mainly as clerical ($n=3141$; 24.1%), service ($n=2203$; 16.9%), and sales ($n=1439$; 11.0%) workers, as well as teachers ($n=1426$; 10.9%) (Table 2).

In all, 885 (6.9%) of the women included in this analysis were likely and 2037 (15.8%) certainly occupationally exposed during pregnancy to oxygenated solvents (Table 2). Among the certainly exposed women, 1785 (13.8% of those included in this analysis) were exposed at a very low level and 252 (2.0%) at least at a low level (Table S2). Mothers occupationally likely exposed to oxygenated solvents were mainly cleaners and helpers (70.0%) (Table 2). Those certainly exposed at a very low level were primarily health-related professionals (91.3%) and hairdressers (8.6%), and those certainly exposed to at least a low level were chemists (49.6%) and hairdressers (32.9%) (Table 2). Alcohols were the most frequent subclass of oxygenated solvents in our study (6.3% of women were classified as likely exposed and 14.9% as certainly exposed), ahead of diethyl ether (13.4% as likely exposed, and none as certainly exposed), and ketones and esters (1.5% likely exposed and 1.3% certainly exposed) (Table S5).

For petroleum solvents, 861 women were classified as possibly occupationally exposed (6.7%), mainly at a low or very low level ($n=858$, 6.6%) (Table S4). Jobs mainly classified as possibly exposed to petroleum solvents were cleaners (60.2%) and chemists (17.7%). White spirit was the most frequent petroleum solvent exposure in our study (5.9% of the women were classified as possibly exposed) followed by special essence (1.6%) (Table S5).

Regarding chlorinated solvents, 190 women (1.5%) were classified as possibly occupationally exposed, at a low or very low level (Table S4). Mothers possibly occupationally exposed to chlorinated solvents were mostly chemists (83.2%) (Table 2). The most frequent chlorinated solvent

exposures involved dichloromethane and trichloromethane (1.3% of women for both chemicals) (Table S5).

3.3 Maternal occupational solvent exposure and intrauterine fetal growth

We observed a nonsignificantly higher risk of SGA status among children of mothers likely exposed to oxygenated solvents ($OR_{adjusted} = 1.24$; 0.99 to 1.55) but not for children of mothers who were certainly exposed (certainly exposed at a very low level: $OR_{adjusted} = 1.01$; 0.85 to 1.20; certainly exposed at least at a low level: $OR_{adjusted} = 1.28$; 0.86 to 1.90) (Table 3). The risk of an SGA newborn was statistically significantly higher among mothers who were occupationally exposed to petroleum solvents ($OR_{adjusted} = 1.26$; 1.01 to 1.57), but the association was not statistically significant for maternal exposure to chlorinated solvents ($OR_{adjusted} = 1.31$; 0.83 to 2.06) (Table 3). A significant excess risk for a SAG newborn appeared for women certainly exposed at least at a low level to oxygenated solvents who worked into the third trimester ($OR_{adjusted} = 1.75$; 1.11 to 2.75) (Table 4). The estimates for exposure to petroleum solvents, although not significant, were in the same range as for the main analyses when stratifying for trimester of starting maternity leave (during the first or second trimester: $OR_{adjusted} = 1.34$; 0.96 to 1.89; third trimester: $OR_{adjusted} = 1.20$; 0.85 to 1.72) (Table 4).

No statistically significant associations were observed between maternal occupational exposure to oxygenated, petroleum, or chlorinated solvents and birthweight as a continuous variable (Table 3). When trimester of maternal leave during pregnancy was considered, birthweight was significantly lower in the children of mother exposed to petroleum solvents who worked into the third trimester ($\beta_{adjusted} = -47.37g$; -89.33 to -5.42) (Table 4).

HC was lower among children of mothers certainly exposed to at least a low level of oxygenated solvents ($\beta_{adjusted} = -0.27$; -0.44 to -0.10) (Table 3) or exposed to chlorinated solvents ($\beta_{adjusted} = -0.25$; -0.44 to -0.06) (Table 3). The association between petroleum solvents and HC was not statistically significant ($\beta_{adjusted} = -0.05$; -0.15 to 0.04) (Table 3). After mutual adjustment for exposure to oxygenated and chlorinated solvents, oxygenated solvent exposure to at least a low level remained statistically significant ($\beta_{adjusted} = -0.25$; -0.47 to -0.03), but chlorinated solvent exposure was not ($\beta_{adjusted} = -0.07$; -0.32 to 0.18) (Table 5). HC was lower among the children of mothers certainly exposed to at least a low level of oxygenated solvents ($\beta_{adjusted} = -0.28$; -0.49 to -0.07) or exposed to chlorinated solvents ($\beta_{adjusted} = -0.29$; -0.53 to -0.05) for those mothers who worked into the third trimester (Table 4). These associations were not observed, however, when women stopped working during the first or second trimester of pregnancy (certainly exposed to oxygenated solvents at least at a low level: $\beta_{adjusted} = -0.16$; -0.50 to 0.18; exposure to chlorinated solvents: $\beta_{adjusted} = -0.19$; -0.55 to 0.17) (Table 4).

Sensitivity analyses

Results about SGA status and HC remained similar when we used a probability of exposure of 50% as the threshold for defining mothers certainly exposed to oxygenated solvents (Table S6).

We observed no statistically significant associations when children of mothers certainly exposed to oxygenated solvents were aggregated in the same group, regardless of the intensity of exposure (Table S7).

Additional adjustment for the mode of delivery did not change the associations between occupational exposure to oxygenated and chlorinated solvents, and HC at birth (Table S8).

4. DISCUSSION

We report an increased risk of SGA newborn among mothers occupationally exposed during pregnancy to petroleum solvents, as well as among women who were occupationally exposed to oxygenated solvents at least at a low level and who worked into their third trimester of pregnancy. For birthweight as a continuous variable, a significantly lower birthweight was observed only for infants of mothers still working during the third trimester and exposed to petroleum solvents; no risk was observed for other solvents or other time periods. Finally, HC was lower among the children of mothers occupationally exposed to oxygenated or chlorinated solvents, especially those working into their third trimester. Our results remained stable in sensitivity analyses.

