Maternal Tobacco Smoking During Pregnancy and Children's Emotional and Behavioral Trajectories: The EDEN Mother–Child Birth Cohort Study

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ABSTRACT

Introduction: The nature of the relationship between maternal tobacco smoking during pregnancy and the occurrence of children's behavioural problems is still a matter of controversy. We tested this association using data collected among a sample of pregnant women and their offspring followed from birth to early adolescence (age 12 years), accounting for multiple parent, child, and family characteristics.

Methods : Data come from 1424 mother-child pairs participating in the EDEN mother-child cohort in France. Using repeated measures (3, 5.5, 8 and 11.5 years) of the mother-reported Strengths and Difficulties Questionnaire, we estimated trajectories of children's emotional and behavioural difficulties. Two aspects of maternal smoking were studied: the timing (non-smoker, smoking during the periconceptional period or throughout pregnancy) and the level of use (cigarettes/day) during the first trimester of pregnancy. Robust Poisson regression models controlled for confounding factors including maternal mental health and socioeconomic characteristics using propensity scores with the overlap weighting technique.

Results: Contrary to bivariate analyses, in propensity score-controlled regression models, maternal smoking throughout pregnancy was no longer significantly associated with offspring emotional or behavioural difficulties. Maternal heavy smoking (≥10cigarettes/day) remained significantly associated with intermediate levels of conduct problems (RR 1.25 95%CI 1.19-1.31)

Conclusion: The association between maternal smoking in pregnancy and offspring emotional and behavioural difficulties appears to be largely explained by women's other characteristics. However, maternal heavy smoking appears to be related to offspring behavioural difficulties beyond the role of confounding characteristics.

Keywords: smoking, pregnancy, behavior, ADHD, cohort study, offspring

Implications: The relationship between maternal smoking during pregnancy (in 2 modalities: timing and level of smoking) and behavioural difficulties in children is still a matter of debate. While the relationship between any maternal tobacco use and offspring behavioural difficulties appears to be largely explained by confounding factors, heavy maternal smoking in the first trimester of pregnancy seems to be associated with offspring behavioural difficulties beyond the socioeconomic and mental health characteristics transmitted across generations.

INTRODUCTION

Prenatal cigarette smoking is a major and preventable cause of morbidity and mortality for both mother and child. It increases the risk of obstetrical and neonatal complications such as prematurity and/or low birth weight (1). After birth, it is also associated with an increase in sudden infant deaths and respiratory disorders (1). Moreover, several studies have found an association between prenatal smoking and some behavioural symptoms in the offspring. Among these disorders, attention deficit and hyperactivity disorder (ADHD) is one of the most frequently diagnosed mental disorders in children, with an estimated global prevalence of 5.3% (2). Most studies investigating the association between maternal smoking and ADHD have found a significant association (3–6). However, these associations are most consistently significant in studies that do not control for unmeasured confounders (e.g., genetic). Prenatal smoking has been associated with other externalizing behaviours such as conduct disorders (7). Findings on the association between prenatal smoking and internalizing symptoms in the offspring are less consistent; some studies find a positive association (8) while others do not (3).

Children whose mothers smoke during pregnancy seem to have elevated levels of behavioural difficulties, yet the causal nature of this association is still a matter of controversy, as this association could be due to confounding by socio-economic, psychological or inherited factors (5). Some studies have explored these associations by trying to better account for genetic factors. Most sibling-discordant studies reported no statistically significant association between maternal smoking and offspring risk of ADHD has been found although results depend on measurements of both the environment and the offspring outcome (4,9–12). But these studies may be biased due to non-shared confounders and potential selection bias (13). Thapar *et al* studied this association in a population of children born through Assisted Reproduction Techniques (ART), comparing genetically unrelated and related offspring to the woman who had the pregnancy. They found no significant association between prenatal smoking and ADHD suggesting that the previously observed association between maternal smoking in pregnancy and ADHD might be the result of an inherited risk for externalizing

symptoms (14). Similar results were found for conduct disorders (15). Nevertheless, children born through ART do not represent well the general population, as their families are characterized by high socioeconomic position and low maternal smoking rates (16).

The French context is ideal for studying the consequences of maternal smoking during pregnancy due to the higher tobacco consumption levels than in other European countries. In 2016, 16.3% of women smoked tobacco in the third trimester of pregnancy, putting France 20th highest in terms of levels of maternal smoking among 22 European countries with available data (17). Thus, in France maternal tobacco smoking is more widespread and may be less influenced by genetic factors than in other settings (18). In a previous study conducted using data from the EDEN mother-child birth cohort, we reported that children exposed to maternal smoking had an increased risk of having elevated levels of symptoms of hyperactivity/inattention at the age of five as measured using the SDQ, even after controlling for confounding factors (3). However, a limitation of this study is that we examined children's behaviour at one single point in time. In most children, behavioural difficulties decrease during middle childhood (19) and whether persistent difficulties are associated with prenatal exposure to tobacco is uncertain.

The timing and level of smoking during pregnancy are two aspects of tobacco use that could influence the child's behaviour. First, early pregnancy is the period of embryogenesis, whereas late pregnancy is the period of brain maturation and growth and smoking throughout pregnancy could be deleterious (20,21). Second, several studies have found that any level of maternal smoking has effect on offspring health (22), and others have found that some complications related to maternal smoking appear to follow a dose-related pattern (23). In particular, some studies found that maternal smoking of at least 10 cigarettes per day during pregnancy was most likely to be associated with children's externalizing behaviours (24,25).

The objective was to study the association between maternal smoking during pregnancy (smoking time period and level of smoking) and the child's emotional and behavioural trajectories from age 3 to age 11.5 years, using data from the French EDEN (Étude des Déterminants pré et post-

natals précoces du développement psychomoteur et de la santé de l'ENfant) mother-child cohort, with and without controlling for multiple confounding factors.

