Master of Public Health

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Pregnant and stressed: The impact of maternal prenatal depression and anxiety symptomatology on child emotional and behavioural development trajectories in the EDEN cohort

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List of acronyms

ADHD	Attention-deficit hyperactive disorder
App	Average Posterior Probability
BIC	Bayesian Information Criterion
CI	Confidence Interval
CNIL	National Commission of Informatics and Liberty (Commission Nationale Informatique et Liberté)
EDEN	Study of the determinants of child development and health (Etude des Déterminants du développement et de la santé de l'Enfant)
FCS	Fully Conditional Specification
GBTM	Group-Based Trajectory Modelling
HPA axis	Hypothalamic-pituitary-adrenal axis
IC	Interval de Confidence
ICD-10	International Statistical Classification of Diseases and Related Health Problems-10
INSERM	National Institute of Health and Medical Research (L'Institut national de la santé et de la recherche médicale)
IPLESP	Pierre Louis Institute of Epidemiology and Public Health (Institut Pierre Louis d'Epidémiologie et de Santé Publique)
IPW	Inverse probability weighting
IQ	Intelligence Quotinent
MAR	Missing at Random
MCAR	Missing Completely at Random
MI	Multiple Imputation
MICE	Multiple Imputation using Chained Equations
MLE	Maximum Likelihood Estimation
MNAR	Missing Not at Random
PS	Propensity Score
SARS-Cov-2	severe acute respiratory syndrome-related Coronavirus 2
SD	Standard Deviation
SDQ	Strengths and Difficulties Questionnaire
SE	Standard Error
SMD	Standardised Mean Difference
WHO	World Health Organisation

Abstract (English)

Introduction: *In utero* exposure to prenatal maternal stress as measured through depression and anxiety symptomatology has been associated with adverse emotional and behavioural characteristics up to middle childhood. This study aimed to quantify and characterize the associations in a French sample.

Methods: 1135 children from the EDEN mother–child cohort set up in France were followed from pregnancy to the age of 11 years. Group-based trajectory modelling was used to model trajectories of behavioural and emotional characteristics measured at 4 timepoints via a parent-administered Strengths and Difficulties Questionnaire. Using propensity scores and inverse probability weighting to account for confounding factors, multinomial logistic regressions were used to quantify the associations. Stratified analyses were conducted by sex and reporting psychiatrist visits (1) during pregnancy and (2) from birth to 8 years after.

Results: Compared with children who were not exposed to high levels of maternal depressive symptoms in utero, those who did had a higher likelihood of presenting with high levels of emotional symptoms (OR_{IPW} = 1.90, 95% CI 1.21-2.99), conduct problems (OR_{IPW} = 1.68, 95% CI 1.06-2.64), inattention-hyperactivity (OR_{IPW} = 1.66, 95% CI 1.06-2.61) and peer relationship problems (OR_{IPW} = 1.90, 95% CI 1.06-3.34). Prenatal maternal anxiety was significantly associated with high levels of emotional symptoms (OR_{IPW} = 1.96, 95% CI 1.21-3.16) and low levels of prosocial behaviours (OR_{IPW} = 1.82, 95% CI 1.00-3.30). Females exposed to prenatal depression (OR_{IPW} = 1.89, 95% CI 1.00-3.58) and anxiety (OR_{IPW} = 2.41, 95% CI 1.26-4.63) were more likely to follow a high trajectory of emotional symptoms. Males exposed to prenatal depression (OR_{IPW} = 2.11, 95% CI 1.09-4.10) and anxiety (OR_{IPW} = 2.23, 95% CI 1.03-4.70) were more likely to be classified in the persistently high symptoms trajectory of conduct problems. Males exposed to prenatal maternal depression were additionally more likely to follow a high symptom trajectory of inattention-hyperactivity (OR_{IPW} = 1.88, 95% CI 1.00-3.53) and low symptom trajectory of prosocial behaviours (OR_{IPW} = 2.08, 95% CI 1.05-4.13). No increased risks by prenatal depression and anxiety exposure were identified in children of mothers who reported visiting a psychiatrist either during or up to 8 years after the pregnancy.