Our search found only one study that previously investigated the relation between maternal occupational exposure by solvent families and the risk of SGA status. Desrosiers et al. analyzed data from 2886 mothers and their infants born between 1997 and 2002 in the USA. In this study, industrial hygienists assessed the probabilities of exposure to ten organic solvents: six chlorinated, three aromatic and the petroleum-based mixture Stoddard solvents (also known as mineral spirits or white spirits), and SGA was defined as in our study as birthweight below the 10th centile for a given gestational age at delivery. They found a higher but not statistically significant risk of an SGA neonate when mothers were occupationally exposed to any solvents (OR=1.71; 95%CI: 0.86-3.40), chlorinated solvents (OR=1.70; 95%CI: 0.69-4.01), and aromatic solvents (OR=1.87; 95%CI: 0.78-4.50) but not with Stoddard solvent (OR=0.98; 95%CI: 0.44-2.18) (Desrosiers et al., 2015). This absence of statistical significance might be due to a lack of power (only 23 women (10.1%) with an SGA newborn were exposed to any solvent, 18 (7.9%) to chlorinated solvents, and 7 (3.1%) to aromatic solvents). These studies are partially consistent with our results for aromatic solvents but not for Stoddard solvents, which were the most frequent subclass of petroleum solvent in our study. In addition, Desrosiers et al. did not examine either occupational exposure to oxygenated solvents or the influence of the trimester when pregnancy leave began.

We also highlighted lower birthweight in the newborns of women exposed to petroleum solvents into the third trimester, in line with the study by Ha et al. (Ha et al., 2002). They investigated the association between birthweight and maternal and paternal exposure to organic solvents in 1222 couples employed in a large petrochemical corporation in Beijing, China (Ha et al., 2002). In this study, a trained interviewer assessed parental exposures to organic solvents considering only four petroleum solvents in their definition of organic solvents (benzene, toluene, xylene, and styrene). The authors concluded that maternal exposure to organic solvents is significantly associated with a lower birthweight (-81.7g, 95%CI: -106.3 to -3.1) (Ha et al., 2002).

Only one previous epidemiological study investigated the relation between maternal occupational exposure to solvents and newborn HC (Snijder et al., 2012), analyzing data from 4680 pregnant women participating in the Generation R cohort study from early pregnancy onwards in the Netherlands (2002–2006) (Snijder et al., 2012). Using the JEM developed by Brouwers et al. (Brouwers et al., 2009), Snijder et al. estimated maternal occupational exposure to potential endocrine-disrupting chemicals that included an organic solvent category based on exposure to 6 organic solvents (ethylene glycol ethers, styrene, toluene, xylene, trichloroethylene, and perchloroethylene) but not on most oxygenated and chlorinated solvents. They observed no significant reduction in HC when mothers were exposed to organic solvents (221 pregnant women (4.7%) exposed, β_{adjusted} : -0.00902, standard error: 0.00560, with the p -value and 95%CI not provided). No study has focused on a broader definition of organic solvents including oxygenated solvents, although it is the most frequent solvent family involved in occupational exposure (Garlantézec et al., 2012).

Our results about the impact of oxygenated and petroleum solvents on fetal growth are also consistent with animal studies that have reported associations with several alcohols (ethanol, methanol, propanol, glycol, etc.) (Nelson et al., 1990) and with white spirit (Carrillo et al., 2014), which respectively accounted for the vast majority of oxygenated and petroleum solvent exposures in our study. We think that these solvents might be deleterious at three different levels — at the maternal, placental, or directly at the fetal level, since many solvents can cross the placental barrier (Donald et al., 1991; Elkin et al., 2020; Loch-Caruso et al., 2019; Ungváry and Tátrai, 1985). We have found no evidence that the different solvent families use common mechanisms; we have thus considered these exposures separately. The underlying mechanisms have rarely been investigated except for that of ethanol, which accounts for half of the oxygenated solvents used in France (INRS, 2009). Nelson summarized 13 alcohols administered by inhalation to rats (Nelson et al., 1990), whereas other studies about fetal consequences of alcohol used ingestion models that correspond to the most common nonoccupational maternal exposure during pregnancy. Thus, ethanol ingestion has been reported to affect maternal levels of iron and zinc, creating maternal deficiencies (Naik et al., 2022) that can result in fetal growth restriction by reducing levels of insulin-like growth factor-1 and its receptor activity (Naik et al., 2022). It also affects placental stress response (Gårdebjer et al., 2014) and disrupts trophoblast angiogenic factors (Gualdoni et al., 2021). Trichloroethylene ingestion (chlorinated solvent), on the other hand, increases placental oxidative stress markers in a rat model of fetal growth restriction (Loch-Caruso et al., 2019).

The effects observed with reduced HC are also in accordance with what is known of the neurotoxicity of several alcohols (Nelson et al., 1990) and trichloromethane (Agency for Toxic Substances and Disease Registry, 1997). The effects observed in our study were broader for exposures lasting into the third trimester. In humans, intrauterine fetal growth is quite slow until the 23rd week of gestation, and

then accelerates before peaking around the 34th week (Lepercq and Boileau, 2005). We can thus hypothesize that impairments during the period of fetal growth might have a greater impact on anthropometric parameters at birth. Solvent exposure in late gestation has been shown to cause greater effects in animal studies (Donald et al., 1991).

We used data from a large birth cohort ($n=13,026$ women) with detailed information about a wide range of personal and medical characteristics that allowed us to control for various potential confounders (Charles et al., 2019). Including only women who worked during their pregnancy enabled us to avoid bias from the “healthy worker effect,” since women who were not working might have a higher rate of adverse pregnancy outcomes (Casas et al., 2015). However, we have no data on possible sick leave during pregnancy (we only have the beginning of the maternity leave). Nonetheless, the population selection strategies might have led to some limitations. In particular, the ELFE cohort only included women who gave birth after 33 weeks of gestation, which might have resulted in excluding some premature newborns with severe SGA.