METHODS

Study population:

Data come from the EDEN (Étude des Déterminants pré et post-natals précoces du développement psychomoteur et de la santé de l'ENfant) mother-child cohort whereby 2002 pregnant women were recruited before 22 weeks of gestation (WG) in two French maternity wards (Nancy and Poitiers) between 2003 and 2006, to investigate the prenatal and postnatal determinants of child health and development (26). Children were followed until age 12. Biomedical and sociodemographic characteristics of parents and children were collected repeatedly during pregnancy and childhood, from medical records, face-to-face interviews, and parent's self-completed questionnaires (26). For our study, we used data collected during pregnancy, at birth and at 3, 5.5, 8 and 11.5 years. We excluded mother-child pairs for which no information on prenatal smoking and child's behaviour were available. For child's behaviour data, at least one time point of measurement had to be available. Compared with the 2003 French National Perinatal Survey, women included in EDEN cohort had a higher level of education, lower maternal tobacco consumption during pregnancy, and similar frequencies of preterm birth (26,27). The EDEN cohort received approval from the committee that oversees ethical data collection in France.

Variables:

Exposure: prenatal smoking

Maternal smoking status before and during pregnancy was collected in face-to-face interviews at 22-26 weeks of gestation and at childbirth. Based on this information, maternal smoking during pregnancy was studied in 3 mutually exclusive categories: non-smoker (reference category), maternal periconceptional smoking defined as smoking during the 3 months before or after conception (includes the first trimester of pregnancy), and smoking throughout pregnancy. We initially categorized the exposure in 4 groups: non-smoker, smoker before pregnancy, smoker during the first trimester of pregnancy and smoker throughout pregnancy. However, women smoking in the

3 months before pregnancy (n= 136) and those smoking during the 1st trimester of pregnancy (n = 117) were consistent and associations with offspring behavioural difficulties in these two groups were very similar. Grouping these 2 categories allowed us to increase the statistical power of our analyses. In the “smoking throughout pregnancy” category, the majority of participants reported smoking throughout all 3 trimesters of pregnancy. Indeed, some women in this category differed, but they represent a minority. For example, less than 1% (14/1424) of the women in our study reported not smoking in the periconceptional period but did so in the 2nd and 3rd trimesters. The size of these subsamples was too small to create more categories while maintaining sufficient statistical power. Sensitivity analyses were conducted to ensure that the "smoking throughout pregnancy" group was homogeneous with regard to population characteristics and that associations with behavioural trajectories were not modified by the removal of minority dyads. Then the daily quantification of maternal smoking during the first trimester of pregnancy was used to assess the level of maternal smoking 0, 1-9, ≥ 10 cigarettes/day. Finally, we conducted an additional analysis presented in Appendix 4 using the average amount smoked during the entire pregnancy (0, 1-5, > 5 cigarettes/day).

Outcome Variable: Children’s behavioural and emotional difficulties

Children’s emotional and behavioural difficulties were assessed using the French version of the Strengths and Difficulties Questionnaire (SDQ), completed by the mothers at ages 3, 5.5, 8 and 11.5 (28). The SDQ includes 5 scales of 5 items each: prosocial behaviours, emotional difficulties, conduct problems, hyperactivity/inattention, and peer relationship problems. Each score ranges from 0 to 10, where higher scores indicate greater difficulties, except for the prosocial behaviours scale. The overall SDQ score is obtained by adding scales, except prosocial behaviours. We studied the total SDQ score and its component subscales.

Covariates

Covariates included variables potentially associated with childhood behavioural and emotional difficulties and prenatal smoking.

Children's characteristics included sex assigned at birth (female vs. male), birth order (firstborn vs. not firstborn), childcare type (centre-based childcare, childminder – professional with a state diploma, or informal childcare – primarily parental care), caregiver of the child at 8 months of age (mother exclusively vs other), early learning activities with the parents at 24 months of age (singing, reading stories, games, walking, playing ball: daily or not) and age at school entry (before 3 years vs. after).

Maternal characteristics included maternal age at childbirth (< 30 years vs. ≥ 30 years), educational level (<higher education vs ≥ higher education defined by two or more years of university), cannabis use during pregnancy (yes vs. no), alcohol use in pregnancy (≥ 1 glass of alcohol/week vs. < 1 glass of alcohol/week), behavioural problems during childhood (yes vs. no), speech and language delay during childhood (yes vs. no), social support (yes vs. no), mental health disorders prior to pregnancy (yes vs. no) and psychological difficulties during pregnancy (yes vs. no) ascertained at 22 WG measured with the Center for Epidemiologic Studies Depression (CES-D) questionnaire (cut-off score ≥ 16) (29) or high anxiety measured with the State-Trait Anxiety Inventory (STAI) questionnaire (cut-off score ≥ 85th percentile) (30).

Paternal characteristics included educational level (<higher education vs ≥ higher education defined by two or more years of university), smoking in pregnancy (yes vs. no), speech and language delay during childhood (yes vs. no) and behavioural problems during childhood (yes vs. no).

Family characteristics were study centre (Nancy vs. Poitiers), household income (<1500 euros/month corresponding to the lowest quartile of distribution in the cohort population vs. ≥1500 euros/month), marital status (married vs. other), parental separation between 22 WG and 5 years (yes vs. no).

Statistical analyses

Trajectories of children's emotional and behavioural symptoms were modelled between ages 3 and 11.5, using Group Based Trajectory Modelling (GBTM, PROC Traj in SAS® 9.4) (31), a semiparametric method which allows the identification of groups of children with similar SDQ score (subscale or total) patterns over time. It is a method particularly adapted for the longitudinal study of child behaviour as children may have varying levels of symptoms during childhood. This method allows for its graphical representation for better understanding. At least one time point of SDQ measure is required to model the trajectory. Missing outcomes are handled by GBTM under the missing-at-random (MAR) assumption. Individuals with missing outcome were assigned to their most likely group. The best-fitting model for each SDQ subscale was defined based on a maximized Bayesian Information Criterion (BIC) and group parsimony. To define a good model, the average posterior probabilities of trajectory membership should be at least equal to 0.7, meaning that people within each trajectory had a highly similar longitudinal pattern of change or stability on the variable (31). In our sample, the best models for the total SDQ score and each subscale were a 3-trajectory model corresponding to high, intermediate or low persistent levels of symptoms.

