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The impact of maternal prenatal psychotropic use on children's emotional and behavioral outcomes

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List of acronyms

ACE	Adverse Childhood Experience
AD	Antidepressant
ADHD	Attention Deficit Hyperactivity Disorder
ASD	Autism Spectrum Disorder
BZD	Benzodiazepine
CBP	Centre Biologie Pathologie
CCPPRB	Comité Consultatif de Protection des Personnes dans la Recherche Biomédicale
CES-D	Center for Epidemiologic Studies Depression Scale
CI	Confidence Interval
CNIL	Commission Nationale Informatique et Liberté
DAG	Directed Acyclic Graph
EDEN	Etude des Déterminants du Développement et de La Santé de l'Enfant
EEG	Electroencephalogram
GBTM	Group-Based Trajectory Modeling
LBW	Low Birth Weight
LC-HRMS	Liquid Chromatography - High Resolution Accurate Mass Spectrometry
LTFU	Lost To Follow-Up
MAOI	Monoamine Oxidase Inhibitors
MAR	Missing At Random
MI	Multiple Imputation
MICE	Multiple Imputation by Chained Equations
NA	Not Available
OB/GYN	Obstetrics/ Gynaecology
pmm	Predictive Mean Matching
PPE	Prenatal Psychotropic Exposure
PTB	Preterm Birth
RCT	Randomized Controlled Trials
SDQ	Strength and Difficulty Questionnaire
SNRI	Serotonin–Norepinephrine Reuptake Inhibitor
SSRI	Selective Serotonin Reuptake Inhibitor
STAI	State-Trait Anxiety Inventory
TCA	Tricyclic Antidepressant
UHPLC-MS	Ultra-High Performance Liquid Chromatography-Mass Spectrometry

Abstract

Introduction: Anxiety and depression are among the most prevalent complications of pregnancy. Research on the adverse effects of untreated anxiety and depression on child development, as well as the impact of pharmacotherapy for these conditions, have yielded inconsistent results. Among these studies, a limited number have focused on the child's emotional and behavioral outcomes. Thus, this study aimed to evaluate the association between in-utero exposure to psychotropic medication and adverse emotional and behavioral outcomes.

Method: This study included 1862 mother-child dyads from the EDEN cohort in France. Maternal prenatal psychotropic medication use was assessed through questionnaire data, combined with medical records and testing of meconium samples. Outcome data was gathered through the Strengths and Difficulties Questionnaire (SDQ) at four time points: 3, 5, 8, and 11 years old. Other than linear models, treating the SDQ results both cross-sectionally and longitudinally through SDQ trajectories, binomial, and multinomial logistic regression modes were implemented to investigate the association between the exposure and outcomes. These models controlled for several confounding factors. In addition, we tested whether the effects were modified by child sex.

Results: All individuals who tested positive in the meconium test results, were also identified as having used psychotropic medications through the questionnaire. Among the exposed group, 55.56% initiated medication use during pregnancy, and among unexposed 13.08% used to consume psychotropics before pregnancy. All analyses evaluating the association of in-utero exposure to psychotropics with emotional and behavioral outcomes showed insignificant associations in both unadjusted and adjusted models. The interaction term for the child's sex was also insignificant in all models.

Conclusion: The results of this study suggest that problematic emotional and behavioral outcomes in children are not among the adverse effects of using psychotropics during pregnancy; furthermore, this association does not appear to be modified by the child’s gender.

Keywords: antenatal depression, antenatal anxiety, psychotropic medications, emotional and behavioral development

1. Introduction

1.1. Depression and anxiety during pregnancy

Anxiety and depression can be categorized as common complications of pregnancy. Globally, the prevalence of antenatal depression ranges between 17.0 and 20.7 % (1,2) and 15.2% to 36.5% for anxiety (3,4). Besides the negative impact of these mental health problems on the expecting mother herself, untreated depression has been shown to have neurodevelopmental side effects in the next generation, including hyperactivity of the fetus, increased cortisol and norepinephrine levels, decreased dopamine levels, altered EEG patterns, reduced vagal tone, and stress/depressive-like behaviors in newborns (5,6). Maternal prenatal depression and anxiety have been linked to poorer social-emotional, linguistic, motor, and adaptive behavior development during infancy, childhood, and adolescence (7).

1.2. Pharmacotherapy of depression and anxiety during pregnancy

Although the approaches and guidelines vary among countries, the general tendency is to save pharmacotherapy for severe cases (8–11). There are several classes of antidepressants (ADs) with different adverse effects, such as Selective Serotonin Reuptake inhibitors SSRIs, Serotonin/Norepinephrine Reuptake inhibitors (SNRIs), Tricyclic Antidepressants (TCAs), and Monoamine Oxidase Inhibitors (MAOIs). Among them, SSRIs have fewer adverse effects and more tolerability which leads to their prevalent use (12). BZD are commonly used both for their hypnotic and anxiolytic effects (13). Z drugs (zolpidem, zopiclone, eszopiclone, and zaleplon) are mainly prescribed to manage insomnia (14).

1.2.1. Treatment discontinuation

Even though antenatal depression and anxiety are prevalent and associated with many adverse outcomes, pregnant women are still hesitant to receive pharmacotherapy due to the perceived risks for their unborn child. In a study among well-educated pregnant women, over 90% of the sample considered individual psychotherapy among the top three choices of treatment (15). In this study, 11.6% and 21.5% considered it “definitely acceptable” and “probably acceptable”, respectively, to take medicine during pregnancy if needed (15,16). In another study in the US, the majority of participants indicated that they were most confident in psychosocial therapies and least confident in antidepressants during pregnancy (17).

Healthcare providers are also reluctant to provide antidepressants for pregnant women. In a qualitative focus group study of OB/GYN physicians, advanced practice nurses, and

support and nursing staff, many of them were not confident in treating depression with medication. Participants further noted that community mental health agencies and providers are unwilling to provide pharmacotherapy and tend to discontinue the patient's medicine instead of trying to communicate with the OB physicians; additionally, pharmacists may refuse to refill prescriptions (18).

Together, this leads to a considerable number of women who receive pharmacotherapy to stop their treatment once they become pregnant. In Korea, this can reach up to 95 percent (19). In France, in 2014, 62.5% of ongoing treatments with antidepressants before pregnancy were stopped before conception, most commonly more than 3 months before conception (77.2%)(20). Prevalence of psychotropic medication use during the peripartum decreased by half during the first trimester (21). Nevertheless, for 21.6% of the women who stopped antidepressant treatment after conception, consumption was resumed at a later point during pregnancy (20). Prenatal antidepressant continuation seems to be positively associated with higher education level (22), the severity of depression and length of medication use before pregnancy, and having other psychiatric disorders, and it is negatively associated with substance use (19).

1.2.2 Psychotropic medication use

The prevalence of overall use of antidepressants and anxiolytics during pregnancy varies between 1–13 % across studies (23–25) and is increasing globally, especially for Selective Serotonin Reuptake Inhibitors (SSRIs) (23,25,26). In France, the prevalence of antidepressant use during pregnancy is 25.7 per 1000 (20). They are also the most initiated class of antidepressants during pregnancy (69.9%), and switching to SSRIs during pregnancy is the most frequent treatment adaptation during this period (20).

An association has been detected between using antidepressants during pregnancy and older age (20,23,24), as well as higher levels of education (23). Also, pregnant women who use antidepressants seem to have a greater tendency to smoke, drink, and use cannabis (23), be treated as well with anxiolytics or hypnotics (20), and have other psychiatric disorders and comorbidities (20,24).

The worldwide prevalence of benzodiazepine use during pregnancy is 1.9% (13) and has been relatively stable over time (13). In France, the prescription of anxiolytic drugs in pregnant women is 1.75 percent in the first and second trimesters but increases to 2.17% in the third trimester (21).

An association has been detected between BZD and related medicines' use during pregnancy and having a psychiatric history before pregnancy (27), older age (27,28), higher income (27), more smoking and drinking (28,29) using illicit drugs (28), lower education, and using other psychotropic medicines (30).

1.3. Prenatal psychotropic medication use and child outcomes

Although most psychotropic drugs are generally considered safe during pregnancy, there is still controversy regarding their teratogenicity on child development. Psychotropic medications can pass the placenta and blood-brain barrier, potentially influencing fetal development. Randomized Placebo-Controlled Trials (RCT) on psychotropics are not easily feasible due to justifying ethical criteria (31) and needed sample size, making observational studies substantially important.

Within observational studies, self-reported questionnaires remain the most common method for obtaining information about exposure during pregnancy. This is primarily due to their advantages, such as convenience, low cost, and rapid access to results (32). However, their validity is challenged by the likelihood of social desirability bias, especially considering the associated stigma related to certain exposures during pregnancy that increase the probability of such bias (32). Other possible methods include accessing data through insurance registries and pharmacy claims databases, although the validity of these approaches has not been widely studied, and they provide no information about patient compliance (33) or in-depth knowledge of associated patient characteristics.

1.3.1 Meconium analysis

Meconium, the first feces of a newborn, can be collected 24-48 hours post full-term birth, and later in preterm births (34). Meconium is a direct indicator of placental transfer of chemicals and fetal exposure- its accumulation begins when the fetus starts swallowing at 13-16 weeks gestation (35). Thus, the presence of drugs in meconium reflects cumulative exposure from this period until birth, with a higher likelihood of detecting substances they were exposed to during the last trimester (35,36). In some cases, Benzodiazepine consumed in the delivery process can be detected in meconium (37).