The JEMs we used to assess solvent exposure were developed for the general population in France by the French Institute for Public Health Surveillance during the same period as the ELFE pregnancies (Févotte et al., 2011). Exposure misclassification is likely when using JEMs (Vaktskjold et al., 2014). Most authors investigating the properties of generic JEMs have emphasized that they could plausibly underestimate variability in exposures, since the same probability and levels of exposure are allocated for a given combination (occupation and industrial sector) without considering between-worker variability (for specific tasks, material use, work environments, period or use of different protection devices) (Fritschi, 2019; Ge et al., 2018; Teschke et al., 2002). By assigning the mean exposure level to the whole group, JEMs induce Berkson-type misclassification error, which tends to reduce study power, but leads to little or no bias in the estimators of logistic or linear regression coefficients (Armstrong, 1998).

Another limitation is that the low number of women classified as exposed to petroleum and chlorinated solvents in our study were not sufficient to benefit from the fine level of exposure probability and intensity available in the JEMs. Grouping together various types, probabilities, and intensities of exposure might have diluted possible associations (Teschke et al., 2002). Finally, we could not rule out the possibility that associations observed in our study might be markers of association with other co-exposures that we did not evaluate rather than the direct effect of solvents.

Among our neonatal outcomes, we defined SGA with the French EPOPé unadjusted intrauterine fetal growth charts, developed from the 2010 French Perinatal Survey (FPS). An alternative would have been to use customized charts that include in addition maternal characteristics (height, weight, parity)

associated with fetal weight that better consider each infant's intrinsic growth potential (Mamelle et al., 2006). However, these main variables were included in our adjustment strategy. Another key point in studying fetal growth is to date the pregnancy accurately. The American College of Obstetricians and Gynecologists, the American Institute of Ultrasound in Medicine, the Society for Maternal–Fetal Medicine and the French College of Fetal Echography recommend the use of the craniocaudal length measurement performed during the usual first trimester screening ultrasound (“Collège Français d’Échographie Fœtale,” 2022; The American College of Obstetricians and Gynecologists, 2014), as performed in ELFE cohort. But the inaccuracy of this method is ± 5 -7 days (Obstetrics & Gynecology, 2017). Estimates based on menstrual dates are two to three days higher, on average, than those based on early ultrasound, a difference usually attributed to late ovulation (Morin et al., 2005). Nevertheless, the difference between the date of the last menstrual period and the ultrasound dating has been reported to be a marker of the risk of early growth restriction (Källén, 2004; Morin et al., 2005). Thus, we cannot exclude the possibility that occupational exposure to solvents is responsible for early SGA status and that sonographic correction could have underestimated this effect. Other studies have used fetal growth trajectories based on ultrasound-estimated fetal growth to study SGA status (Snijder et al., 2012). Their method let them differentiate intrauterine growth retardation that occurred in the second or in the third trimester of pregnancy. But it also resulted in selective participation, with mothers with lower socioeconomic status less well represented and required suitable reference charts for fetal growth (Snijder et al., 2012).

We planned in advance to adjust for potential confounders based on a directed acyclic graph, constructing an a priori model of the postulated relations between the maternal occupational solvent exposures, intrauterine growth, and the covariates (Shrier and Platt, 2008) to enable theoretically and expert-based adjustment of sets of covariates. Moreover, in sensitivity analyses, we additionally chose to adjust the models studying HC for the mode of delivery to consider plastic deformation of the fetal head; after vaginal delivery, newborn heads can have a “sugar loaf” appearance because of its increased length and the reduction in its 2 largest dimensions (biparietal and suboccipito-bregmatic) (Schaal, 2012). Babies born by cesarean section will have a rather round head. We also performed two other sensitivity analyses: changing the threshold to consider women as certainly exposed to oxygenated solvent at a probability of exposure above 50% rather than the 90% in the main analyses, and aggregating women certainly exposed to oxygenated solvent at very low and low levels. These results were consistent with the main analyses.

5. CONCLUSION

Our study based on job-exposure matrices highlighted an increased risk of SGA newborns when mothers were occupationally exposed to petroleum and oxygenated solvents. We also observed lower HC when mothers were occupationally exposed to oxygenated or chlorinated solvents. These results were strongest among women who worked into the third trimester of pregnancy. Other studies need to be conducted on this topic to confirm these results and investigate potential co-exposures in the workplace. If these results are confirmed, preventive measures should be reinforced for pregnant women occupationally exposed to solvents especially if they work into their third trimester of pregnancy.