Missing data on covariates were handled using the multiple imputation technique with the fully conditional specification method (10 imputations), based on the assumption that data are MAR (32).

To explore the association between prenatal smoking and trajectories of children's emotional and behavioural difficulties, we first conducted robust Poisson regression models (outcome in 3 SDQ score trajectories for each subscale and for the total SDQ: high score, middle and low persistent scores) (33). Then, we used propensity scores to account for all observed confounding factors, and render the three exposure groups as similar as possible (34). This technique has two main advantages over standard multivariate statistical modelling: 1) it allows the inclusion of a greater number of relevant variables into statistical models; 2) it makes it possible to visualize differences in terms of associated characteristics between exposure groups (34–36). The choice of variables included in the

propensity score was made by taking into account the scientific literature and then, among the potential confounding factors in Table 1, we selected those associated with the study outcome in bivariate statistical analyses. Potential intermediate variables such as prematurity or low birth weight were not included in the final analyses. The list of covariates included in the propensity score we used is available in **Appendices 1 and 2** and under **Tables 2** and **3.**

After observing limited overlap between propensity score densities pertaining to exposure categories, we chose to use the overlap weighting (OW) method (PSweight package in R) (37,38). This technique focuses on the subpopulation whose probabilities to be in the reference and in the exposure group are balanced, given their set of covariates (37,39). By doing so, it attributes a higher weight to observations that contribute the most to the overlap between propensity score densities (38). The standardized mean differences of covariates, before and after overlap weighting, are available in **Appendix 1** for 'Timing of maternal smoking' variable and in **Appendix 2** for 'level of maternal smoking' variable.

Next, for each SDQ subscale and for the total score, we performed a robust Poisson regression analysis of symptoms trajectories by overlap weighting and verified the distribution of the confounding factors afterwards.

Statistical analyses were performed using SAS® 9.4 and R 4.0.4. Risk Ratio and their 95% confidence interval were calculated. A p value < 0.05 was considered statistically significant.

RESULTS

Descriptive analysis

Our study sample consisted of 1,424 mother-child pairs with data on both the exposure and outcome (**Appendix 3**). Compared with families included in our analysis (n= 1,424), those who did not participate (n= 483) were characterized by lower maternal educational level (Low-education level 48.2% vs 41.2%; p< 0.0001), lower paternal educational level (Low-education level 57.5% vs 51.6%; p< 0.0001), lower income (38.0% vs 29.9%; p= 0.04), higher rate of parental separation (41.2% vs 15.1% ; p<0.0001), lower maternal social support (62.3% vs 71.3 %; p< 0.0001), were more often multiparous (60.6% vs 53.6%, p=0.007) and had a lower average age at delivery (28.2, SD=5.1 vs 29.9, SD=4.7 years; p<0.0001). However, there were no significant differences in the proportion of children's sex, prematurity, or age at school entry.

On average 5.3% of data on study covariates were missing, with a maximum of 18.0% for variable "psychological difficulties during pregnancy".

Table 1 shows characteristics of participating children and families according to maternal tobacco smoking status during pregnancy after imputation of missing data. Overall, 17.8 % of mothers smoked during the periconceptional time period, and 14.5% smoked throughout pregnancy. During the first trimester of pregnancy, 8.1% of pregnant women were considered "heavy smokers" (consumption ≥ 10 cig/day) and 13.6% as "light smokers" (consumption < 10 cig/day). In our study population, 48.0% of children were female, and respectively 6.3% of mothers and 10.7% of fathers had behavioural problems in childhood. Socioeconomic factors (lower level of household income, unmarried women at baseline and parental separation), young maternal age, maternal history of behavioural disorders during childhood, maternal mental disorders, and substance abuse (alcohol, cannabis) were significantly associated with prenatal smoking.

Children's trajectory of emotional and behavioural difficulties

Figure 1 shows children's trajectories of emotional and behavioural symptoms between the ages of 3 to 11.5 years. For the total SDQ score and each subscale, the best model was one with 3 distinct trajectories: a low, intermediate, and a high level of symptoms. The average posterior probabilities of group membership were greater than 0.70 for all trajectories in the 3-group model (range 0.73-0.89, m = 0.82) (40). The reference category was the 'low symptom level' trajectory. There was a trend of decreasing symptoms between 3 and 5.5 years in the reference category. All groups remained stable over time. Overall, a high level of overall of emotional and behavioural difficulties was observed in 8.2% of children, the corresponding prevalence rates were 14.4% for conduct problems, 13.3% for symptoms of hyperactivity/inattention, 6.3% for peer relationship problems and 15.9% for emotional difficulties.

Timing of maternal smoking and children's trajectories of emotional and behavioural difficulties

Table 2 shows associations between timing of maternal smoking and children's trajectories of behavioural and emotional difficulties in bivariate analyses and after controlling for child and family characteristics via OW.

In bivariate analyses, compared with non-smoking mothers, those who smoked throughout pregnancy were significantly more likely to have children with intermediate level of emotional and behavioural difficulties (RR 1.23, 95%CI 1.14 to 1.32), and with intermediate level of each SDQ subscales : conduct disorders (RR 1.08, 95%CI 1.05 to 1.11), hyperactivity/inattention (RR 1.13, 95%CI 1.08 to 1.17), emotional symptoms (RR 1.10, 95%CI 1.07 to 1.14), and peer relationship problems (RR 1.12 95% CI 1.09 to 1.15). Additionally, maternal smoking throughout pregnancy was associated with a high level of symptoms of emotional and behavioural difficulties (RR 1.72, 95%CI 1.22 to 2.43) and externalized symptoms: conduct problems (RR 1.32, 95%CI 1.13 to 1.56) and hyperactivity/inattention (RR 1.45 95% CI 1.20 to 1.78). Children of mothers who smoked during the periconceptional period only did not differ in terms of behavioural and emotional symptoms from those whose mothers did not smoke.