The majority of the research using meconium to measure prenatal exposure addresses illicit drug and alcohol exposure (35). Limited studies are focused on antidepressant (AD) and benzodiazepine (BZD) exposures. One study validating the UHPLC-MS/MS method for ADs and BZDs detection in meconium found these drugs in 6 out of 11 self-reported exposed

individuals (two of the negative results were due to second-trimester only and herbal medicine use). Results were negative for the 20 unexposed dyads (36). Another study with 8 AD-exposed and 34 BZD-exposed individuals reported 60% overall agreement for ADs and 40.4% for BZDs, with meconium tests detecting two positive AD and 3 positive BZD cases that were negative in the medical reports (37). Finally, a study by Cortés et al. found 53.8% agreement between exposure and interview results, all the positive results detected by the meconium test were also positive for psychoactive prescription drugs (38).

These studies indicate that detecting the drug or its metabolites in the meconium can confirm the use and could be a useful complementary test for data gathered by interviews or questionnaires (36,37). However, the chances of finding the medication in the meconium decrease with limited exposure time, dosage, or frequency as well as with medications that are difficult to cross the placenta (37). Nevertheless, in all these studies, having a small sample prevents the researchers from making a robust conclusion (36,37).

1.4. Prenatal psychotropic medication use and socio-emotional development

The majority of previous research on psychotropic exposure during pregnancy has focused on neurodevelopmental outcomes, especially Autism (23,39,40) and physical outcomes such as birth weight and preterm birth, with less information available on child emotional and behavioral outcomes (11,41,42). Emotional and behavioral problems are typically defined as "*the inability to establish satisfactory interpersonal relationships with peers, inappropriate behavior or feelings under normal circumstances*" (43). These disorders are commonly categorized as internalizing (e.g., anxiety or depressed mood) and externalizing (e.g., conduct problems or hyperactivity) (44). Childhood behavioral problems can have long-lasting, deleterious effects on individuals' mental health, academic and occupational functioning, and increase their risk of developing more serious issues later in life (45,46).

1.4.1 Antidepressants/SSRIs

Different studies have focused on several neurodevelopmental outcomes of in-utero exposure to ADs/SSRIs. However, compared to SSRIs, there are fewer reports on the reproductive safety profiles of other antidepressants (47).

Several studies examined how offspring’s internalizing and/or externalizing behaviors were affected by prenatal AD exposure, particularly SSRIs, but with diverging results. One study, which did not control for confounders, showed an association between SSRIs and higher levels of both internalizing and externalizing behaviors at 5- 6 years old (48). Two further studies

saw an adverse effect on internalizing behaviors in early and middle childhood when controlling for prenatal and postpartum depression. In both studies, mothers were taking medication at the time of conception. One of them measured the outcome at age 3 (49) the other inspected that at two points; 3 and 6 years old (30). A Finnish national registered-based cohort study has detected a moderately increasing effect of in-utero exposure to SSRI on the cumulative incidence of depression up to the age of 14. In this study, the severity of maternal depressive disorder remained as residual confounding. (40). However, other studies found no association between prenatal SSRI or AD exposure and later internalizing and/or externalizing behavior problems (23,40,50). Likewise, a Danish National Birth Cohort study reported that prenatal antidepressant exposure was not associated with abnormal behavioral problems at 4-5 years old (23).

Studies focusing on prenatal antidepressant exposure and Attention deficit hyperactivity disorder (ADHD) and Autism spectrum disorder (ASD) have examined more in particular the vulnerability of the fetus after exposure during different trimesters (26) and most importantly they have adjusted for different confounders (26,51) . The results of the different original studies have been summarized in several meta-analyses. In one meta-analysis, the association between ADs and ADHD was not significant when the reference group was mothers with untreated psychiatric disorders during pregnancy (52). However, another meta-analysis showed that the association stays significant for both of these outcomes when the control group is all unexposed women (random risk ratio=1.55 (CI: 1.31–1.78), and 1.38 (CI: 1.13–1.69) for ASD and ADHD respectively). However, the results were insignificant when the analysis was restricted to women with a history of affective disorder and also for sibling studies (51).

1.4.2 Benzodiazepines (BZD) and Z drugs

Compared to antidepressants, there are fewer studies focused on the adverse effects of BZDs and Z drugs during pregnancy; therefore, much less evidence on their impact on child development is available.

A well-designed study detected a small significant increase in the risk of internalizing behavior problems in children exposed to BZD in the uterus when compared to unexposed at the age of 1.5 (β= 0.25, CI: 0.01–0.49) and 3 years old (β= 0.26, CI: 0.002–0.52) in an adjusted model (53). In another study, the result for the same association became insignificant when performing several sensitivity tests including negative control exposure analysis (28), and the

third study focusing on clonazepam exposure and internalizing problems did not reach significance (54).

No significant associations have been discovered with externalizing behavior. (28,53,55). An association between BZD exposure and poorer personal-social behavior at 18 months was only seen in unadjusted analyses, but once relevant confounders were accounted for, this association was no longer significant (10). Likewise, in 6 years old children, the association between aggressive behavior and anxiety symptoms was not significant (55). No significant associations between Z-drugs and behavior development outcomes have been reported (10,28,53).

Only late-pregnancy exposure to BZDs was linked to a slight increase in the incidence of ADHD traits at age five after adjustment for confounding (10,14). However, no association was shown between the same class of BZD medicines and an increased risk of ADHD features if they were given in the second trimester; and no increase in ADHD traits was detected if the child was exposed to Z drugs or any combination of BZDs and Z-drugs (10). Also, no association was found in children of mothers who used BZDs for indications other than anxiety or depression (55).

1.5. Research objectives

Pregnancy is a critical period in a mother's life and adverse conditions during this time may significantly impact the offspring. Therefore, ensuring a healthy and manageable pregnancy is important for maternal and child well-being. Conducting studies on pregnant women, especially on the safety of medication, is both essential and challenging.

Previous research on the use of psychotropic medication during pregnancy and its impact on child development has limitations, leading to inconsistencies and unreliable results. These include the relatively small sample sizes, the failure to account for relevant confounders, and the short follow-up as most studies focused on child outcomes in infancy and middle childhood. Thus, the need for further research in this domain remains present, especially regarding the potential impact on children’s social and emotional development.

The overall objective of this work is to study the association between the pharmacotherapy of maternal prenatal mental health problems and offspring's emotional and behavioral outcomes.

Specific objectives:

1. To investigate and compare characteristics of subgroups of the study sample based on their psychotropic consumption before and during the pregnancy
2. To estimate the risk of emotional and behavioral adverse outcomes in the offspring of mothers who used psychotropic medicines during pregnancy

In this study, we aim to advance the field by incorporating the results of the meconium test to determine prenatal exposure, a method rarely studied in this context. Additionally, we will address key limitations of previous research by controlling for maternal anxiety and depression during pregnancy, as well as other potential confounders such as prenatal substance use and sociodemographic characteristics. This approach allows for more robust inferences about the impact of prenatal psychotropic treatment on child outcomes.

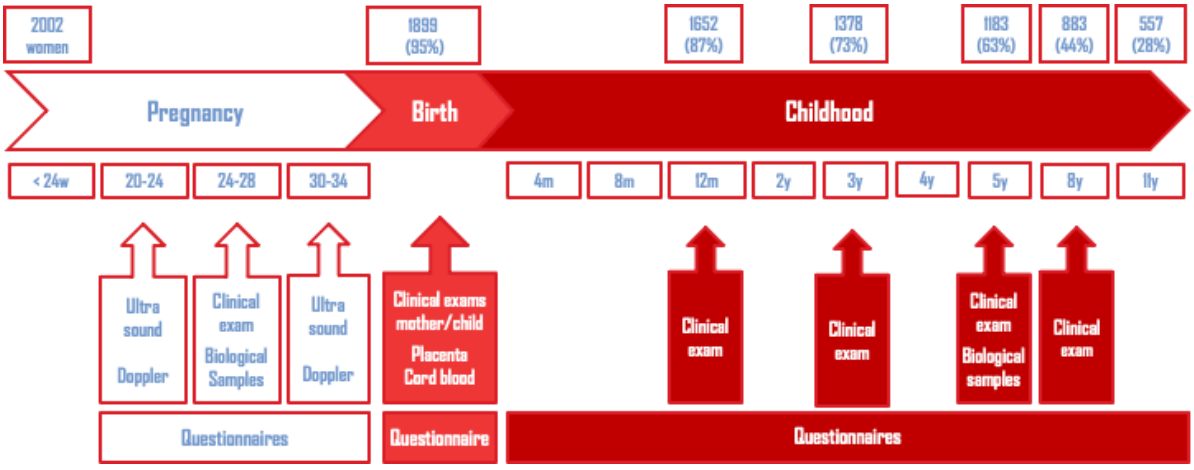
2. Method

2.1. Study sample

The French EDEN (Etude des Déterminants du développement et de la santé de l'Enfant) mother-child cohort, is a longitudinal study focused on studying the prenatal and early postnatal determinants of child health and development. The cohort consists of women enrolled between 2003 and 2006 in the university maternity clinics of Nancy and Poitiers, France, recruited during pregnancy before their 24th week of amenorrhea. Exclusion criteria were multiple pregnancies, known diabetes before pregnancy, French illiteracy, or planning to move out of the region within the next 3 years (56).

The EDEN cohort initially enrolled 2002 women during pregnancy, after which participants and their children were followed up for up to 11 years through visits to research centers, questionnaires, clinical examinations by midwives or other healthcare practitioners, and collection of biological samples at different time points (see figure 1).