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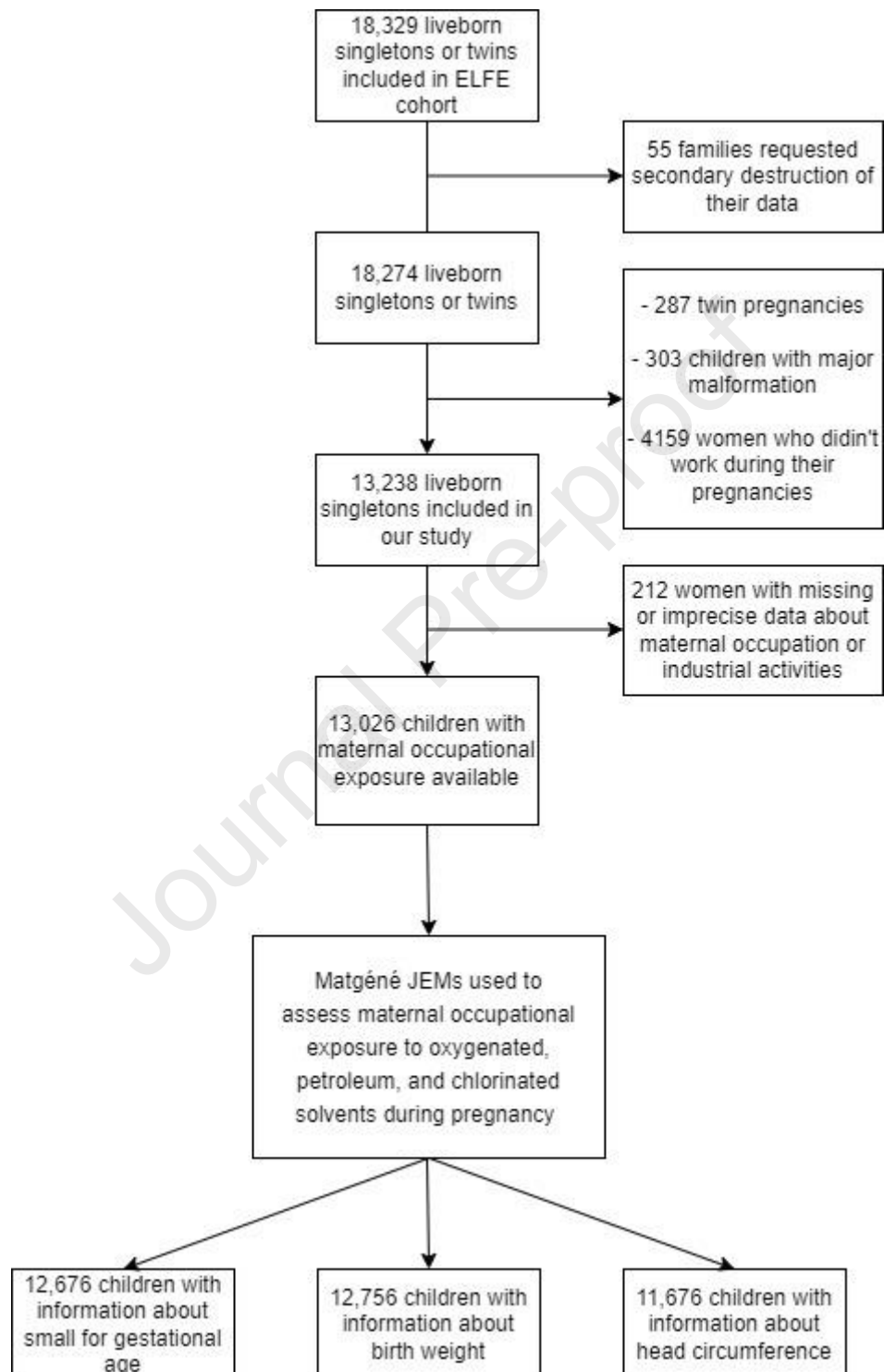
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FIGURE

Figure 1. Flow chart of the study population



TABLES

Table 1. Description of the 12,676 women of the ELFE cohort who worked during pregnancy and for whom exposure was known for at least one organic solvent and their risk factors for a small-for-gestational-age (SGA) neonate.

		Total		Non-SGA		SGA	
		N	%	N	%	N	%
Total		12,676	100	11,444	90.3	1232	9.7
Maternal age (years)	< 25	1237	9.8	1092	9.6	145	11.8
	25–29	4159	32.9	3744	32.8	415	33.8
	30–34	4682	37.0	4269	37.4	413	33.7
	≥ 35	2566	20.3	2312	20.2	254	20.7
Maternal education level	Post-secondary education	8282	65.6	7527	66.0	755	61.3
	Baccalaureate	2289	18.1	2047	17.9	242	19.7
	Primary and secondary education	2065	16.3	1831	16.1	234	19.0
Body mass index (kg/m²)	< 18.5	921	7.3	775	6.8	146	12.0
	18.5–25	8475	67.6	7648	67.5	827	68.1
	25–30	2113	16.9	1948	17.2	165	13.6
	> 30	1034	8.2	957	8.5	77	6.3
Parity	0 children	5918	46.7	5172	45.2	746	60.7
	1 or more children	6749	53.3	6265	54.8	484	39.3
Smoking during pregnancy	Nonsmoker	10,307	82.0	9436	83.2	871	71.3
	Stopped smoking during pregnancy	134	1.1	114	1.0	20	1.6
	Smoker	2129	16.9	1797	15.8	332	27.1
Alcohol consumption during pregnancy	No	10,160	80.4	9161	80.3	999	81.5
	Yes	2476	19.6	2249	19.7	227	18.5
High blood pressure during pregnancy	No	12,110	98.0	10,964	98.3	1146	95.9
	Yes	244	2.0	195	1.7	49	4.1
Diabetes mellitus or gestational diabetes	No	11,142	92.7	10,054	92.6	1088	93.6
	Yes	874	7.3	799	7.4	75	6.4
Prematurity	No	12,151	95.9	11,003	96.1	1148	93.2
	Yes	525	4.1	441	3.9	84	6.8
Mode of delivery	Vaginal delivery	8639	69.2	7828	69.5	811	66.5
	Instrumental delivery	721	13.8	1564	13.9	157	12.9
	Cesarean section	2119	17.0	1867	16.6	252	20.6
Infant's sex	Male	6466	51.0	5863	51.2	603	48.9
	Female	6210	49.0	5581	48.8	629	51.1

Table 2. Description of occupational activities and solvent exposure among women of the ELFE cohort who worked during pregnancy and for whom organic solvent exposure is known for at least one solvent family (n = 13,026 women).