After controlling for child and family characteristics via OW associations between timing of maternal smoking and offspring emotional and behavioural difficulties were reduced and no longer statistically significant.

Level of maternal smoking and children's trajectories of emotional and behavioural difficulties

Table 3 shows associations between maternal smoking level during the first trimester of pregnancy and children's trajectories of behavioural and emotional difficulties in bivariate analyses and after controlling for child and family characteristics via OW.

In bivariate analyses, compared with children of non-smoking mothers, children of "heavy smokers" were more likely to have a high likelihood of having intermediate and high level emotional and behavioural difficulties (RR 1.44, 95%CI 1.34 to 1.54 and RR 1.93, 95%CI 1.30 to 2.85 respectively) as well as intermediate and high levels of each subscale (except for high level of peer relationship problems) : conduct disorders (RR 1.28, 95%CI 1.26 to 1.30 and RR 2.02, 95%CI 1.81 to 2.27 respectively), symptoms of hyperactivity-inattention (RR 1.19, 95%CI 1.14 to 1.24 and RR 1.87, 95%CI 1.55 to 2.24 respectively) , emotional symptoms (RR 1.15, 95%CI 1.11 to 1.18 and RR 1.32, 95%CI 1.10 to 1.58 respectively) and peer relationship problems (RR 1.11, 95%CI 1.08 to 1.15).

After controlling for child and family characteristics via OW, compared with children of non-smoking mothers, children of "heavy smokers" were significantly more likely to have intermediate level symptoms of conduct problems (RR 1.25 95% CI 1.19 to 1.31). The association between children of "heavy smokers" and intermediate level of symptoms of overall emotional and behavioural difficulties was observed but did not reach statistical significance (RR 1.26 95% CI 0.95 to 1.67).

The additional analysis which we conducted to test the role of the average number of cigarettes smoked during the entire pregnancy (**Appendix 4**) shows a significant association between heavy smoking and children's high level of the total SDQ score as well as externalizing symptoms, compared with children of non-smoking mothers in bivariate analyses. In propensity score analyses, heavy smoking during the entire pregnancy remained significantly associated with intermediate and high trajectories of conduct problems.

DISCUSSION

Main results:

Our study, conducted using data from a French mother-child cohort, explored two aspects of prenatal smoking: the timing of smoking during pregnancy (non-smoker, maternal periconceptional smoking and smoking throughout pregnancy) and the level of smoking during the first trimester of pregnancy (0, 1-9, ≥ 10 cigarettes/day). It shows that timing of maternal smoking during pregnancy is not associated with trajectories of behavioural and emotional difficulties in children, while the level of smoking during the first trimester is. Especially, "smoking throughout pregnancy" is associated in bivariate analyses with intermediate levels of the total SDQ and each subscale, as well as with high level for the total SDQ and for externalizing symptoms. But these results were no longer statistically significant after controlling for confounding factors. In addition, maternal heavy smoking in the 1st trimester of pregnancy does predict children's intermediate level of conduct problems, although our analyses focusing on high levels of children's difficulties although there was not enough statistical power.

Our findings are novel in that they focus on children's emotional and behavioural difficulties through early adolescence, and suggest that maternal high levels of smoking are a relevant risk factor above and beyond of other parental and child characteristics. Some of the studies conducted using novel designs (ex. Discordant siblings, children born through ART) may fail to include heavy smokers, which may in part explain null findings. Our data suggest that future investigations examining children's emotional and behavioural difficulties would gain in precision by focusing on maternal heavy smoking rather than any exposure.

Limitations and strengths:

We need to acknowledge some study limitations. First, the study was conducted in two separate cities in France and is not nationally representative. The study population was more educated and had a higher socioeconomic level than the general French population. Women

included in EDEN smoke less than those in the general population, and the women who smoke the most are probably not included in the cohort. However, EDEN sample contains heterogeneous profiles of women, comparable levels of prematurity or admission to intensive care unit and the rate of smoking in the 3rd trimester remains high at 14.5% allowing the study of this exposure (26).

Second, our analyses lack of statistical power for some analyses, particularly focusing on high levels of children's difficulties. This could lead to finding insignificant results when relationships could potentially exist. Third, self-reporting of prenatal smoking can induce non-disclosure or underestimation of levels of smoking due to social desirability bias, especially during pregnancy (41). This might lead to an underestimation of the link between maternal smoking during pregnancy and offspring outcomes in our study. Fourth, children's emotional and behavioural symptoms were reported by the mother, which may introduce bias. Although some studies indicate good agreement between the mother's findings and those of other observers (42), information from multiple informants may provide more valid and accurate measures of children's behaviour than the mother's reports alone and should be emphasized in future research designs (43). A multi-rater approach may be needed because it would reflect a more comprehensive measure of complex behaviour (44). Although the SDQ is a symptom scale, which does not allow clinical diagnosis, it is a tool with good psychometric properties that allows a rapid identification of disorders that should lead the child to a medical consultation (28). The SDQ is a validated scale to detect emotional and behavioural difficulties in children. However, the use of other scales such as the Connors scale could have provided evidence of a greater effect of maternal smoking on ADHD and should be considered in future research (45).

Our study also has several strengths. First, it is a large cohort study with prospective follow-up of pregnant women and their offspring from birth to early adolescence (12 years), with repeated measures of multiple characteristics of children and their families. Maternal smoking status was collected during pregnancy (26) and we analysed different components of children's behaviour. Second, the French context, with its high prevalence of prenatal smoking, with 16.3% of women

smoking tobacco in the third trimester of pregnancy in 2016, is an interesting setting to study this phenomenon and its consequences on health (17). Third, we used propensity scores, which allow to take into account several confounding factor to test causal inference in observational data by making exposures groups comparable (38).