Conclusion: Prenatal maternal depression and anxiety are associated with increased risks of adverse emotion-behavioural outcomes in children. The associations with specific outcomes differ by sex and are buffered by accessing psychiatric care both during and after pregnancy. The study provides further evidence that failure to address mental health during pregnancy would be a missed opportunity to intervene and support children and families.

Key words: Prenatal stress, depression, anxiety, child development, EDEN cohort.

1. Introduction

1.1. Prenatal stress

The World Health Organisation (1) conceptualises health as a state of complete physical, mental and social well-being and not merely the absence of disease or infirmity. The Lancet Global Burden of Disease analysis (2) found depression and anxiety to be the top causes of morbidity in countries at all income levels, and the prevalence of both is particularly high among women. For women, pregnancy is a period of particular vulnerability to mental health difficulties as it entails numerous emotional, physical, and social changes requiring complex adaptation. Socioeconomic, social, and cultural contexts modulate individual ability to adapt to these changes, and failure to adapt can lead to higher levels of stress. Yet, the clinical definition of stress has been debated for decades - reflecting the conceptual, behavioural, psychosocial, and physiological complexity of the phenomenon. Across the scientific literature, maternal prenatal stress is commonly interpreted as an umbrella term encompassing a multitude of factors including cognitive and affective states associated with distress or negative mood (i.e. frustration, anxiety, depression) (3). Additionally, quantification of the phenomenon varies as some studies measure stress through 'objective' measures such as the experience of stressful events during pregnancy (4), while others assess 'subjective' stress using clinical questionnaires on depression, anxiety, or perceived stress (5). In practise, it may be important to distinguish between objective and subjective, as well as different types of subjective stress (i.e. anxiety, depression) firstly as they may exert different effects on the foetus, and secondly as the conditions may require management through different interventions (psychotherapy, antidepressants, anxiolytics, mindfulness etc.) (6).

Although perinatal mental illness is the leading cause of maternal morbidity and mortality in high-income countries (7), it has long fallen behind physical health in attention, funding and action. Symptomatology of depression and anxiety are estimated to impact between 10% and 25% of all pregnancies in high-income countries (8-11) and up to 65% in low- and middle-income countries (12-14). Additionally, people experiencing socioeconomic vulnerabilities are at heightened risk of perinatal mood disorders (15-17). Lack of social and partner support, current or previous exposure to different forms of abuse and violence, as well as personal or family history of any common mental disorder have been identified as key risk factors for the development of prenatal stress (14, 18).

1.2. Associations with child outcomes

Prenatal maternal stress is a public health issue with far-reaching consequences due to its dual impact on the mother-child dyad. In addition to morbidity and mortality experienced by the mother, the foetus is undergoing rapid development, which is strongly influenced by the

characteristics of the prenatal environment (19). The 'Developmental Origins of Health and Disease (DOHaD) hypothesis' (20) suggests that the *in utero* environment can have long-term consequences for infant and child development by setting probabilistic parameters for both adaptive and maladaptive outcomes. Additional to foetal programming, maternal risk might be transmitted to children via genetic mechanisms, postnatal exposure to maternal negative cognitions, behaviours, and affects, as well as more stressful contexts of the children's lives. Postpartum factors from negative affect to inadequate parenting practices may be mediators on the pathway from prenatal stress to child developmental outcomes (18).