		Oxygenated (NA=116)								Petroleum (NA=129)				Chlorinated (NA=50)			
		Not exposed				Certainly exposed at a very low level				Not exposed		Possibly exposed		Not exposed		Possibly exposed	
		N	%	N	%	N	%	N	%	N	%	N	%	N	%	N	%
Total	13,026	9988	77.4	885	6.9	1785	13.8	252	2.0	12,036	93.3	861	6.7	12,786	98.5	190	1.5
Professional, technical, and related workers	5355	3729	70.3	283	5.3	1125	21.2	165	3.1	5025	95.2	253	4.8	5163	96.8	172	3.2
Medical, dental, veterinarians, pharmacists	700	201	28.7	235	33.6	238	34.0	26	3.7	700	100.0	0	0.0	700	100.0	0	0.0
Nurses, midwives, medical x ray technicians	912	25	2.7	0	0.0	887	97.3	0	0.0	912	100.0	0	0.0	912	100.0	0	0.0
Architects, engineers, and related technicians	382	346	90.8	25	6.6	0	0.0	10	2.6	314	82.2	68	17.8	367	97.3	10	2.7
Statisticians, mathematicians, systems analysts	35	35	100.0	0	0.0	0	0.0	0	0.0	35	100.0	0	0.0	35	100.0	0	0.0
Teachers	1426	1426	100.0	0	0.0	0	0.0	0	0.0	1426	100.0	0	0.0	1426	100.0	0	0.0
Social workers	511	511	100.0	0	0.0	0	0.0	0	0.0	511	100.0	0	0.0	511	100.0	0	0.0
Chemists, biologists, and related workers	180	41	23.6	8	4.6	0	0.0	125	71.8	27	15.1	152	84.9	19	10.7	158	89.3
Jurists, journalists, and related workers	663	663	100.0	0	0.0	0	0.0	0	0.0	663	100.0	0	0.0	663	100.0	0	0.0
Other professional and technical workers	546	481	96.2	15	3.0	0	0.0	4	0.8	437	93.0	33	7.0	530	99.3	4	0.7
Managerial workers	465	453	100.0	0	0.0	0	0.0	0	0.0	453	100.0	0	0.0	465	100.0	0	0.0
Clerical and related workers	3141	3141	100.0	0	0.0	0	0.0	0	0.0	3141	100.0	0	0.0	3132	100.0	0	0.0
Stenographers, typists	526	526	100.0	0	0.0	0	0.0	0	0.0	526	100.0	0	0.0	526	100.0	0	0.0
Bookkeepers, cashiers	896	896	100.0	0	0.0	0	0.0	0	0.0	896	100.0	0	0.0	896	100.0	0	0.0
Other clerical and related workers	1719	1,719	100.0	0	0.0	0	0.0	0	0.0	1719	100.0	0	0.0	1,710	100.0	0	0.0
Sales workers	1439	1416	100.0	0	0.0	0	0.0	0	0.0	1439	100.0	0	0.0	1436	100.0	0	0.0
Technical saleswomen, commercial travelers	206	206	100.0	0	0.0	0	0.0	0	0.0	206	100.0	0	0.0	206	100.0	0	0.0
Saleswomen, shop assistants	727	721	100.0	0	0.0	0	0.0	0	0.0	727	100.0	0	0.0	724	100.0	0	0.0
Other sales workers	506	489	100.0	0	0.0	0	0.0	0	0.0	506	100.0	0	0.0	506	100.0	0	0.0
Service workers	2203	917	41.7	540	24.6	659	30.0	83	3.8	1672	75.9	530	24.1	2191	99.5	11	0.5
Cleaners and helpers	750	224	30.0	522	70.0	0	0.0	0	0.0	232	30.9	518	69.1	750	100.0	0	0.0
Nurses' aides	504	0	0.0	0	0.0	504	100.0	0	0.0	504	100.0	0	0.0	504	100.0	0	0.0
Hairdressers, beauticians	237	0	0.0	0	0.0	154	65.0	83	35.0	237	100.0	0	0.0	237	100.0	0	0.0
Other service workers	712	693	97.3	18	2.5	1	0.1	0	0.0	699	98.3	12	1.7	700	98.5	11	1.5
Agricultural workers	101	85	85.9	14	14.1	0	0.0	0	0.0	96	96.0	4	4.0	101	100.0	0	0.0
Production workers	321	246	82.3	48	16.1	1	0.3	4	1.3	209	73.9	74	26.1	297	97.7	7	2.3
Textile workers	34	27	87.1	4	12.9	0	0.0	0	0.0	24	85.7	4	14.3	34	100.0	0	0.0
Food and beverage processors	117	97	94.2	2	1.9	0	0.0	4	3.9	98	97.0	3	3.0	116	100.0	0	0.0
Electronic or metal processors	17	6	35.3	10	58.8	1	5.9	0	0.0	0	0.0	15	100.0	11	68.8	5	31.3
Material handlers and related equipment operators	55	45	88.2	6	11.8	0	0.0	0	0.0	43	95.6	2	4.4	46	100.0	0	0.0
Other production workers	98	71	73.2	26	26.8	0	0.0	0	0.0	44	46.8	50	53.2	90	97.8	2	2.2
Other or unknown occupations	1	1	100.0	0	0.0	0	0.0	0	0.0	1	100.0	0	0.0	1	100.0	0	0.0

NA: not available

Table 3. Relation between exposure to solvents by solvent family and the risk of SGA status, birthweight, and head circumference (N=13,026 children).

Solvent	Exposure	Not SGA: N (%)	SGA: N (%)	SGA (OR (95% CI))		Birthweight (β (95% CI))		Head circumference (β (95% CI))	
				Crude OR (95% CI)	Adjusted OR* (95% CI)	Crude β (95% CI)	Adjusted β ** (95% CI)	Crude β (95% CI)	Adjusted β ** (95% CI)
Oxygenated	Not exposed	8783 (76.7)	924 (75.0)	ref	ref	ref	ref	ref	ref
	Likely exposed	762 (6.7)	104 (8.4)	1.30 (1.05;1.61)	1.24 (0.99;1.55)	-39.42 (-71.96; -6.88)	-16.45 (-44.49; 11.59)	-0.09 (-0.19; 0.02)	-0.03 (-0.13; 0.06)
	Certainly exposed at a very low level	1579 (13.8)	168 (13.6)	1.01 (0.85;1.20)	1.01 (0.85;1.20)	-13.62 (-37.48; 10.23)	-4.32 (-24.35; 15.71)	-0.06 (-0.13; 0.02)	-0.03 (-0.10; 0.03)
	Certainly exposed at least at a low level	212 (1.9)	29 (2.4)	1.30 (0.88;1.93)	1.28 (0.86;1.90)	-37.05 (-96.43; 22.32)	-37.99 (-88.16; 12.17)	-0.26 (-0.44; -0.08)	-0.27 (-0.44; -0.10)
Petroleum	Not exposed	10,590 (92.5)	1118 (90.7)	ref	ref	ref	ref	ref	ref
	Possibly exposed	737 (6.4)	103 (8.4)	1.32 (1.07;1.64)	1.26 (1.01;1.57)	-36.76 (-69.52; -4.00)	-21.19 (-49.41; 7.02)	-0.10 (-0.20; 0.01)	-0.05 (-0.15; 0.04)
Chlorinated	Not exposed	11,236 (98.2)	1205 (97.8)	ref	ref	ref	ref	ref	ref
	Possibly exposed	163 (1.4)	22 (1.8)	1.26 (0.80;1.97)	1.31 (0.83;2.06)	-54.92 (-122.69; 12.86)	-55.75 (-113.43; 0.65)	-0.26 (-0.47; -0.05)	-0.25 (-0.44; -0.06)