Interpretation of findings:

We hypothesized that prenatal smoking would be associated with children's emotional and behavioural difficulties based on a plausible biological mechanism. Nicotinic acetylcholine receptors regulate critical aspects of brain maturation and studies suggest that carbon monoxide and nicotine could induce alterations in brain structure and function through chronic placental hypoxemia and foetal growth restriction, but also by directly affecting brain structure and neurotransmission (46).

While a previous study found a significant association between persistent prenatal smoking throughout pregnancy and ADHD in the offspring at 5 years of age (3), our work suggests that this effect might not persist over time when studying symptom trajectories from 3 to 11.5 years. Sutin et al. had some comparable results in the Australian context when looking at mother reporting externalizing symptoms between 4 and 14 years (42). Additional studies investigating the long-term effects of prenatal smoking are needed to explore this phenomenon. In addition, our results are consistent with several sibling-discordant studies which found no association between smoking during pregnancy and ADHD in the offspring after adjusting for potential confounders, using the amount smoked during pregnancy (9) or a dichotomous variable for smoking without specifying the amount or timing of prenatal exposure (10). Our results also support previous findings suggesting that prenatal smoking is associated with conduct disorders (7).

Although we found no significant association between persistent prenatal smoking and high levels of behavioural and emotional problems in the offspring when controlling for confounding factors, other negative effects of smoking on women and children are well known and multiple such as premature birth and obstetrical complications (1). Therefore, women should still be encouraged to

stop smoking during pregnancy whenever possible. During pregnancy, described as a window of opportunity in which the perception of health risk is increased, it seems important to detect smoking and social vulnerability factors. In France, the early prenatal interview, proposed systematically since May 2020, allows an early and systematic identification of vulnerable situations collecting data on maternal mental health, social context, and addictive behaviours (47,48). This early identification is essential to support women and propose personalized prevention strategies. It would be interesting to conduct studies to evaluate the impact of this measure on the occurrence of behavioural disorders in children.

Although some of our results were no longer statistically significant after taking into account family and child characteristics with propensity scores, we found that children of "heavy smokers" during the 1st trimester tend to have elevated levels of conduct problems, even after controlling for potential confounders. Thus, smoking level seems to be an interesting indicator to study offspring behavioural difficulties.

Many factors may be involved in the potential association between prenatal smoking and the occurrence of emotional and behavioural difficulties among children. Women who smoke and do not quit tobacco during pregnancy and “heavy smokers” are different from those who do not smoke at all. In particular, many socio-demographic factors are associated with continued smoking during pregnancy including younger maternal age, low socio-economic level, parity, and marital status and they also have an increased prevalence of psychological difficulties (49). Socio-economic characteristics and maternal mental health may contribute to the occurrence of behavioural difficulties in the offspring (50,51). Behavioural problems in children could also be due to inherited factors or other characteristics such as psychosocial context rather than a direct effect of prenatal tobacco exposure (4,14).

CONCLUSION:

The observed association between maternal prenatal smoking and offspring behavioural difficulties appears to be largely explained by women's psychosocial context. However, our findings suggest that high levels of prenatal tobacco exposure in first trimester may be related to child's behavioural difficulties, beyond the socioeconomic and mental health characteristics transmitted from one generation to the next.

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REFERENCES

1. Cnattingius S. The epidemiology of smoking during pregnancy: smoking prevalence, maternal characteristics, and pregnancy outcomes. Nicotine Tob Res. 2004 ;6 Suppl 2:S125-140.

2. Polanczyk G, de Lima MS, Horta BL, Biederman J, Rohde LA. The worldwide prevalence of ADHD: a systematic review and metaregression analysis. Am J Psychiatry. 2007;164(6):942–8.

3. Melchior M, Hersi R, van der Waerden J, et al. Maternal tobacco smoking in pregnancy and children's socio-emotional development at age 5: The EDEN mother-child birth cohort study. Eur psychiatr. 2015;30(5):562–8.

4. Obel C, Zhu JL, Olsen J, et al. The risk of attention deficit hyperactivity disorder in children exposed to maternal smoking during pregnancy - a re-examination using a sibling design. J Child Psychol Psychiatry. 2016;57(4):532–7.

5. Dong T, Hu W, Zhou X, et al. Prenatal exposure to maternal smoking during pregnancy and attention-deficit/hyperactivity disorder in offspring: A meta-analysis. Reprod Toxicol. 2018;76:63–70.

6. Thakur GA, Sengupta SM, Grizenko N, Schmitz N, Pagé V, Joober R. Maternal smoking during pregnancy and ADHD: a comprehensive clinical and neurocognitive characterization. Nicotine Tob Res. 2013;15(1):149–57.

7. Hutchinson J, Pickett KE, Green J, Wakschlag LS. Smoking in pregnancy and disruptive behaviour in 3-year-old boys and girls: an analysis of the UK Millennium Cohort Study. J Epidemiol Community Health. 2010;64(1):82–8.

8. McCrory C, Layte R. Prenatal exposure to maternal smoking and childhood behavioural problems: a quasi-experimental approach. J Abnorm Child Psychol. 2012;40(8):1277–88.

9. Skoglund C, Chen Q, D'Onofrio BM, Lichtenstein P, Larsson H. Familial confounding of the association between maternal smoking during pregnancy and ADHD in offspring. J Child Psychol Psychiatry. 2014;55(1):61–8.

10. Gustavson K, Ystrom E, Stoltenberg C, et al. Smoking in Pregnancy and Child ADHD. Pediatrics. 2017;139(2).

11. Lindblad F, Hjern A. ADHD after fetal exposure to maternal smoking. Nicotine Tob Res. 2010;12(4):408–15.

12. Knopik VS, Neiderhiser JM, de Geus E, Boomsma D. The Importance of the Prenatal Environment in Behavioral Genetics: Introduction to Special Issue. Behav Genet. 2016;46(3):281–5.

13. Frisell T, Öberg S, Kuja-Halkola R, Sjölander A. Sibling comparison designs: bias from non-shared confounders and measurement error. Epidemiology. 2012;23(5):713–20.