The body's biological response to psychological stress is instigated by the sympathetic nervous system and the hypothalamic-pituitary-adrenal (HPA) axis, which alter placental metabolism of maternal steroids (21). The developing foetus is thus exposed to more stress biomarkers such as glucocorticoids and pro-inflammatory cytokines (22), leading to increased activation of the foetal HPA axis and alterations in hippocampal neuronal development. Findings from structural neuroimaging studies have revealed stress-induced changes in foetal brain anatomy, including deficits in grey and white matter volumes, hippocampus, amygdala and corpus callosum in response to *in utero* stress exposure (23). The hippocampus contains numerous glucocorticoid receptors, rendering it vulnerable to stress biomarker exposure, and is postulated to link abnormal HPA axis activity to the emergence of mental health disorders. Ultimately, the foetal changes could manifest in developmental outcomes such as greater cortisol and behavioural stress reactivity in the child (24).

Evolutionarily, these biological changes likely formed part of an adaptive cascade as prenatal stress can be regarded as an early indicator of the postnatal environment (25). For instance, developing anxious traits may render the offspring more vigilant and alert to danger, while high levels of conduct disorder and aggression may act as adaptive traits in situations where survival depends on willingness to explore novel environments or fight off predators (26). Additionally, DiPietro *et al.* (27) found that levels of prenatal anxiety and depressive symptoms were associated with more advanced motor and cognitive development at age 2. The authors suggest mild to moderate levels of psychological stress may enhance child maturation in healthy populations. Although these traits may increase an individual's propensity to reach safety and survive in situations of danger, persistent activation of the stress response that characterises modern social stress leads to physiological and experiential overload (26). A variety of evidence from clinical, pre-clinical and neuroimaging studies link in utero stress exposure to numerous adverse outcomes such as low birth weight and preterm birth (17, 28), as well as features not confined to the neonatal period in the mental, emotional and behavioural domains. Various studies have identified associations between prenatal exposure to stress and developmental delays, poorer cognition, difficult temperament

(24), behavioural dysregulation, internalising and externalising problems (4, 19, 29), Autistic Spectrum Disorders (ASD), Attention-Deficit Hyperactive Disorder (ADHD) (30) and other psychiatric disorders (10).

There is no consensus regarding the characteristics of transmission of prenatal stress to offspring (31). It is also not clear whether all types of stress assert similar effects (5, 32, 33), as the biological and interpersonal mechanisms of action may differ, thus leading to different types of difficulties. Individual adaptive skills and reporting style are rarely accounted for (34). A review by Van den Bergh *et al.* (24) did not identify a specific vulnerable period of gestation, however postulated outcomes may vary depending on the trimester of exposure to stress, and time of development of specific brain areas and circuits, stress system, and immune system.

Bennett *et al.* (8) report the prevalence of depression generally increases as the pregnancy progresses. Additionally, approximately half of the people experiencing postnatal depression also experienced prenatal depression (35). Untreated depression continuing into the postnatal period can lead to difficulties in the mother-child attachment, which may further impair of the child‘s neuro-behavioural development and lead to negative long-term socioemotional consequences (36). Better characterisation of the development mechanisms of adverse outcomes and factors leading to vulnerability is warranted to facilitate timely, targeted, and specific interventions.

1.3. Child emotional and behavioural characteristics

Emotional and behavioural characteristics of children are shaped in a series of complex relationships between factors at multiple stages of the developmental cascade (19, 37). There are multiple ways of conceptualising behavioural and emotional problems in different domains. According to the American Psychiatric Association Dictionary of psychology (38), externalizing problems are characterized primarily by actions in the external world, such as hyperactivity, acting out, hostility and aggression. These may in extreme cases present through clinical Conduct Disorder and ADHD. Internalizing problems are characterised by emotional processes within the self, such as anxiety and depression, and may manifest through difficulties in interpersonal relationships.

Although emotional and behavioural problems do not constitute a clinical diagnosis, they nevertheless assert a significant negative impact on the individual, the family and society. If left unaddressed, child emotional and behavioural problems are commonly associated with poor academic, occupational, and psychosocial functioning. Maladjustments may impede learning, restrict access to activities and social opportunities, and require management via significant human and financial resources. Early childhood emotional problems can develop into panic disorder, generalized anxiety disorder (GAD), social phobias, OCD and depression

(37). Sutherland and Brunwasser (39) and Glover (25) assert that the vulnerability to specific outcomes differs by child biological sex.