*Adjusted for maternal education level, smoking status, alcohol consumption, and maternal body mass index

** Adjusted for gestational age (linear and quadratic form), newborn sex, maternal education level, smoking status, alcohol consumption, and maternal body mass index

Table 4. Relation between exposure to solvents by solvent family and the risk of SGA, birthweight, and head circumference for women who stopped working during the first, second (N= 4896 children), or third trimester of pregnancy (N= 6968 children).

	Solvent	Exposure-0.	SGA: N	SGA		Birthweight		Head circumference	
				Crude OR (95% CI)	Adjusted OR* (95% CI)	Crude β (95% CI)	Adjusted β ** (95% CI)	Crude β (95% CI)	Adjusted β ** (95% CI)
Women who stopped working during their first or second trimester of pregnancy	Oxygenated	Not exposed	319	ref	ref	ref	ref	ref	ref
		Likely exposed	20	1.26 (0.92; 1.74)	1.23 (0.89; 1.72)	-38.28 (-88.83; 12.27)	-18.57 (-61.29; 24.16)	-0.02 (-0.17; 0.14)	0.01 (-0.14; 0.15)
		Certainly exposed at a very low level	90	0.95 (0.74; 1.21)	0.96 (0.75; 1.23)	-16.83 (-52.23; 18.57)	-15.96 (-45.18; 13.26)	-0.04 (-0.15; 0.06)	-0.04 (-0.13; 0.06)
		Certainly exposed at least at a low level	5	-	-	8.71 (-113.02; 131.02)	13.73 (-88.42; 115.88)	-0.12 (-0.49; 0.24)	-0.16 (-0.50; 0.18)
	Petroleum	Not exposed	414	ref	ref	ref	ref	ref	ref
		Possibly exposed	48	1.40 (1.01; 1.92)	1.34 (0.96; 1.89)	-26.26 (-78.50; 25.98)	-21.91 (-66.54; 22.71)	-0.02 (-0.18; 0.14)	-0.01 (-0.16; 0.14)
	Chlorinated	Not exposed	457	ref	ref	ref	ref	ref	ref
		Possibly exposed	7	-	-	-30.26 (-162.87; 102.34)	-49.09 (-159.17; 60.99)	-0.20 (-0.60; 0.19)	-0.19 (-0.55; 0.17)
Women who stopped working during their third trimester of pregnancy	Oxygenated	Not exposed	501	ref	ref	ref	ref	ref	ref
		Likely exposed	38	1.31 (0.92; 1.85)	1.28 (0.90; 1.84)	-50.34 (-99.68; -1.00)	-32.91 (-75.90; 10.07)	-0.16 (-0.33; -0.01)	-0.11 (-0.26; 0.04)
		Certainly exposed at a very low level	59	1.02 (0.77; 1.36)	1.01 (0.76; 1.35)	4.86 (-31.62; 41.33)	2.83 (-28.38; 34.04)	-0.04 (-0.16; 0.08)	-0.03 (-0.14; 0.08)
		Certainly exposed at least at low level	23	1.77 (1.13; 2.79)	1.75 (1.11; 2.75)	-64.03 (-134.82; 6.75)	-58.23 (-119.29; 2.84)	-0.30 (-0.53; -0.08)	-0.28 (-0.49; -0.07)
	Petroleum	Not exposed	583	ref	ref	ref	ref	ref	ref
		Possibly exposed	38	1.22 (0.87; 1.74)	1.20 (0.85; 1.72)	-65.08 (-113.39; -16.76)	-47.37 (-89.33; -5.42)	-0.20 (-0.36; -0.05)	-0.14 (-0.29; 0.01)
	Chlorinated	Not exposed	610	ref	ref	ref	ref	ref	ref
		Possibly exposed	14	1.37 (0.78; 2.40)	1.39 (0.79; 2.46)	-75.90 (-157.84; 6.04)	-64.72 (-135.11; 5.68)	-0.32 (-0.58; -0.05)	-0.29 (-0.53; -0.05)

*Adjusted for maternal education level, smoking status, alcohol consumption, and maternal body mass index

** Adjusted for gestational age (linear and quadratic form), newborn sex, maternal education level, smoking status, alcohol consumption and maternal body mass index

Table 5. Relation between exposure to solvents and head circumference (solvents statistically associated with reduced head circumference, mutually adjusted) (N=13,026 children).

Solvent	Exposure	Head circumference (β (95% CI)) **
Oxygenated	Not exposed	ref
	Likely exposed	-0.04 (-0.13; 0.06)
	Certainly exposed at a very low level	-0.04 (-0.10; 0.03)
	Certainly exposed at least at a low level	-0.25 (-0.47; -0.03)
Chlorinated	Not exposed	ref
	Possibly exposed	-0.07 (-0.32; 0.18)

**Adjusted for gestational age (linear and quadratic form), newborn sex, maternal education level, smoking status, alcohol consumption, maternal body mass index, oxygenated solvent exposure, and chlorinated solvent exposure.

SUPPLEMENTAL MATERIAL

Figure S1. Directed acyclic graph representing the causal assumptions used for covariate selection

The DAG was created with DAGitty version 2.3 (<http://dagitty.net/>).