14. Thapar A, Rice F, Hay D, et al. Prenatal smoking might not cause attention-deficit/hyperactivity disorder: evidence from a novel design. Biol Psychiatry. 2009 15;66(8):722–7.

15. Rice F, Harold GT, Boivin J, Hay DF, van den Bree M, Thapar A. Disentangling prenatal and inherited influences in humans with an experimental design. PNAS Proceedings of the National Academy of Sciences of the United States of America. 2009;106(7):2464–7.

16. Tong VT, Kissin DM, Bernson D, et al. Maternal Smoking Among Women With and Without Use of Assisted Reproductive Technologies. J Womens Health (Larchmt). 2016;25(10):1066–72.

17. Euro-Peristat Project. European Perinatal Health Report. Core indicators of the health and care of pregnant women and babies in Europe in 2015. 2018. Available www.europeristat.com.

18. Pasman JA, Demange PA, Guloksuz S, et al. Genetic Risk for Smoking: Disentangling Interplay Between Genes and Socioeconomic Status. Behavior Genetics. 2022;52(2):92–107.

19. Mellor D. Normative data for the strengths and difficulties questionnaire in Australia. Australian Psychologist. 2005;40(3):215–22.

20. Govaert P, Triulzi F, Dudink J. The developing brain by trimester. Handb Clin Neurol. 2020;171:245–89.

21. Falk L, Nordberg A, Seiger A, Kjaeldgaard A, Hellström-Lindahl E. Smoking during early pregnancy affects the expression pattern of both nicotinic and muscarinic acetylcholine receptors in human first trimester brainstem and cerebellum. Neuroscience. 2005;132(2):389–97.

22. Liu B, Xu G, Sun Y, et al. Maternal cigarette smoking before and during pregnancy and the risk of preterm birth: A dose–response analysis of 25 million mother–infant pairs. PLOS Medicine. 2020 18;17(8):e1003158.

23. Ko TJ, Tsai LY, Chu LC, et al. Parental Smoking During Pregnancy and Its Association with Low Birth Weight, Small for Gestational Age, and Preterm Birth Offspring: A Birth Cohort Study. Pediatrics & Neonatology. 2014 1;55(1):20–7.

24. Stene-Larsen K, Borge AIH, Vollrath ME. Maternal smoking in pregnancy and externalizing behavior in 18-month-old children: results from a population-based prospective study. J Am Acad Child Adolesc Psychiatry. 2009;48(3):283–9.

25. Markussen Linnet K, Obel C, Bonde E, et al. Cigarette smoking during pregnancy and hyperactive-distractible preschooler's: a follow-up study. Acta Paediatr. 2006;95(6):694–700.

26. Heude B, Forhan A, Slama R, et al. Cohort Profile: The EDEN mother-child cohort on the prenatal and early postnatal determinants of child health and development. Int J Epidemiol. 2016;45(2):353–63.

27. Blondel B, Coulm B, Bonnet C, Goffinet F, Le Ray C. Trends in perinatal health in metropolitan France from 1995 to 2016: Results from the French National Perinatal Surveys. Journal of Gynecology Obstetrics and Human Reproduction. 2017;46(10):701–13.

28. Goodman R. The Strengths and Difficulties Questionnaire: a research note. J Child Psychol Psychiatry. 1997;38(5):581–6.

29. Radloff LS. The CES-D Scale: A Self-Report Depression Scale for Research in the General Population. Applied Psychological Measurement. 1977 1;1(3):385–401.

30. Spielberger, C. D., Gorsuch, R. L., Lushene, P. R., Vagg, P. R., & Jacobs, A. G. (1983). Manual for the state-trait anxiety inventory (Form Y). Palo Alto: Consulting Psychologists Press, Inc. - Recherche Google [Internet]. [cited 2021 17].

31. Nagin DS, Odgers CL. Group-based trajectory modeling in clinical research. Annu Rev Clin Psychol. 2010;6:109–38.

32. Liu Y, De A. Multiple Imputation by Fully Conditional Specification for Dealing with Missing Data in a Large Epidemiologic Study. Int J Stat Med Res. 2015;4(3):287–95.

33. Zou G. A modified poisson regression approach to prospective studies with binary data. Am J Epidemiol. 2004 1;159(7):702–6.

34. Austin PC, Stuart EA. Moving towards best practice when using inverse probability of treatment weighting (IPTW) using the propensity score to estimate causal treatment effects in observational studies. Stat Med. 2015 10;34(28):3661–79.

35. Brookhart MA, Schneeweiss S, Rothman KJ, Glynn RJ, Avorn J, Stürmer T. Variable Selection for Propensity Score Models. American Journal of Epidemiology. 2006 15;163(12):1149–56.

36. Austin PC. An Introduction to Propensity Score Methods for Reducing the Effects of Confounding in Observational Studies. Multivariate Behavioral Research. 2011 31;46(3):399–424.

37. Zhou T, Tong G, Li F, Thomas L. PSweight: An R Package for Propensity Score Weighting Analysis. 2020;

38. Zhou Y, Matsouaka RA, Thomas L. Propensity score weighting under limited overlap and model misspecification. Stat Methods Med Res. 2020;29(12):3721–56.

39. Li F, Morgan KL, Zaslavsky AM. Balancing Covariates via Propensity Score Weighting. Journal of the American Statistical Association. 2018 2;113(521):390–400.

40. Gaudreau P, Amiot C, Vallerand R. Trajectories of Affective States in Adolescent Hockey Players: Turning Point and Motivational Antecedents. Developmental psychology. 2009 1;45:307–19.

41. Dietz PM, Homa D, England LJ, et al. Estimates of nondisclosure of cigarette smoking among pregnant and nonpregnant women of reproductive age in the United States. Am J Epidemiol. 2011 1;173(3):355–9.

42. Sutin AR, Flynn HA, Terracciano A. Maternal cigarette smoking during pregnancy and the trajectory of externalizing and internalizing symptoms across childhood: Similarities and differences across parent, teacher, and self reports. J Psychiatr Res. 2017;91:145–8.