1.4. Research aims and objectives

While multiple studies report strong associations between prenatal stress and outcomes that are maladaptive in modern environments, others have found low to moderate or no effects. Factors that impact vulnerability and resilience to specific outcomes remain poorly characterised, and even the exact definition of prenatal stress differs due to a lack of consensus on its conceptualisation. Understanding the aetiology of maladaptive emotional and behavioural characteristics in different populations is vital to design effective interventions, prevent difficulties, and best support children throughout their development. Maternal mental health is an early modifiable influence on children's development and thus, identifying at-risk individuals and addressing treatment and support needs within antenatal care may help reduce associated burden on the next generation. Characterisation of maladaptive behaviour trajectories well into teenage years may additionally allow to differentiate risks for preliminary early childhood difficulties from persistent antisocial behaviour.

This study sits within the Devstress project conducted as a multicentre initiative in-between the Institut Pierre Louis d'Epidemiologie et de Sante Publique (IPLESP), INSERM U1136 in Paris and the Bordeaux Population Health Research Centre, INSERM 1219. The project combines clinical epidemiology with pre-clinical approaches in animal models to characterise the biological and social mechanisms leading to adverse developmental outcomes attributed to prenatal maternal stress. The mental health issues experienced by people of all genders who experience pregnancy is beyond the scope of this study, and thus the focus will be solely on women/mothers.

The study will have the following objectives:

1. Quantify the association between maternal prenatal stress observed through self-reported anxiety and depression symptomatology and developmental trajectories of five subtypes of emotional and behavioural characteristics in the longitudinal French EDEN birth cohort.
2. Assess sex differences in vulnerability to specific outcomes.
3. Explore potential effect modification by whether the mother reports accessing psychiatric services (i) during pregnancy and (ii) up to 8 years after the birth.

2. Methods

2.1. The EDEN Cohort

This study uses data from the EDEN cohort (Etude des Déterminants pré- et postnatals précoces du développement et de la santé de l'ENfant). The EDEN cohort consists of mother-child pairs recruited antenatally before 24 weeks amenorrhea in 2003-2006 from two maternity units in France (Nancy and Poitiers) during prenatal visits to the departments of Obstetrics and Gynaecology. On average, women were enrolled at 15 weeks amenorrhea (range: 8-26). Exclusion criteria included multiple pregnancies, pre-pregnancy diabetes (as these carry specific risks not investigated through the cohort), French illiteracy (as the information was obtained through self-report questionnaires) and reporting a plan to relocate outside of the region within 3 years (to maximise retention). Participants who gave informed consent (53% of invited women) were regularly followed since pregnancy. Complete details on participation and attrition are available in the EDEN cohort profile paper by Heude *et al.* (40). Compared to a nationally representative sample of pregnant women in France in 2003, EDEN study participants had higher educational attainment, but were similar in other key sociodemographic characteristic and birth outcomes. Over the follow-up period, attrition rates were highest in families in which the mother was young, had a low educational level and low income, did not live with the child's father or had psychological difficulties in pregnancy (40).