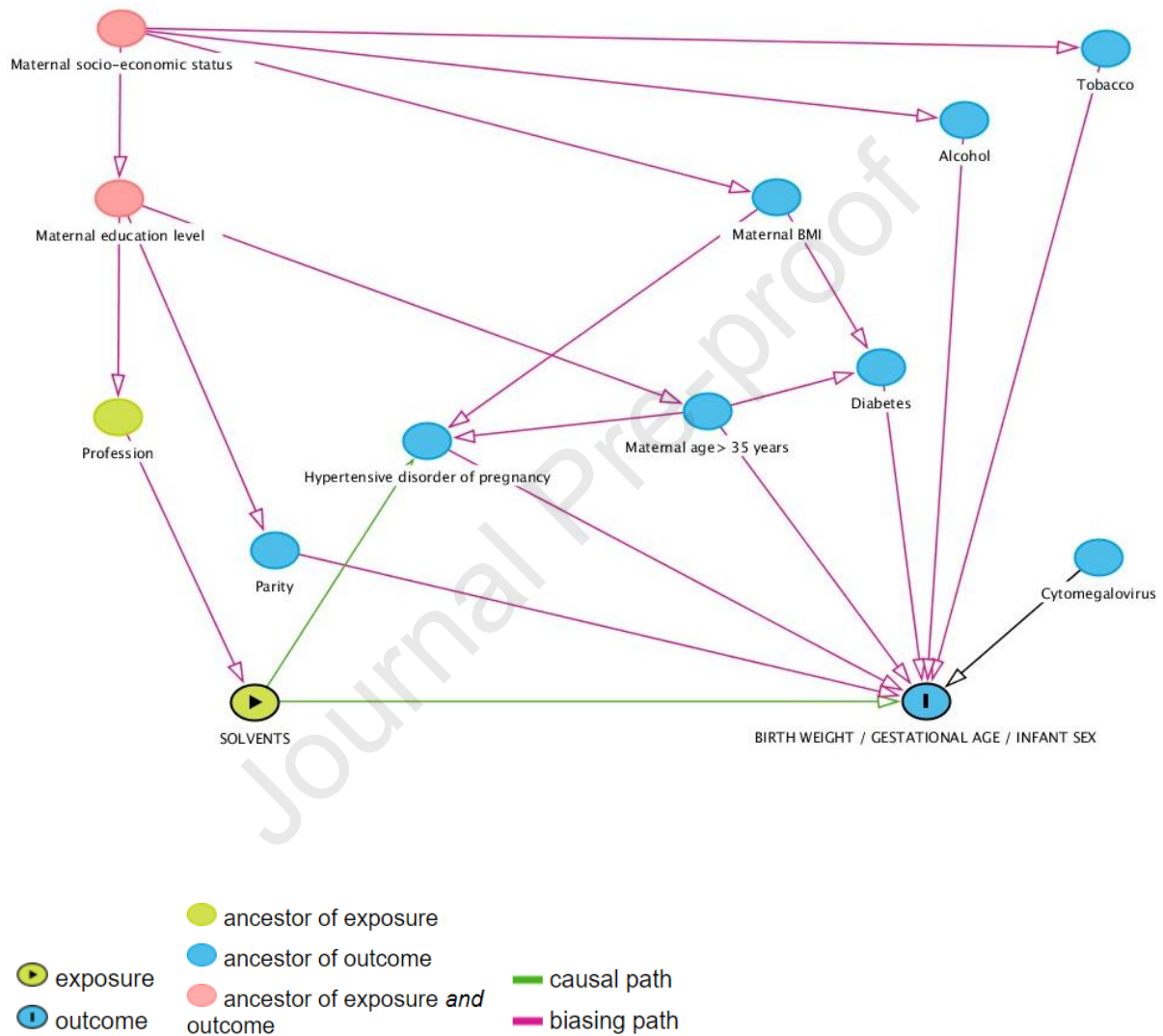


Table S1. Notation of probability and level of exposure for each group of solvents in the JEM.

	Oxygenated solvents	Petroleum solvents	Chlorinated solvents
Probability of exposure	0: not exposed 10: [1%–10%] 20:]10%–20%] 30:]20%–30%] 40:]30%–40%] 50:]40%–50%] 60:]50%–60%] 70:]60%–70%] 80:]70%–80%] 90:]80%–90%] 100: > 90%	0: < 1 % 1: [1%–10%] 2:]10%–50%] 3:]50%–90%] 4: > 90 %	0: not exposed 10: [1%–10%] 20:]10%–20%] 30:]20%–30%] 40:]30%–40%] 50:]40%–50%] 60:]50%–60%] 70:]60%–70%] 80:]70%–80%] 90:]80%–90%] 100: > 90%
Level of exposure	1: very low 2: low 3: moderate 4: high	1: low 2: moderate 3: high	1: very low 2: low 3: moderate 4: high

Table S2. Probability and level of occupational exposure to oxygenated solvents for women of the ELFE cohort who worked during pregnancy (N=12,910 women).

Oxygenated solvents		Level of exposure				
Probability of exposure		Not exposed (N)	Very low (N)	Low (N)	Moderate (N)	Total (N)
Not exposed	<i>Not exposed</i>	9988				9988
]1%–10%]	<i>Likely exposed</i>		15			15
]10%– 20%]			23			23
]20%–30%]			18			18
]30%–40%]			220	8		228
]40%–50%]			13		1	14
]50%–60%]			516			516
]60%–0%]			2	1		3
]70%–80%]			51	9	2	62
]80%–90%]			1	5		6
> 90%	<i>Certainly exposed</i>		1785	249	3	2037
Total		9988	2644	272	6	12,910

Table S3. Probability and level of occupational exposure to petroleum solvents for women of the ELFE cohort who worked during pregnancy (N=12,897 women).

Petroleum solvents		Level of exposure			
Probability of exposure		Not exposed (N)	Low (N)	Moderate (N)	Total (N)
Not exposed	<i>Not exposed</i>	12,036			12,036
]1%–10%]	<i>Possibly exposed</i>		743		743
]10%–50%]			79	1	80
]50%–90%]			24		24
> 90 %			12	2	14
Total		12,036	858	3	12,897

Table S4. Probability and level of occupational exposure to chlorinated solvents for women of the ELFE cohort who worked during pregnancy (N=12,976 women).