43. Dirks MA, De Los Reyes A, Briggs-Gowan M, Cella D, Wakschlag LS. Annual Research Review: Embracing not erasing contextual variability in children's behavior – theory and utility in the selection and use of methods and informants in developmental psychopathology. Journal of Child Psychology and Psychiatry. 2012;53(5):558–74.

44. Ekblad MO, Rolan E, Marceau K, et al. Disruptive Behavior in Siblings Discordant for Exposure to Maternal Smoking During Pregnancy: A Multi-rater Approach. Nicotine Tob Res. 2020 16;22(8):1330–8.

45. Motlagh MG, Sukhodolsky DG, Landeros-Weisenberger A, et al. Adverse Effects of Heavy Prenatal Maternal Smoking on Attentional Control in Children With ADHD. J Atten Disord. 2011 Oct;15(7):593–603.

46. Ekblad M, Korkeila J, Lehtonen L. Smoking during pregnancy affects foetal brain development. Acta Paediatr. 2015;104(1):12–8.

47. Décret n° 2016-1479 du 2 novembre 2016 relatif aux modalités de mise en œuvre de l'expérimentation de mise en place systématique d'une consultation et d'un suivi spécialisés destinés à toute femme enceinte consommant régulièrement des produits du tabac. JORF n°0257 du 4 novembre 2016. Available from : https://www.legifrance.gouv.fr/eli/decret/2016/11/2/AFSP1626908D/jo/texte.

48. Article 62 de la Loi n°2019-1446 du 24 décembre 2019 de financement de la sécurité sociale pour 2020. JORF du 27 décembre 2019. Available from: :https://www.legifrance.gouv.fr/eli/loi/2019/12/24/CPAX1927098L/jo/article_62.

49. Schneider S, Schütz J. Who smokes during pregnancy? A systematic literature review of population-based surveys conducted in developed countries between 1997 and 2006. Eur J Contracept Reprod Health Care. 2008;13(2):138–47.

50. Van der Waerden J, Galéra C, Larroque B, et al. Maternal Depression Trajectories and Children's Behavior at Age 5 Years. J Pediatr. 2015;166(6):1440-1448.e1.

51. Rowland AS, Skipper BJ, Rabiner DL, et al. Attention-Deficit/Hyperactivity Disorder (ADHD): Interaction between socioeconomic status and parental history of ADHD determines prevalence. J Child Psychol Psychiatry. 2018;59(3):213–22.

Variables (%)	Overall (n=1,424)	Non-smoker (n=965)	Maternal periconceptional smoking (n=253)	Maternal smoking throughout pregnancy (n=206)	p values
Child characteristics					
Sex assigned at birth (female)	48.0	46.8	50.2	50.5	0.4678
Birth order (firstborn)	46.4	43.9	56.1	46.1	0.0023
Childcare type					0.0301
Centre-based childcare	36.4	38.0	37.1	29.1	
Childminder	42.8	43.0	42.3	42.7	
Informal childcare*	20.6	19.0	20.6	28.2	
Schooling at age 3	65.9	65.5	64.4	69.4	0.4846
Child's activities with the parents					
Caregiver of the child** at 8 months (mother)	73.1	73.0	69.6	78.2	0.1167
Early learning activities***at 24 months (daily)	87.4	86.6	88.9	88.8	0.4878
Maternal characteristics					
Age at child's birth < 30 years	47.5	43.3	57.7	54.9	<.0001
Low education level****	41.2	36.2	43.9	61.2	<.0001
Maternal smoking during the 1st trimester					<.001
Non-smoker	78.3	100.0	53.8	6.8	
"Light smoker" (>0 and <10cig/day)	13.6	0.0	31.6	55.1	
"Heavy smoker" (≥10cig/day)	8.1	0.0	14.6	38.0	
Cannabis use during pregnancy	1.6	0.2	3.6	5.3	<.0001
Alcohol use during pregnancy ≥ 1 glass/week	29.9	25.9	41.1	34.9	<.0001
Behavioural problems as child	6.3	6.0	3.6	10.7	0.0063
Speech and language delay as child	15.5	14.0	17.8	19.4	0.0775
Lack of social support	28.7	28.1	29.6	30.6	0.7240
Preexisting mental disorder	14.2	11.5	18.6	20.9	0.0002
Psychological difficulties during pregnancy	28.7	26.0	34.0	35.0	0.0045
Paternal characteristics					
Smoking during pregnancy	39.0	27.2	57.3	72.3	<.0001
Low-education level****	51.6	48.4	49.4	69.4	<.0001
Behavioural problems as child	10.7	9.4	12.7	14.1	0.0780
Speech and language delay as child	30.1	29.3	29.3	35.0	0.2639
Family characteristics					
Study centre (Nancy)	48.0	49.7	49.4	38.4	0.0108
Household income <€1500 / month during pregnancy	29.9	26.3	29.3	47.1	<.0001
Marital status at baseline (married)	56.0	64.8	47.1	30.1	<.0001
Parental separation between 22 WG and 5 years	15.1	12.4	19.4	22.3	0.0002

Table 1- Characteristics of the study population according to maternal tobacco smoking status during pregnancy (EDEN mother-child cohort study, n= 1,424).