Figure 1: data collection waves and methods for the EDEN cohort



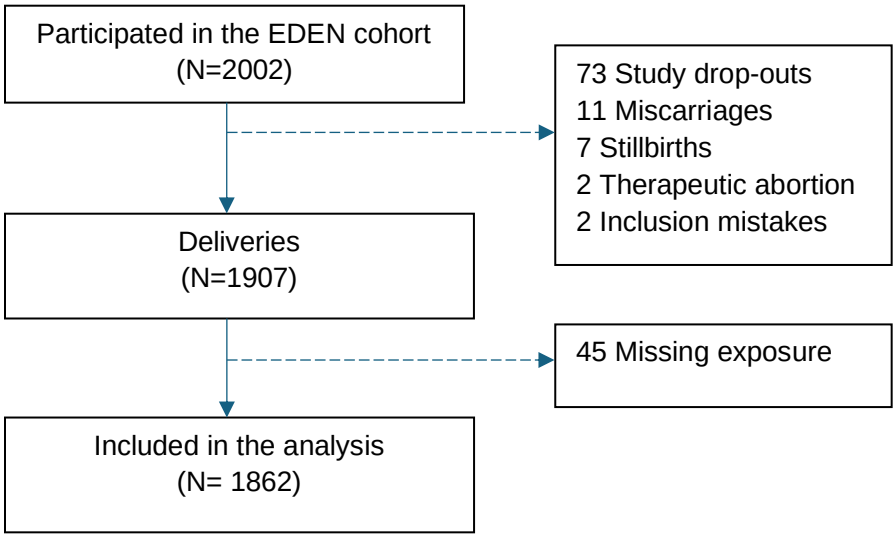
The study has collected a wide range of data on maternal health, environmental exposures, and child growth and development. It also has a biobank and DNA bank to store biological samples for further analysis.

The main difference between the sample of the EDEN cohort and the 2003 French National Perinatal Survey (Enquête National Perinatal, ENP) was the higher education level of participants in the EDEN cohort. The EDEN study was approved by the Kremlin Bicêtre ethics

committee (CCPPRB) and the French data privacy organization CNIL (Commission Nationale Informatique et Liberté) (56).

For the current study, we included women who remained in the study at least until delivery, and for whom information on their prenatal medication use was available. This resulted in an overall study sample of 1862 mother-child pairs (see Figure 2 study flow chart)

Figure 2. Flow chart of the study sample



2.2. Variables

2.2.1. Exposure: Maternal prenatal psychotropic use

To create a variable indicative of maternal prenatal psychotropic use, we based ourselves on three data sources. First, between 24 and 28 weeks of amenorrhea, participants were asked by a trained interviewer if they had used any hypnotics, anxiolytics, and anti-depressants since the start of their pregnancy (*Depuis le début de votre grossesse, avez-vous pris les médicaments suivants ? : des somnifères, des tranquillisants ou anxiolytiques, des antidépresseurs*). The same question was asked once again after giving birth at the data collection during their maternity stay (*Pendant votre grossesse, avez-vous pris les médicaments suivants : des somnifères, des tranquillisants ou anxiolytiques, des antidépresseurs*). The possible answers were (1) Yes, (2) No and (3) I don't know.

Second, any medication use was also noted as free text in the obstetrical file and retrieved. The answers were used to make a categorical variable with three levels: Individuals who used medications belonging to the groups of interest (hypnotics, anxiolytics, and antidepressants) were assigned to level 1. Among the remaining population, level 2 was assigned to individuals using Hydroxyzine, which is typically categorized as an antihistamine but is also used for treating anxiety during pregnancy and is considered a preferred molecule (57,58). Finally, level 0 was assigned to individuals who used other medications.

Third, for all women who indicated yes/ don't know on the previously mentioned questions and for whom their child's meconium samples were collected at birth, the biological samples were sent to le Centre Biologie Pathologie (CBP), Institut de Biochimie et Biologie Moléculaire, pôle Toxicologie et Genopathies, Unité Fonctionnelle de Toxicologie UF8724 du CHU de Lille to identify the presence or absence of psychotropics in the samples by use of Liquid chromatography-mass spectrometry (LC-HRMS) analyses. The results of these analyses were reported as the presence of specific molecules or their metabolites.

Based on these three data sources, our main exposure variable was created, (prenatal psychotropic exposure - PPE), a categorical variable grouping the individuals according to the absence or presence of psychotropic medicine use during pregnancy. Women were classified as exposed if they answered "yes" to any relevant questions in the questionnaire regardless of whether the medication name appeared in their medical file or the meconium test results. The participants who mentioned using a psychotropic in the free text but did not answer the mentioned questions in the questionnaire, or whose answers were either "No" or " I don't know " (4 participants) were also considered as exposed. Positive meconium test results were consistent with the questionnaire responses. A second version of the exposure was also created with an extended definition of medication used by including *Hydroxyzine* as well.

Participants were considered as not exposed when they answered "No" to all of the questions and did not mention the name of any psychotropic medicine of interest to this study in the free text, and the results of the meconium test were negative or not available.

The rest of the study group was categorized as NA (not available). This group consisted of people who answered "I don't know" or missed at least one question, answered "No" to the other questions, did not mention using any psychotropics in the free text, and had negative or unavailable results for their meconium test.

In addition, we were interested in investigating the treatment changes before and during the pregnancy. For this purpose, we created an indicator variable that demonstrated participants' treatment trajectory with hypnotics, anxiolytics, and antidepressant medications when becoming pregnant. The variable was made using the exposure variable (PPE) and the answers to the question asked in the same questionnaire between 24 and 28 weeks of amenorrhea about their pre-pregnancy exposure to hypnotics, anxiolytics, and anti-depressants (*Dans l'année qui a précédé le début de votre grossesse, avez-vous pris les médicaments suivants? : des somnifères, des tranquillisants ou anxiolytiques, des antidépresseurs*). The participants were divided into four groups based on using psychotropic medicines before and during pregnancy; 1) individuals who continued their treatment (continuation), 2) initiated the treatment during pregnancy (initiation), 3) or had consumed psychotropics before pregnancy but stopped using them during pregnancy (discontinuation), and 4) the ones who never used them (no treatment).

2.2.2. Child outcomes: emotional and behavioral problems

The child's emotional and behavioral problems were assessed using the Strength and Difficulty Questionnaire (SDQ) (59,60), which was completed by the mother at the ages of 3, 5, 8, and 11. The SDQ consists of 5 scales and 25 questions (5 questions for each scale); four negative (emotional symptoms, conduct problems, symptoms of hyperactivity/inattention, and peer connection issues) and one positive (prosocial behaviors) scale.) Questions could be answered as "not true" (0 point), "somewhat true" (1 point), or "very true" (2 points); therefore, the overall score for each scale can vary from 0 to 10. Besides the scores for each subscale, it is also possible to calculate the total score (60). In different studies, the SDQ has shown reliability, test-retest reliability, and invariance across sex, age, and survey language (including French), making it a valid tool for epidemiological research and clinical purposes (60–62). The parent version of SDQ is considered a valid measure to use for longitudinal epidemiological studies to detect change over time in child emotional and behavioral problems (63).

The evolution and the persistence of emotional and behavioral problem symptoms from 3 years to 11 years old were chosen as the main outcome of the study. For this purpose, trajectory variables previously developed by Kallas et al were used. These variables were made using group-based trajectory modeling (GBTM) and identified three trajectory paths in each of the SDQ scales and the total SDQ, that classify children into subgroups based on who consistently exhibits low, moderate, or high levels of SDQ scores over time (64). In the current study sample, overall, 9.34% of children belonged to the high-level total score. Respectively,

13.22% and 7.75% of children belonged to the high-level emotional and peer (relation) scores; 14.98% and 14.63% to the high-level conduct and hyperactivity/attention problems score; and finally, 7.58% belonged to the low-level trajectory of the prosocial behavior score.

In addition, supplementary variables were made for each child's age, based on the SDQ scores and their validated cut-off points both for the total SDQ results and for each scale (65). These variables were then used to create a cumulative binary variable, indicating problematic or non-problematic SDQ scores for each individual.

Finally, at each age, the SDQ scores of emotional and (peer) relation categories were summed to make a continuous variable for internalizing problems; the same was done to conduct and hyperactivity (attention) scales to obtain an externalizing problem variable.

2.2.3. Covariates

Many factors can confound the association between psychotropic medicine use and child behavior problems. The most relevant covariates were selected for inclusion based on a created DAG (Supplementary figure 1). Based on the review of the literature, the most important ones are the untreated anxiety or depression of the mother (5,66–68,55,7). The scores on the French version of the State-Trait Anxiety Inventory (STAI) (69) and Center for Epidemiologic Studies Depression Scale (CES-D) (70) questionnaires completed by participants at weeks 24-28 were used to measure the prenatal anxiety and depression levels of the participants, respectively.

STAI suggests 20 statements like “I am worried” or “I feel at ease” and asks the participants to choose an option on a scale of “not at all” (1 point) to “very much so” (4 points) based on their current feelings. As a result, the total score range is 20-80, with higher scores showing more risk of impairment. In this study, the upper quantile (80^{th} percentile) was considered “High” to make a binary variable (71).

Similarly, in the CES-D questionnaire 20 terms like “I felt sad” or “I enjoyed life” were included and participants were asked to choose an option based on a Likert scale about how often they felt like that during the past week. The options ranged from “rarely or none of the time” (0 points) to “most or all of the time” (3 points). The overall score range is 0- 60 and a score of 16 and above are categorized as depression cases (70).Binary variable was made based on this cut-off (high vs. low score).

Other covariates are substance use (44,67,72), including smoking (68), alcohol, or marijuana (73) use by the mother during pregnancy. Mothers' responses on using each of these

substances at any time during their pregnancy were extracted from the questionnaires and a joint variable was made showing any substance use during pregnancy (yes vs. no).

Mothers' characteristics including age (20,23,24), education level (23,44), relationship status (44,68,14) the economic status of the household (14,44), and parity (14) could also affect the association. Related variables were obtained from the responses to the questionnaire. As age was not linearly related to the outcome it was cut by the mean (≤ 29 years vs. >29 years). Due to its ordinal nature, education level was analyzed as a discrete quantitative variable (<high school, vocational high school, high school, bac+2, >bac+2), living with the father (yes vs. no), having an income of less than 1500 euros per month (yes vs. no), and parity (firstborn yes vs. no).