Chlorinated solvents		Level of exposure		
Probability of exposure		Not exposed (N)	Very low (N)	Total (N)
Not exposed	<i>Not exposed</i>	12,786		12,786
]1%–5%]	<i>Possibly exposed</i>		164	164
]5%–10%]			14	14
]10%–50%]			1	1
]50%–55%]			11	11
Total		12,786	190	12,976

Table S5. Probability of occupational exposure to subgroups of solvents for women of the ELFE cohort who worked during pregnancy (N=13,026 women).

			Likely exposed	Certainly exposed at a very low level	Certainly exposed at least at a low level
Solvents	Subgroups	N exposed (%)	N exposed (%)	N exposed (%)	N exposed (%)
Oxygenated	Alcohols	2758 (21.2)	815 (6.3)	93 (0.7)	1850 (14.2)
	Diethyl ether	1742 (13.4)	1742 (13.4)	0	0
	Ethylene glycol	1 (0.008)	1 (0.008)	0	0
	Ketones and esters	367 (2.8)	189 (1.5)	93 (0.7)	85 (0.6)
	Tetrahydrofurane	30 (0.2)	30 (0.2)	0	0
Petroleum	Benzene	8 (0.06)	7 (0.05)	0	1 (0.001)
	Fuel	19 (0.1)	18 (0.1)	0	1 (0.001)
	Kerosene	16 (0.1)	16 (0.1)	0	0
	Special essence	206 (1.6)	205 (1.6)	0	1 (0.001)
	White spirit	748 (5.8)	737 (5.7)	0	11 (0.1)
Chlorinated	Dichloromethane	166 (1.3)	166 (1.3)	0	0
	Tetrachloroethylene	13 (0.1)	13 (0.1)	0	0
	Trichloroethylene	9 (0.07)	9 (0.07)	0	0
	Trichloromethane	163 (1.3)	163 (1.3)	0	0

Table S6. Relation between exposure to oxygenated solvents and the risk of SGA status, birthweight, and head circumference (threshold with a probability of exposure > 50 %) (N=13,026 children).

Solvent	Exposure			SGA		Birth weight		Head circumference	
		Not SGA: N (%)	SGA: N (%)	Crude OR (95% CI)	Adjusted OR* (95% CI)	Crude β (95% CI)	Adjusted β ** (95% CI)	Crude β (95% CI)	Adjusted β ** (95% CI)
Oxygenated	Not exposed	8783 (90.5)	924 (9.5)	ref	ref	ref	ref	ref	ref
	Likely exposed	256 (87.7)	36 (12.3)	1.34 (0.94;1.91)	1.33 (0.93;1.91)	-42.38 (-97.01; 12.25)	-24.75 (-70.45; 20.95)	-0.07 (-0.22; 0.12)	-0.03 (-0.19; 0.12)
	Certainly exposed at a very low level	2068 (89.8)	236 (10.2)	1.08 (0.93;1.26)	1.06 (0.91;1.24)	-20.53 (-41.79; 0.73)	-1.87 (-20.24; 16.50)	-0.07 (-0.13; -0.003)	-0.03 (-0.09; 0.03)
	Certainly exposed at least at a low level	229 (88.8)	29 (11.2)	1.20 (0.81; 1.78)	1.19 (0.80;1.77)	-28.19 (-85.66; 29.29)	-34.21 (-83.49; 15.07)	-0.24 (-0.42; -0.06)	-0.25 (-0.42; -0.09)

*Adjusted for maternal education level, smoking status, alcohol consumption, and body mass index

** Adjusted for gestational age (linear and quadratic form), newborn sex, maternal education level, smoking status, alcohol consumption, and body mass index

Table S7. Relation between exposure to oxygenated solvents and the risk of SGA status, birthweight, and head circumference (certainly exposure to oxygenated solvent, aggregated) (N=13,026 children).

Solvent	Exposure	Not SGA: N (%)	SGA: N (%)	SGA		Birthweight		Head circumference	
				Crude OR (95% CI)	Adjusted OR* (95% CI)	Crude β (95% CI)	Adjusted β ** (95% CI)	Crude β (95% CI)	Adjusted β ** (95% CI)
Oxygenated	Not exposed	8783 (90.5)	924 (9.5)	ref	ref	ref	ref	ref	ref
	Likely exposed	762 (6.7)	104 (8.4)	1.30 (1.05-1.61)	1.24 (0.99-1.55)	-39.42 (-71.96; -6.88)	-16.45 (-44.49; 11.59)	-0.09 (-0.19; 0.02)	-0.03 (-0.13; 0.06)
	Certainly exposed	1791 (90.1)	197 (9.9)	1.05 (0.89-1.23)	1.04 (0.89-1.23)	-16.51 (-39.08; 6.07)	-8.42 (-27.38; 10.55)	-0.08 (-0.15; -0.01)	-0.06 (-0.13; 0.01)

*Adjusted for maternal education level, smoking status, alcohol consumption, and body mass index

** Adjusted for gestational age (linear and quadratic form), newborn sex, maternal education level, smoking status, alcohol consumption, and body mass index

Table S8. Relation between exposure to solvents by family and head circumference (additionally adjusted for the mode of delivery) (N=13,026 children).

Solvent	Exposure	Head circumference (β (95% CI)) ***
Oxygenated	Not exposed	ref
	Likely exposed	-0.04 (-0.13; 0.06)
	Certainly exposed at a very low level	-0.03 (-0.09; 0.04)
	Certainly exposed at least at a low level	-0.27 (-0.44; -0.10)
Petroleum	Not exposed	ref
	Possibly exposed	-0.06 (-0.16; 0.03)
Chlorinated	Not exposed	ref
	Possibly exposed	-0.25 (-0.43; -0.06)

***Adjusted for gestational age (linear and quadratic form), newborn sex, maternal education level, smoking status, alcohol consumption, body mass index, and mode of delivery

Declaration of interests

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

☐ The authors declare the following financial interests/personal relationships which may be considered as potential competing interests:

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