* Informal childcare: parents or others non-professional caregivers

** Care activities: preparing the meal, feeding, waking at night, changing nappies, bathing, accompanying to the doctor

*** Early learning activities with the child: singing, reading a story, games, walking, playing ball

**** Low level of education: <higher education

WG, Weeks of gestation

	SDQ Subscales		Bivariate analyses				Propensity scores weighted analyses (overlap weighting) *			
			Maternal smoking during the periconceptional period (n=253) vs non-smoker (n= 965)		Maternal smoking throughout pregnancy (n=206) vs non-smoker (n=965)		Maternal smoking during the periconceptional period (n=253) vs non-smoker (n= 965)		Maternal smoking throughout pregnancy (n=206) vs non-smoker (n=965)	
			RR	95% CI	RR	95% CI	RR	95% CI	RR	95% CI
	Total SDQ score	L	Reference		Reference		Reference		Reference	
		I	1.04	0.95 to 1.13	1.23	1.14 to 1.32	1.01	0.85 to 1.19	1.05	0.84 to 1.32
		H	1.25	0.86 to 1.81	1.72	1.22 to 2.43	0.81	0.38 to 1.74	0.95	0.37 to 2.42
Externalizing symptoms	**Conduct problems**	L	Reference		Reference		Reference		Reference	
		I	1.02	0.99 to 1.05	1.08	1.05 to 1.11	1.02	0.97 to 1.08	1.02	0.93 to 1.12
		H	1.03	0.85 to 1.25	1.32	1.13 to 1.56	0.91	0.62 to 1.32	0.98	0.61 to 1.57
	Hyperactivity/Inattention	L	Reference		Reference		Reference		Reference	
		I	1.00	0.95 to 1.05	1.13	1.08 to 1.17	0.98	0.91 to 1.07	1.00	0.87 to 1.14
		H	1.12	0.90 to 1.41	1.45	1.20 to 1.78	0.95	0.63 to 1.45	0.90	0.50 to 1.59
Internalizing symptoms	**Emotional symptoms**	L	Reference		Reference		Reference		Reference	
		I	1.04	1.00 to 1.07	1.10	1.07 to 1.14	1.01	0.95 to 1.08	1.03	0.94 to 1.30
		H	1.00	0.84 to 1.20	1.06	0.87 to 1.28	0.91	0.63 to 1.31	0.96	0.54 to 1.72
	Peer relationship problems	L	Reference		Reference		Reference		Reference	
		I	1.01	0.98 to 1.04	1.12	1.09 to 1.15	1.00	0.95 to 1.06	1.05	0.98 to 1.12
		H	0.94	0.61 to 1.44	1.15	0.74 to 1.79	0.66	0.27 to 1.60	0.83	0.21 to 3.12

Table 2- Timing of maternal smoking and children's trajectories of behavioural and emotional difficulties from ages 3 to 11.5 years (EDEN mother-child cohort study, n= 1,424)

Robust Poisson regression and overlap weighting analyses (95%CI), reference group: non smoking mothers

H, High trajectory; I, Intermediate trajectory; L, Low trajectory; SDQ, Strengths and Difficulties Questionnaire

RR : Risk Ratio

* Covariate included in the propensity score model were: centre, social support, family status, parental separation, household income, sex assigned at birth, birth order, early learning activities, mental health disorders prior to pregnancy, psychological maternal difficulties during pregnancy, paternal smoking during pregnancy, maternal and paternal language delay during childhood, maternal and paternal behavioural problem during childhood, maternal and paternal educational level

	SDQ Subscales		Bivariate analyses				Propensity scores weighted analyses (overlap weighting) *			
			Light smokers (n= 193) *vs* non-smokers (n=1116)		Heavy smokers (n= 115) *vs* non-smokers (n=1116)		Light smokers (n= 193) *vs* non-smokers (n=1116)		Heavy smokers (n= 115) *vs* non-smokers (n=1116)	
			RR	95% CI	RR	95% CI	RR	95% CI	RR	95% CI
	Total SDQ score	L	Reference		Reference		Reference		Reference	
		I	1.15	1.05 to 1.25	1.44	1.34 to 1.54	1.09	0.89 to 1.32	1.26	0.95 to 1.67
		H	1.24	0.82 to 1.85	1.93	1.30 to 2.85	0.95	0.26 to 3.39	1.02	0.14 to 7.67
Externalizing symptoms	**Conduct problems**	L	Reference		Reference		Reference		Reference	
		I	0.96	0.93 to 1.00	1.28	1.26 to 1.30	0.95	0.86 to 1.07	1.25	1.19 to 1.31
		H	1.08	0.88 to 1.32	2.02	1.81 to 2.27	0.89	0.50to 1.60	1.52	0.92 to 2.55
	Hyperactivity/Inattention	L	Reference		Reference		Reference		Reference	
		I	1.06	1.01 to 1.11	1.19	1.14 to 1.24	1.01	0.91 to 1.12	1.02	0.79 to 1.31
		H	1.31	1.05 to 1.64	1.87	1.55 to 2.24	1.11	0.67 to 1.84	1.19	0.48 to 2.97
Internalizing symptoms	**Emotional symptoms**	L	Reference		Reference		Reference		Reference	
		I	1.02	0.99 to 1.06	1.15	1.11 to 1.18	1.02	0.94 to 1.10	1.08	0.94 to 1.24
		H	0.84	0.66 to 1.07	1.32	1.10 to 1.58	0.88	0.45 to 1.72	1.21	0.49 to 3.00
	Peer relationship problems	L	Reference		Reference		Reference		Reference	
		I	1.14	1.11 to 1.16	1.11	1.08 to 1.15	1.10	1.05 to 1.16	1.02	0.87 to 1.20
		H	0.97	0.58 to 1.64	1.15	0.67 to 2.01	0.75	0.15 to 3.83	0.75	0.03 to 17.61

Table 3- Level of maternal smoking and children's trajectories of behavioural and emotional difficulties from ages 3 to 11.5 years (EDEN mother-child cohort study, n= 1,424)

Robust Poisson regression and overlap weighting analyses (95%CI), reference group: non smoking mothers

H, High trajectory; I, Intermediate trajectory; L, Low trajectory; SDQ, Strengths and Difficulties Questionnaire

RR : Risk Ratio

* Covariate included in the propensity score model were: centre, social support, family status, parental separation, household income, sex assigned at birth, birth order, early learning activities, mental health disorders prior to pregnancy, psychological maternal difficulties during pregnancy, paternal smoking during pregnancy, maternal and paternal language delay during childhood, maternal and paternal behavioural problem during childhood, maternal and paternal educational level