Other factors that are associated with maternal prenatal mental health and child outcomes were also considered based on literature review and subject knowledge: Family migration background (first generation/ second generation/ French), country of origin (France: yes vs. no), adverse childhood experience of the mother (ACE) (not having any experience vs. having at least one experience), whether the mother has a social support system (68) (two variables: having the father's support (yes vs.no), and support of others (yes vs.no))

The mediator role of Low birth weight (LBW) (5,44,74) and preterm birth (PTB) (5,11,44,74,75) were also considered as well as the modifier effect of the child's sex (44,76). Therefore, binary variables of small for gestational age (yes vs. no), preterm birth (yes vs. no), and child sex (male vs. female) variables were used.

2.3. Statistical analyses

All analyses were performed in the R programming language (R version 4.3.2, R Studio version 2023.12.0+369)

2.3.1. Descriptive statistics

In the first step, we compared the included study sample with those that were excluded based on the availability of our exposure variable. Then as a second step within the study sample, we compared the group for which we have the outcome variable (the ones for whom the SDQ result was available at least 2 timepoints out of 4 (3, 5, 8, and 11 years old)) against those for whom we had the results for 1 or none and were considered Lost to Follow-Up (LTFU); for this purpose, the chi-square test, Fisher's exact test or the Wilcoxon rank-sum test were used.

The main characteristics of the studied population of pregnant women, categorized by their exposure status to psychotropic medication, were also assessed using the chi-square test, Fisher's exact test, or the Wilcoxon rank-sum test, depending on the type of variable.

Chi-squared test, Fisher's exact test, and Kruskal-Wallis rank sum test were used to evaluate the characteristics of the study sample more in-depth based on their treatment path; followed by the pairwise Fisher exact test, to further investigate differences between subgroups.

2.3.2. Multiple imputation

For handling the missing values in the dataset, the Multiple Imputation by Chained Equations (MICE) method has been implemented. This approach was preferred over other methods such as listwise deletion (excluding any case with missing data), which leads to non-response bias and reduces statistical power. Also, in comparison to multiple imputation, simple imputation (by mean) decreases variability between individuals' responses, biases correlations with other variables and overstates precision (77,78). MI generates many complete datasets with varying imputed values for the missing data. These datasets are then analyzed separately and combined to produce a single set of results (pooling) (79). MI requires generating several predictions for the missing values; therefore, the analyses of multiply imputed data account for the uncertainty in the imputations and produce appropriate standard errors (77).

To make the missing at random (MAR) assumption of MICE (77) more possible, all positive predictive variables were included in the subset for imputation of the covariates and outcome. Moreover, longitudinal studies with sufficient follow-up data reduce the dependency on the MAR assumption (80).

In this subset, an average of 1.66% of the values in covariate columns is missing; maximum of 7.67% for alcohol use during pregnancy. 329 (17.29%) individuals have missing values in any of the covariates. The number of imputations was chosen as 20 based on the proportion of missing values.

The "mice" package on R was used to do the process. The number of iterations (maxit) was kept as default 5 to be increased if convergence (stabilization of imputed values) was not achieved. The diagnostic plots provided by the package were used to see if the imputed values stabilized. Predictive mean matching (pmm) was used for predicting continuous variables and Polytomous logistic regression (polyreg) for categorical variables (81). Based on Donald B. Rubin's formula $Tm=(1+\gamma_0/m)T\infty$, where γ_0 is the (true) population fraction of missing information and T is the variance estimate. If m (number of imputations) is set to 20, $Tm/T\infty$ will be 1.0086.

This means the variance is 0.86% and the standard deviation is 0.43% (√1.0086) larger compared to the ideal m=∞ (82).

2.3.3. Regression

To quantify the association between in-utero psychotropic exposure and SDQ results, different models were implemented based on the type of outcome variable. For the trajectory SDQ outcome, multinomial logistic regression was implemented choosing the "low" probability as a reference group for the total score and all the negative scales (emotional symptoms, conduct problems, symptoms of hyperactivity/inattention, and peer connection issues) and the "High" group probability for the positive scale (prosocial).

Simple and multiple linear regression models were used for evaluating the association between the exposure and continuous SDQ results for internalizing and externalizing behavioral problems at each of the studied ages (3, 5, 8, and 11 years), and logistic regression models were implemented for dichotomous total SDQ and each of the subscales.

The confounders were included in the model based on the DAG (Directed acyclic graph) and a bivariate testing p-value < 20%. The results were pooled from all imputed datasets.

To assess whether the sex of the child acts as an effect modifier, an interaction term was included between the child's sex and the exposure variable in all multivariable models. The significance of the interaction term was evaluated to determine if the relationship between the independent variable and the outcome variable differed by the child’s gender.

To verify if the results hold when the criteria of defining the exposure widened, sensitivity tests were performed by running the same analyses once more including *Hydroxyzine* consumers in the exposed group. Finally, results for the original dataset with complete cases were compared to those of the imputed datasets.

3. Results

3.1. Description of the study sample

3.1.1. Descriptive analysis of the excluded population and LTFU

A total of 140 mother-child dyads were excluded from the study; 61% of those were recruited at the Nancy study center and 39% at the Poitiers study center. Analysis comparing the excluded group to the included group indicates that the excluded group had a higher proportion of individuals with high anxiety scores (30% vs 18%), coming from households with income lower than 1500 euro per month (36% vs 17%), and non-French country of origin (16% vs 4.1%). Other characteristics were not significantly different between the excluded and included groups. However, it should be considered that for many of the characteristic variables, information was available for less than half of the excluded group.

Out of 1862 dyads included in the study, 768 dyads for which the SDQ result of the child was not available at least 2 timepoints of measurement (3, 5, 8, and 11 years old) were considered lost to follow-up (LTFU). As shown in Supplementary Table 1, the proportion of the exposed group to the not exposed group is not significantly different among the people that stayed in the study and the loss to the follow-up group; this is true for all criteria of exposure.

Nevertheless, individuals with less favorable emotional and socioeconomic characteristics were more likely to withdraw from the study. The prevalence of having high depression and anxiety scores was higher among those LTFU (31 and 22% vs 22 and 15% respectively). Additionally, these individuals were more likely to have experienced (at least one) adverse childhood event, use substances during their pregnancy, have low incomes (less than 1500 euros/month), and come from immigrant backgrounds (first or second generation) and be non-French. Also, women who were not living with a partner, those without support from the child's father or other individuals, and those for whom this was not their first pregnancy, were more likely to leave the study. Furthermore, a higher proportion of LTFU withdrew from the Nancy study center (56% vs 44%).

3.1.2. Description of the study sample

Table 1 presents the characteristics of the study sample based on their exposure (yes vs no) to psychotropic medication.

The study comprised 1862 mother-child dyads, of which 155 mothers (8.32%) used psychotropic medications during pregnancy, while 1707 mothers (91.68%) did not.

The study sample was recruited almost equally from two centers: 949 participants (51%) were from the Nancy center, and 913 participants (49%) were from the Poitiers center.

Among the study sample, 52.39% of the children were male and 47.61% were female.

Table 1. Characteristics of the study sample (EDEN cohort, France) (N= 1862)

Characteristics	Exposure to psychotropics		
	No, N = 1,707 [1]	Yes, N = 155 [1]	p-value [2]
Study center			0.019*
Nancy	856 (50%)	93 (60%)	
Poitiers	851 (50%)	62 (40%)	
Child's sex (male)	907 (53%)	64 (41%)	0.005*
Depression (High)	395 (23%)	68 (44%)	<0.001*
Anxiety (High)	283 (17%)	52 (34%)	<0.001*
Household income (<1500€/month)	273 (16%)	34 (22%)	0.048*
Any substance consumption	783 (49%)	70 (48%)	0.900
Educational level (mother)			0.700
<High school	122 (7.2%)	12 (7.7%)	
Vocational high school	349 (20%)	38 (25%)	
High school	307 (18%)	28 (18%)	
Bac+2	379 (22%)	28 (18%)	
>Bac+2	548 (32%)	49 (32%)	
Mother's age (≤29)	830 (49%)	83 (54%)	0.200
ACE of the mother (at least one)	486 (28%)	60 (39%)	0.005*
Having partner support	1,651 (98%)	141 (96%)	0.300
Having others support	1,647 (97%)	143 (95%)	0.300
Living as a couple	1,602 (95%)	132 (90%)	0.008*
Parity (firstborn)	762 (45%)	68 (44%)	0.800
number of siblings			0.900
0	648 (40%)	60 (41%)	
1	629 (39%)	52 (36%)	
2	234 (15%)	24 (17%)	
≥ 3	102 (6.3%)	9 (6.2%)	
Migration status			0.072
1st generation	44 (2.6%)	5 (3.3%)	
2nd generation	53 (3.1%)	10 (6.5%)	
French	1,607 (94%)	138 (90%)	
Country of origin (France)	1,637 (96%)	148 (95%)	0.800
Small for gestational age	152 (8.9%)	20 (13%)	0.100
Preterm birth	87 (5.1%)	20 (13%)	<0.001*

[1] n (%)
[2] Pearson's Chi-squared test; Fisher's exact test
* significant p-value <5%

As is to be expected, women who used psychotropic medications during pregnancy had a higher prevalence of depression and/or anxiety (44 and 34% vs 23 and 17 % respectively).

A significantly larger proportion of the exposed group had experienced at least one adverse childhood event (36% vs 25%). Additionally, these women generally had worse financial status; 22% of the exposed women came from households with an income of less than 1500 euros per month, compared to 16% in the non-exposed group; And significantly higher percentage of women in the exposed group were not living with a partner (10%) compared to the unexposed group (5%). The risk of preterm birth was more than twice as high for children in the exposed group compared to the non-exposed group.

The use of alcohol, tobacco, and marijuana was not significantly different between exposed and unexposed groups. Furthermore, exposure to psychotropic medications was not significantly related to having the support of the child's father or other support systems.

When hydroxyzine users were included in the exposed group, migration status, and birth weight differences also reached significance, while other factors remained similar as described above.

There was no significant association between age and exposure to psychotropics when age was categorized according to the mean. When analyzing age as a continuous variable, a significant difference (p-value: 0.029) was observed: mothers in the exposed group were, on average, one year older than those in the unexposed group. (mean: 30.46 vs 29.41).

3.1.3. Descriptive analysis of the population based on treatment decision trajectory

Table 2 displays the characteristics of the groups according to the different treatment paths after becoming pregnant. Supplementary Table 2 shows the results of the accompanying pairwise analysis.

In this study sample, 76.55% of the women who used psychotropic medication before pregnancy stopped their medication during pregnancy, while 23.45% continued using it. Among the exposed group, 55.56% initiated medication use during pregnancy. The decision to continue or stop psychotropic medication during pregnancy was significantly associated solely with anxiety and depression; a greater proportion of the women with high anxiety and depression scores belonged to the group that continued medication, compared to the group that tended to discontinue it (42 and 57% vs 25 and 38%, respectively). However, the difference between

treatment initiation and treatment discontinuation is not significant. (p-value= 1.00 and 0.43 respectively; Supplementary Table 2)

Table 2. Characteristics of the population subgroups based on the treatment decision trajectory (EDEN cohort)

Characteristic	Treatment trajectory (before/ during pregnancy medicine use)				
	No treatment N = 1,475[1]	Continuation N = 68[1]	Initiation N = 85[1]	Discontinuation N = 222[1]	p-value[2]
Child's sex (male)	788 (53%)	30 (44%)	34 (40%)	115 (52%)	0.052
Depression (High)	309 (21%)	38 (57%)	28 (33%)	83 (38%)	<0.001*
Anxiety (High)	225 (15%)	28 (42%)	22 (26%)	56 (25%)	<0.001*
Household income (<1500€/month)	230 (16%)	18 (27%)	16 (19%)	39 (18%)	0.087
Any substance consumption	664 (48%)	42 (64%)	27 (35%)	114 (55%)	0.001*
Educational level (mother)					0.620
<High school	101 (6.9%)	3 (4.4%)	9 (11%)	20 (9.0%)	
Vocational high school	298 (20%)	20 (29%)	17 (20%)	45 (20%)	
High school	261 (18%)	14 (21%)	14 (16%)	45 (20%)	
Bac+2	334 (23%)	10 (15%)	17 (20%)	44 (20%)	
>Bac+2	480 (33%)	21 (31%)	28 (33%)	67 (30%)	
Mother's age (≤29)	714 (49%)	36 (55%)	46 (54%)	110 (50%)	0.600
ACE of the mother (at least one)	403 (27%)	32 (48%)	28 (33%)	79 (36%)	<0.001*
Having partner support	1,435 (98%)	61 (98%)	79 (94%)	206 (94%)	0.001*
Having others support	1,426 (97%)	59 (92%)	83 (98%)	211 (95%)	0.082
Living as a couple	1,388 (95%)	59 (92%)	72 (88%)	204 (92%)	0.009*
Parity(firstborn)	642 (44%)	28 (41%)	39 (46%)	116 (52%)	0.100
number of siblings					0.574
0	547 (39%)	26 (41%)	33 (41%)	97 (47%)	
1	550 (39%)	22 (35%)	30 (38%)	75 (37%)	
2	212 (15%)	10 (16%)	13 (16%)	21 (10%)	
≥ 3	89 (6.4%)	5 (7.9%)	4 (5.0%)	12 (5.9%)	
migration status					0.088
1st generation	36 (2.4%)	3 (4.5%)	2 (2.4%)	7 (3.2%)	
2nd generation	42 (2.9%)	3 (4.5%)	7 (8.2%)	10 (4.5%)	
French	1,395 (95%)	61 (91%)	76 (89%)	204 (92%)	
Country of origin (France)	1,415 (96%)	64 (94%)	83 (98%)	213 (96%)	0.700
Small for gestational age	132 (8.9%)	9 (13%)	11 (13%)	20 (9.0%)	0.400
Preterm birth	73 (5.0%)	7 (11%)	13 (15%)	14 (6.3%)	<0.001*

[1] n (%)
[2] Pearson's Chi-squared test; Fisher's exact test
* significant p-value <5%

The proportion of substance users was lowest in the initiation group (35%). In comparison, the no treatment group had a significantly higher proportion of substance users (48%). While the discontinuation and continuation groups had significantly more substance

users than the no treatment group (55 and 64%, respectively), the difference between these two groups was not significant (p-value: 0.203). The proportion of individuals with adverse childhood experiences appeared higher among women who used psychotropic medication prior to pregnancy (continuation 48% and discontinuation 36%) compared to those who never used medication (no treatment group 27%).

Preterm birth rates were significantly higher among women who initiated psychotropic medication during pregnancy (15%) compared to those who stopped (6.3%) or never used (5.0%) these medications. This increase was not observed when comparing the group who started consuming medication before pregnancy with any of the unexposed subgroups (discontinuation and no treatment).

We observed no significant difference between the ages of the various treatment trajectory groups, whether applying the categorized age variable (p-value: 0.60) or continuous age variable (p-value: 0.20) for the analysis.

3.2. Associations between exposure and outcome

3.2.1. Regression analyses

The result of the unadjusted and adjusted associations between in-utero exposure to psychotropics and children's trajectories of emotional and behavioral development is demonstrated in Table 3.

Both before, and after covariate adjustment, these associations are not significant for either total SDQ results, or any of the SDQ subscales. These results did not change when running the sensitivity analysis between broader exposure criteria (including Hydroxyzine). (Supplementary table 3. A)

In the unimputed dataset analyses, the association between intermediate trajectory in the emotional subscale of the SDQ is significantly associated with psychotropic exposure. (OR 2.21, CI: 1.03- 4.78) (Supplementary table 3. B). This association is also significant for the exposure including Hydroxyzine, (OR: 2.22, CI: 1.09- 4.52).

Simple and multiple linear regression models were used for continuous SDQ results for internalizing and externalizing behavioral problems, and logistic regression models for dichotomous total SDQ, and each of the subscales. (Supplementary Tables 4 and 5)

The association between psychotropic exposure and internalizing and externalizing problems measured at different time points (3, 5, 8, and 11 years old) was insignificant in both

unadjusted and adjusted models. Similarly, the association between psychotropic exposure and binary SDQ outcomes was insignificant for the total SDQ score and all subscales.

Table 3. Association between psychotropic exposure during pregnancy and the trajectory emotional and behavioral outcome of the child (dataset imputed for covariates and outcome) (N= 1862)

SDQ outcome		Unadjusted[1]			Adjusted[2]		
		OR	CI	p-value	OR	CI	p-value
Total	L	Ref			Ref		
	I	1.07	0.68- 1.69	0.78	1.01	0.54- 1.89	0.97
	H	1.36	0.68- 2.8	0.39	1.36	0.53- 3.48	0.51
Emotional	L	Ref			Ref		
	I	1.22	0.78- 1.92	0.39	1.3	0.67- 2.50	0.44
	H	1.44	0.80- 2.59	0.23	0.95	0.40- 2.30	0.92
Peer Relation	L	Ref			Ref		
	I	1.08	0.70- 1.67	0.74	0.84	0.48- 1.50	0.56
	H	1.46	0.70- 3.040	0.31	0.94	0.35- 2.50	0.90
Conduct	L	Ref			Ref		
	I	1.12	0.65- 1.94	0.68	1.08	0.56- 2.08	0.83
	H	1.19	0.62- 2.26	0.60	1.18	0.47- 2.95	0.71
Attention	L	Ref			Ref		
	I	1.12	0.65- 1.94	0.68	0.96	0.52- 1.78	0.89
	H	1.19	0.62- 2.26	0.60	1.03	0.42 2.52	0.95
Prosocial	L	0.93	0.42- 2.08	0.87	0.76	0.27- 2.18	0.62
	I	0.96	0.65- 1.43	0.85	0.96	0.55- 1.67	0.89
	H	Ref			Ref		

[1] Bivariable multinominal logistic regression

[2] Multivariable multinominal logistic regression, adjusted for study center, depression, anxiety, substance use, mother's education level, living as a couple, parity, mother's age, ACE, small for gestational age and preterm birth

p-value <5%,

H: high-level symptoms; I: intermediate-level symptoms; L: low-level symptoms; SDQ: Strengths, and Difficulties Questionnaire; Ref: reference.

3.2.2. Stratified analysis by child sex

The interaction term for the child's sex and psychotropic exposure was not significant for any of the adjusted and adjusted analyses. Therefore, we did not pursue any further moderation analyses by child sex.

4. Discussion

This study aimed to estimate the risk of emotional and behavioral adverse outcomes in the offspring of mothers who used psychotropic medications during pregnancy, compared to children of mothers who did not. For this purpose, questionnaire data from 1862 mother-child dyads was investigated and complemented with the results of biological tests on the infants' meconium. We also aimed to further investigate the characteristics of the women relative to their psychotropic medication consumption status before and during pregnancy.

Overall, we did not observe any significant associations between the maternal use of psychotropic medication during pregnancy and adverse socio-emotional trajectories between ages 3-11 years in their children, compared to women who did not take treatment. These results were confirmed when studying the effects at separate child ages, as well as when broadening the definition of our exposure group by including Hydroxyzine.

In both exposed and unexposed groups, the consumption subgroups (divided according to previous treatment) exhibit significant differences in some characteristics within each group. However, it is unlikely that these differences impact the accuracy of this study when categorizing exposed and unexposed groups or in assessing the probability of the outcomes; since it is more probable that the child’s brain is affected by the exposures during the pregnancy rather than prepregnacy exposures.

4.1. Association between demographic and psychosocial factors and treatment decision trajectories

The proportion of women who stopped using medication after becoming pregnant (76.55%) aligns with other studies conducted in France (77.2%) (20,21), Additionally, the prevalence of psychotropic exposure (8.32% - 10.94% without/with Hydroxyzine) aligns with the global prevalence range (1% - 13%)(23–25); confirming the literature's findings on the hesitancy toward using antidepressants and anxiolytics during pregnancy. Pairwise analysis indicated that there are some differences in the characteristics between those who started medication before pregnancy and those who initiated it during pregnancy. The same is true for the two subgroups of the unexposed (discontinuation vs. never used).

In this study sample, the proportions of pregnant women with high scores in anxiety and depression tests are 18.17% and 25.15%, respectively. The prevalence of anxiety is comparable to global reports (15.2- 36.5%) (3,4), but the prevalence of depression appears to be higher (globally:17.0- 20.7 %) (1,2). The proportion of individuals with high depression and

anxiety scores is higher in the exposed group compared to the unexposed group. (44 and 34% vs 23 and 17 % respectively). This has been similar to other studies focusing on any psychotropic exposure (28,30,48,54). Despite receiving medication prenatally, the "Continuation" group has the highest proportions of individuals with high anxiety and depression scores in the second pregnancy trimester (42 and 57%, respectively). It should be considered that this group includes individuals who continued medication without interruption, those who adjusted their dosage or switched medications when becoming pregnant, and those who stopped and resumed (as it happens to 21.6% of cases that stop consumption) (20). Practitioners sometimes switch medications (20) when a woman becomes pregnant, a decision surrounded by debate about its benefits vs the potential risk of relapse of depression (11). Furthermore, physiological changes during pregnancy necessitate medication dosage adjustments (83), a need often neglected due to a lack of data in this domain (84). In this case, it is possible that at 24-28 weeks, when the questionnaires measuring anxiety and depression were administered these individuals had stopped their medication or needed dosage adjustment. Additionally, there might be cases of more severe or treatment-resistant forms of anxiety and depression in the continuation group (19). As the exposure was assessed through a pooled measurement of two questionnaires, combined with medical records and biological tests assessed at birth we are unfortunately unable to determine the specific medication use pattern according to pregnancy trimester.

Both the initiation and discontinuation groups have significantly higher proportions of individuals with high anxiety and depression scores compared to the no treatment group, which is to be anticipated. Due to the way we construed our exposure variable, some of the people with high levels of anxiety/depression at 24-28 weeks could have initiated pharmacotherapy later. But it is also possible that the reason is the high prevalence of undertreatment. This, combined with the reluctance of mothers and medical staff to start pharmacotherapy, likely contributes to the high levels of anxiety and depression among those indicated as taking medication. However, the initiation and discontinuation groups do not significantly differ among them in the proportion of high anxiety and depression scores. One explanation could be that these two groups experience similar levels of anxiety and depression, but external factors that we were unable to measure, such as doctors' decisions and or the source of information they use (85) guide their choice between pharmacotherapy and other alternatives; the alternatives could be individual or group psychotherapy (15), mindfulness-based interventions (MBIs) (86), yoga (87).

Contrary to the existing literature, this study did not detect any association between substance use (23) and the level of exposure. It should be considered that the prevalence of smoking (88) and alcohol consumption during pregnancy is high in France (89). The prevalence of smoking during pregnancy between 2003-2006 (when the study sample was recruited) was 21- 19% respectively (88) and in a study in central France in 2006 only 53% never consumed alcohol (89). This could be one of the reasons explaining the insignificant results. Another explanation could be the different characteristics of the individuals categorized into one group of exposed or unexposed. When dividing them into subgroups, those with similar prepregnancy psychotropic consumption show more similar patterns in substance use during pregnancy. Thus, there is no significant difference between substance use and the decision to continue or discontinue treatment, unlike a reviewed study (19); the same for no treatment and initiation group.

Furthermore, the initiation group has the lowest proportion of substance users. Considering the previously discussed anxiety and depression levels in this group, it could be argued that more individuals in this group chose medication over other (more adverse) coping strategies like substance use. On the other hand, the continuation group, which has a higher proportion of women with high depression scores, uses chemical coping significantly more than the initiation group which could be due to the undertreatment or severity of their disease, or comorbid substance use disorder.

In this study, no association was detected between education level and the exposure level or decision to continue or discontinue medication use contrary to a previous study (22). In the literature, both high (23) and low (30) levels of education were found to be associated with the use of psychotropic medications during pregnancy. These results should be interpreted considering the overall high education level of the EDEN cohort participants (90) and a low number of studies reporting on this association.

Other studies have detected an association between a mother's age and psychotropic medication use during pregnancy (20,23,24). In this study, no association was detected when age was categorized. However, inconsistencies emerged when age was analyzed as a continuous variable. This discrepancy could stem from a potential nonlinear effect of age. Additionally, the partial loss of information during categorization should be taken into account.

Moreover, in this study sample, a significantly higher proportion of pregnant women in the exposed group lived in households with lower incomes (91). This may indicate an indirect

association, with anxiety and depression acting as mediators when low income may lead to elevated levels of anxiety and depression, which in turn increases the need for pharmacotherapy. The same logic can describe the higher proportion of mothers who experienced at least one adverse childhood experience (92) and were less likely to live with the child's father as a couple (92) in the exposed group compared to the unexposed group as anticipated in the DAG.

The higher prevalence of preterm birth among only the group that initiated medication during pregnancy, and not those with continuous use, needs further biological evaluation focusing on potential pharmacokinetic and pharmacodynamic differences of the psychotropics at the beginning of the treatment and in constant use in relation to fetal gestation.

4.2. Association between in-utero exposure to psychotropics and later emotional behavioral outcomes in children

The analyses examining the association between in-utero exposure to psychotropic medications (focused on BZDs, Z-drugs, SSRIs, and SNRIs) and children's emotional and behavioral trajectory outcomes between 3 and 11 years old was not significant in both unadjusted and adjusted models for total SDQ scores and all its subscales. For sensitivity analysis, a more inclusive exposure variable was used, and in addition, the model was tested on the unimputed dataset and with the binary SDQ outcomes (problematic vs nonproblematic), yielding similar insignificant results.

The only significant association found was between exposure (without hydroxyzine) and the emotional component of the SDQ in the adjusted model on the unimputed data. However, according to multiple testing theory, performing several statistical tests on the same dataset increases the probability of finding an association by chance alone. To address this issue, more strict criteria for determining statistical significance should be implemented. One common method is the Bonferroni Correction, which involves dividing the desired significance level (0.05 in this study) by the number of tests performed (93). In this study, a minimum of 36 tests have been conducted; Consequently, a p-value above 0.0014 (0.05/36) is not considered significant. This applies to the mentioned association, which has a p-value of 0.042. Therefore, we should consider this one significant association with caution.

Regarding the study design, we used more inclusive criteria for exposure compared to other studies that focused on specific medication groups, such as benzodiazepines. While the

latter approach can provide more precise conclusions about the adverse effects of a particular medication group, our broader criteria aimed to capture a wider range of potential exposures.

In the literature, generally two different methods are used to measure exposure: self-reported questionnaires and registry resources, such as insurance websites or pharmacy databases. Although the latter provides more detailed information about the type and duration of medication, it does not account for patient compliance, leading to some uncertainty about the actual exposure. Conducting a confirming biological test (e.g. meconium test) gives a more accurate idea of fetal exposure.

Considering the outcomes, focusing on ages three and older seems valid since there is a correlation between early emotional and behavioral problems and later abnormalities. Detecting emotional problems in the first years of life is challenging due to underdeveloped verbal and communication skills, and because these issues often develop later (44). Nevertheless, there is less loss to follow-up in the early years.

Nevertheless, our insignificant result aligns with other studies on this subject (10,23,40,50,51,55). In previous studies, the association was significant in the unadjusted model (10,40) in some cases, but became insignificant when major confounders such as anxiety and depression, were taken into account. (51) Overall the results of this study align with these results and suggest that in-utero exposure to psychotropics is not conclusively associated with an increased risk of adverse emotional and behavioral outcomes.

Sex interaction was not significant in this study. Some studies investigating the association of other exposures such as maternal anxiety, the mother's BMI, and the child's intelligence on behavioral outcomes, as measured by the SDQ questionnaire, have reported different results for boys and girls (94–96). Yet, previous studies focusing on similar exposures and outcomes as we did have also not detected any modifying effect for the child's gender. (97,98)

4.3. Strengths and limitations

This study has several strengths. First, it addresses a critical need in a vulnerable population. The unique situation of pregnant women results in a paucity of health information about them. Additionally, the study focuses on stigmatized exposure and tries to produce information about its actual risk. Second, our exposure measure was not only based on self-reported questionnaires but complemented by information from women's medical records and the dosing of molecules in infants' meconium. Among the few previous studies that included

meconium biological testing as a supplemental measure, this one had a large sample size (300) in comparison to similar research (31- 145). Third, in this study, we investigated socio-emotional outcomes that only a limited number of studies have studied on, and at different ages up to early adolescence. Additionally, a validated questionnaire (SDQ) was implemented to assess child outcomes at four stages of the children's lives, which improves result accuracy.

However, we also need to note some limitations. The EDEN cohort participants on average, had a higher level of education compared to the general population. This, combined with the less favorable socioeconomic status of those lost to follow-up (LTFU), suggests that the study sample might not be representative of the general French population. While this study's sample size is comparable to other studies investigating similar exposures and outcomes there were limitations in power. when compared to broader research, due to the specific focus on pregnancy and the uncommon nature of the exposure.

In the absence of robust confirming evidence of exposure, such as hair tests or assurance registries, the reliance on broad questions to measure exposure and self-reported answers could be problematic. Participants' understanding of these questions and their answers are influenced by their prior knowledge of the medications. The high level of indication overlap for the medications in question contributes to this problem. For instance, although SSRIs are categorized as antidepressants, the FDA has approved their use for several conditions such as bipolar disorder and certain anxiety and panic disorders. Additionally, they have off-label uses for other diseases like fibromyalgia (12). Additionally, the data collection process conducted by an interviewer introduces the possibility of social desirability bias, and recall bias may be present in the result of questions inquiring about prepregnancy medicine use.

Furthermore, the lack of detailed information regarding the duration and dosage of medication use makes it difficult to classify individuals into subgroups. Consequently, this hinders our ability to draw robust conclusions about the safety or potential adverse effects of specific medications or classes of medications or accurately evaluate the impact of dosage, duration of use, or the timing of exposure (such as which trimester it occurred in) on the child’s emotional and behavioral outcome.

Finally, given the possible advancements in the pharmacotherapy of mental health disorders during pregnancy, the EDEN cohort data may be dated. Thus, interpreting the results in the context of current practices requires considering these potential changes (99).

5. Conclusion/Recommendations/Implications

The results of this study suggest that psychotropic medication use during pregnancy does not lead to an elevated risk of emotional and behavioral problems in children. However, the current findings do not provide clinically practical information due to the study limitations.

Several studies have demonstrated the adverse effects of untreated anxiety and depression during pregnancy on both the mother and child, particularly emotional and behavioral problems in children (5–7). These childhood issues can affect important aspects of an individual's future and adult life, making this a crucial public health matter. Therefore, addressing it by devising efficient guidelines is essential. It should also be considered that pharmacotherapy for anxiety, depression, or sleep problems is an easier and more accessible method for many pregnant women with high levels of psychological distress, compared to other methods like psychotherapy (100).

As the consumption of psychotropics during pregnancy is highly influenced by the perspectives of individuals (15–17) and healthcare professionals' views on its risk-benefit ratio (8,9,18), understanding the reasons behind this significant distribution disparity demands further qualitative and quantitative investigation. The increasing number of studies in this domain enhances the potential for robust meta-analyses, which could validate these results and pave the way for further research on specific exposures, such as particular medication classes. If the same results hold in a meta-analysis, it will facilitate the ethical justification for randomized controlled trials (RCTs). Consequently, this could lead to more precise information about the risk/benefit of using these medications compared to untreated anxiety or depression, which can then be used in clinical practice and preparing guidelines for anxiety and depression treatment during pregnancy.

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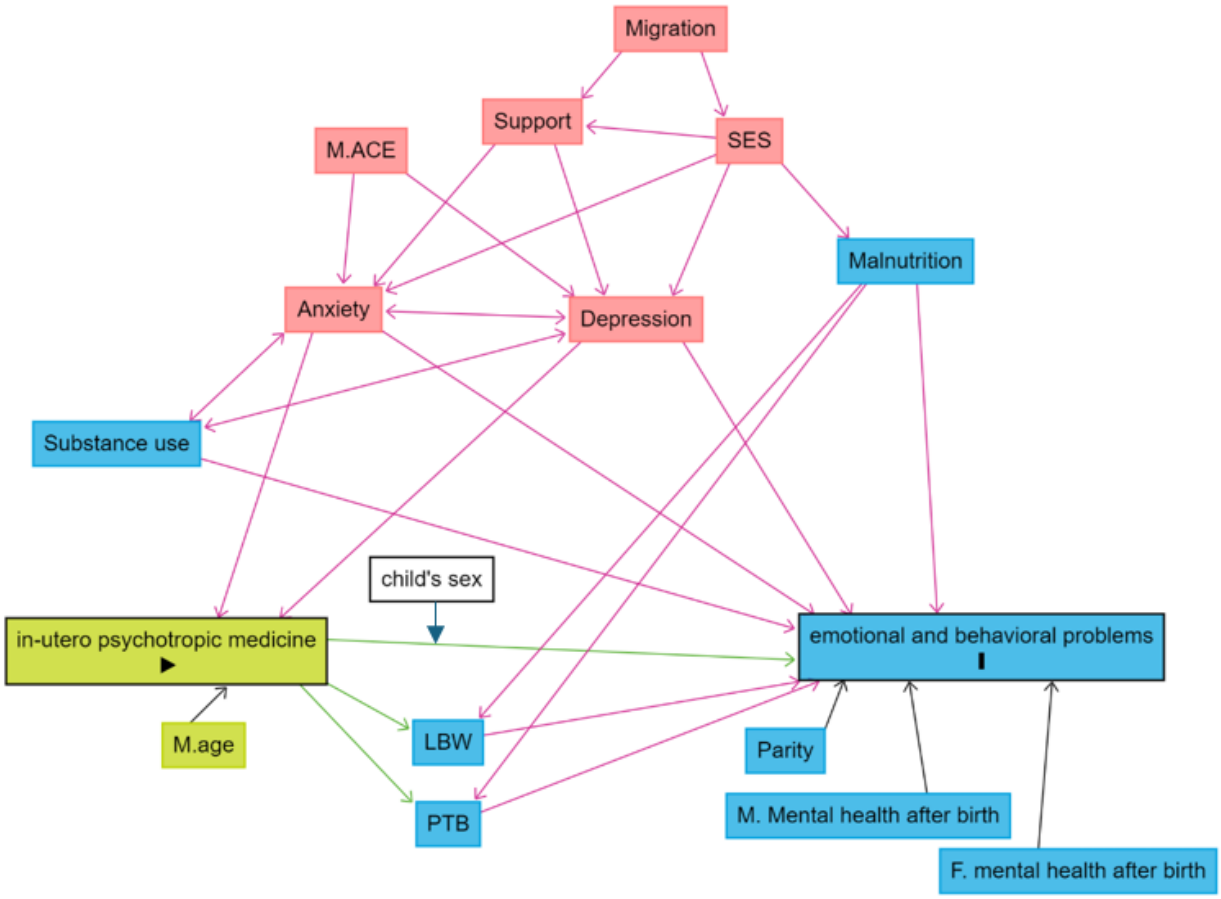
List of Appendices

Supplementary Figure 1. Directed acyclic graph (DAG)



Supplementary Table 1. Characteristics of LTFU based on Trajectory SDQ Outcome			
Characteristic	**Lost to follow-up (LTFU)**		
	No, N = 1,135 [1]	**Yes, N = 768** [1]	**p-value** [2]
Psychotropic consumption	85 (7.6%)	70 (9.4%)	0.2
Psychotropic consumption including hydroxyzine	110 (9.8%)	92 (12%)	0.08
Study center			<0.001*
Nancy	532 (48%)	417 (56%)	
Poitiers	588 (53%)	325 (44%)	
Child's sex (male)	592 (53%)	379 (51%)	0.500
Depression (High)	242 (22%)	221 (31%)	<0.001*
Anxiety (High)	173 (15%)	162 (22%)	<0.001*
Household income (<1500€/month)	115 (10%)	192 (26%)	<0.001*
Smoking (yes)	234 (21%)	266 (36%)	<0.001*
Alcohol consumption (yes)	317 (30%)	189 (29%)	0.700
Cannabis consumption (yes)	13 (1.2%)	19 (2.7%)	0.018*
Substance consumption (yes)	474 (44%)	379 (55%)	<0.001*
Educational level (mother)			<0.001*
<High school	45 (4.0%)	89 (12%)	
Vocational high school	191 (17%)	196 (26%)	
High school	191 (17%)	144 (19%)	
Bac+2	265 (24%)	142 (19%)	
>Bac+2	428 (38%)	169 (23%)	
Mother's age (≤29)	599 (54%)	314 (42%)	<0.001*
ACE (at least one)	281 (25%)	265 (36%)	<0.001*
Having partner support (yes)	1,097 (99%)	695 (95%)	<0.001*
Having others support (yes)	1,093 (98%)	697 (95%)	<0.001*
Living as a couple (yes)	1,071 (97%)	663 (91%)	<0.001*
Parity (firstborn)	529 (47%)	301 (41%)	0.005*
Number of siblings			0.014*
0	467 (43%)	241 (36%)	
1	395 (37%)	286 (42%)	
2	150 (14%)	108 (16%)	
≥ 3	68 (6.3%)	43 (6.3%)	
Migration status			<0.001*
1ere generation	11 (1.0%)	38 (5.1%)	
2eme generation	19 (1.7%)	44 (6.0%)	
French	1,088 (97%)	657 (89%)	
Country of origin (France)	1,093 (98%)	692 (93%)	<0.001*
Small for gestational age (yes)	104 (9.3%)	68 (9.2%)	>0.9
Preterm birth (yes)	68 (6.1%)	39 (5.3%)	0.500

1 n (%)
2 Pearson's Chi-squared test; Fisher's exact test
* significant p-value <5%

Supplementary table 2. Comparison between subgroups with different treatment decision trajectories						
Characteristics	cont : init[1]	cont : no[1]	cont : disc[1]	init : no[1]	init : disc[1]	no : disc[1]
depression	0.005*	<0.001*	0.011*	0.015*	0.429	<0.001*
anxiety	0.0553	<0.001*	0.0138*	0.0145*	1	<0.001*
Substance use	<0.001*	0.012*	0.203	0.027*	<0.001*	0.064
ACE of mother	0.0686	<0.001*	0.0857	0.263	0.69	0.013*
Partner's support	0.241	1	0.317	0.027*	1	<0.001*
Any support	1	1	0.578	1	0.579	0.003*
Living as couple	0.425	0.23	1	0.007*	0.257	0.069
Preterm birth	0.473	0.0786	0.28	<0.001*	0.022*	0.413

1 p-value of pairwise Fisher exact test
* significant p-value <5%
cont: Continue, init: Initiation , disc : discontinue, no : no treatment

Supplementary Table 3. A. Association between psychotropic exposure during pregnancy (Including hydroxyzine) and the trajectory emotional and behavioral outcome of the child (dataset imputed for covariates and outcome) (N= 1862)

SDQ outcome		**Unadjusted[1]**			**Adjusted [2]**		
		OR	**CI**	**p-value**	**OR**	**CI**	**p-value**
Total	L	Ref			Ref		
	I	1.22	0.83- 1.80	0.31	1.15	0.67- 1.99	0.61
	H	1.51	0.84- 2.70	0.16	1.46	0.65- 3.26	0.36
Emotional	L	Ref			Ref		
	I	1.30	0.86- 1.98	0.22	1.28	0.69- 2.35	0.43
	H	1.62	0.96- 2.73	0.07	1.20	0.55- 2.59	0.65
Peer Relation	L	Ref			Ref		
	I	1.13	0.75- 1.70	0.55	0.92	0.55- 1.54	0.74
	H	1.56	0.82- 2.99	0.18	1.13	0.45- 2.79	0.80
Conduct	L	Ref			Ref		
	I	1.23	0.75- 2.02	0.40	1.27	0.69- 2.33	0.44
	H	1.39	0.80- 2.42	0.24	1.34	0.58- 3.11	0.49
Attention	L	Ref			Ref		
	I	1.09	0.71- 1.69	0.69	1.03	0.59- 1.77	0.93
	H	1.15	0.67- 1.96	0.62	0.98	0.45- 2.15	0.96
Prosocial	L	0.88	0.63- 1.30	0.73	0.73	0.27- 1.98	0.53
	I	0.91	0.42- 1.83	0.60	0.89	0.54- 1.47	0.64
	H	Ref			Ref		

[1]Bivariable multinominal logistic regression

[2] Multivariable multinominal logistic regression adjusted for study center, depression, anxiety, substance use, mother's education level, living as a couple, parity, mother's age, ACE, small for gestational age and preterm birth

*p-value<5%

H, high-level symptoms; I, intermediate-level symptoms; L, low-level symptoms; SDQ, Strengths and Difficulties Questionnaire; Ref, reference group.

Supplementary Table 3. B. Association between psychotropic exposure during pregnancy and the trajectory emotional and behavioral outcome of the child (unimputed dataset) (N= 1120)

SDQ outcome		Unadjusted[1]			Adjusted[2]		
		OR	CI	p-value	OR	CI	p-value
Total	L	Ref			Ref		
	I	2.68	1.84- 4.89	0.95	1.21	0.62- 2.38	0.58
	H	4.39	2.08- 19.68	0.27	1.69	0.51- 5.47	0.40
Emotional	L	Ref			Ref		
	I	3.95	2.31- 9.54	0.21	**2.21**	**1.03- 4.78**	**0.042***
	H	4.79	2.22- 21.65	0.19	0.99	0.31- 3.11	0.98
Peer Relation	L	Ref			Ref		
	I	2.92	1.9- 5.95	0.79	0.81	0.40- 1.62	0.55
	H	5.7	2.21- 45.04	0.17	0.8	0.20- 3.18	0.75
Conduct	L	Ref			Ref		
	I	2.86	1.87- 5.87	0.85	1.27	0.61- 2.67	0.52
	H	2.87	1.68- 8.57	0.89	1.84	0.65- 5.16	0.25
Attention	L	Ref			Ref		
	I	2.69	1.83- 5	0.96	0.95	0.48- 1.88	0.89
	H	2.62	1.61- 6.95	0.92	1.01	0.31- 3.25	0.99
Prosocial	L	1.93	1.28- 5.65	0.39	0.25	0.03- 2.00	0.19
	I	2.25	1.67-3.62	0.37	0.71	0.37- 1.35	0.30
	H	Ref			Ref		

[1]Bivariable multinominal logistic regression

[2] Multivariable multinominal logistic regression adjusted for study center, depression, anxiety, substance use, mother's education level, living as a couple, parity, mother's age, ACE, small for gestational age and preterm birth

* significant p-value <5%

H, high-level symptoms; I, intermediate-level symptoms; L, low-level symptoms; SDQ, Strengths and Difficulties Questionnaire; Ref, reference group.

Supplementary table 4. Association between psychotropic exposure during pregnancy and internalizing and externalizing outcomes (dataset imputed for covariates and outcome) (N= 1862)

SDQ outcome	Child's age	Unadjusted [1]			Adjusted [2]		
		β	p-value	CI	β	p-value	CI
Internalizing problems	3	0.27	0.524	-0.57 - 1.11	-0.41	0.384	-1.33 - 0.52
	5	0.16	0.687	-0.64 - 0.97	-0.44	0.450	-1.59 - 0.71
	8	1.07	0.211	-0.64 - 2.78	-0.08	0.923	-1.70 - 1.54
	11	0.21	0.670	-0.75 - 1.17	-0.06	0.914	-1.21 - 1.90
Externalizing problems	3	0.21	0.649	-0.70 - 1.12	-0.06	0.914	-1.21 - 1.90
	5	0.03	0.942	-0.80 - 0.86	-0.11	0.837	-1.14 - 0.92
	8	0.10	0.899	-1.45 - 1.64	-0.08	0.923	-1.70 - 1.54
	11	0.11	0.833	-0.93 - 1.15	0.01	0.985	-1.44 - 1.44

[1] Bivariable (simple) linear model

[2] Multivariable (multiple) linear model adjusted for study center, depression, anxiety, substance use, mother's education level, living as a couple, parity, mother's age, ACE, small for gestational age and preterm birth

*p-value<5%

Supplementary table 5. Association between psychotropic exposure during pregnancy and binary emotional and behavioral outcome of the child (dataset imputed for covariates and outcome) (N= 1862)

SDQ outcome	Unadjusted [1]			Adjusted [2]		
	OR	p-value	CI	OR	p-value	CI
Total	1.27	0.250	0.84- 1.91	0.76	0.488	0.36- 1.63
Emotional	1.21	0.368	0.80- 1.83	0.92	0.760	0.52- 1.61
Peer Relation	1.32	0.203	0.86- 2.03	1.22	0.512	0.67- 2.22
Conduct	1.08	0.744	0.68- 1.71	1.36	0.352	0.71- 2.60
Attention	1.20	0.347	0.82- 1.76	0.96	0.878	0.54- 1.68
Prosocial	1.29	0.210	0.87- 1.92	0.99	0.987	0.54- 1.82

[1] Bivariable logistic regression model

[2] Multivariable logistic regression model adjusted for study center, depression, anxiety, substance use, mother's education level, living as a couple, parity, mother's age, ACE, small for gestational age and preterm birth

* p-value<5%

Abstract in French

L’impact de l’utilisation prénatale de psychotropes par la mère sur les résultats émotionnels et comportementaux de l’enfant

Résumé

Introduction: L'anxiété et la dépression font partie des complications les plus courantes de la grossesse. Les recherches sur les effets néfastes de l'anxiété et de la dépression non traitées sur le développement de l'enfant, ainsi que sur l'impact de la pharmacothérapie sur ces affections, ont donné des résultats incohérents. Parmi ces études, un nombre limité se sont concentrées sur les résultats émotionnels et comportementaux de l'enfant. Ainsi, cette étude visait à évaluer l'association entre l'exposition in utero à des médicaments psychotropes et les conséquences émotionnelles et comportementales indésirables.

Méthode: Cette étude a inclus 1862 dyades mère-enfant de la cohorte EDEN en France. L'utilisation maternelle de médicaments psychotropes prénatals a été évaluée au moyen de données de questionnaire, combinées à des dossiers médicaux et à des tests d'échantillons de méconium. Les données sur les résultats ont été recueillies au moyen du questionnaire sur les forces et les difficultés (SDQ) à quatre moments : 3, 5, 8 et 11 ans. Outre les modèles linéaires, traitant les résultats du SDQ de manière transversale et longitudinale via des trajectoires SDQ, des modes de régression logistique binomiale et multinomiale ont été mis en œuvre pour étudier l'association entre l'exposition et les résultats du SDQ. Ces modèles contrôlaient plusieurs facteurs de confusion. De plus, nous avons testé si les effets étaient modifiés par le sexe de l'enfant.

Résultats: Toutes les personnes dont les résultats du test de méconium étaient positifs ont été identifiées comme ayant consommé des médicaments psychotropes grâce au questionnaire. Parmi le groupe exposé, 55,56 % ont commencé à prendre des médicaments pendant la grossesse, et parmi les non exposés, 13,08 % ont consommé des psychotropes avant la grossesse. Toutes les analyses évaluant l'association de l'exposition in utero aux psychotropes avec les résultats émotionnels et comportementaux ont montré des associations non significatives dans les modèles non ajustés et ajustés. Le terme d'interaction pour le sexe de l'enfant était également insignifiant dans tous les modèles.

Conclusion: Les résultats de cette étude suggèrent que les problèmes émotionnels et comportementaux chez les enfants ne font pas partie des effets indésirables de l'utilisation de

psychotropes pendant la grossesse ; cette association ne semble pas modifiée par le sexe de l’enfant.

Mots-clés: dépression prénatale, anxiété prénatale, médicaments psychotropes, développement émotionnel et comportemental