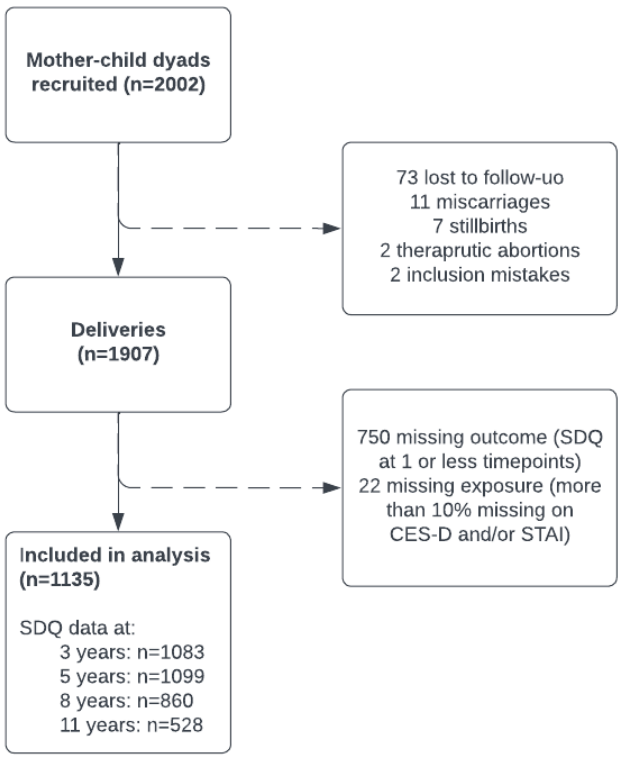

Figure 1. *Flowchart of the study sample inclusion.*

Analyses in this study were based on mother-child dyads where responses to at least 90% of questions on prenatal anxiety and depression symptomatology were available, as well as children's behavioural scores in at least two of the four possible study waves at 3, 5, 8, and 11 years of age. Based on these criteria, 1135 mother-child dyads were included in the sample (Figure 1). Characteristics of the excluded pairs are shown in Supplementary table 1.

2.2. Variables

2.2.1. Exposure: Maternal prenatal stress

Depressive symptoms were measured using the French version of the Centre for Epidemiologic Studies Depression Scale (CES-D) (41). Women were presented with 20 statements regarding mood states in the previous week such as "I felt lonely," "People were unfriendly," and "My sleep was restless," and responded whether the statement was true on a Likert scale ranging from none (0) to all (3) of the time. The overall score could range between 0 to 60 and a cut-off of 16 or above is generally recommended for inferring high levels of depressive symptomatology (42). Individuals with a score of 16 or more must have reported experiencing either: (i) a minimum of 6 of the 20 symptoms in the CES-D with persistence for most of the previous week, (ii) or a majority of the symptoms on the scale for shorter periods of time. The internal consistency in the present sample measured via the Cronbach's Alpha was $\alpha = 0.852$; 95% CI 0.828 - 0.872. Overall, 96 mothers (8.5% of the sample) were missing one or two responses in the CES-D: 74 were missing one response and 22 were missing two responses).

Anxiety symptoms were measured using the State Anxiety Inventory (STAI) (Cronbach's Alpha $\alpha = 0.91$; 95% CI 0.897 - 0.92) (43). The 20 statements depicting current emotional states such as "I feel calm," "I feel frightened" and "I feel indecisive," were rated from not at all (1) to very much (4) reflecting how the individual feels at the moment they are completing the test and summed as a score ranging from 20 to 80. A score of 38 or above (the 80^{th} percentile of the score distribution in the EDEN cohort prior to applying inclusion criteria (44)) was used to dichotomise the scale. Overall, 116 (10.2%) women were missing one or two responses (79 were missing one response and 37 were missing two responses).

Both the CES-D and STAI have good psychometric properties (45) and have been validated for use in pregnant populations. Incomplete answers for those missing 10% of less of the questions were replaced with the person mean of all other answers. This approach is supported by the high internal consistency measured by the Cronbach's Alphas of both scales. Additionally, previous evidence (46-48) has shown person-mean provides a reliable estimate in Likert ratings if the proportion of respondents with missing data as well as the proportion of missing items are low.

2.2.2. Outcome

Children's emotional and behavioural patterns were assessed using the French version of the parent-reported Strengths and Difficulties Questionnaire (SDQ) (49). The questionnaire was completed by the children's mothers at ages 3, 5, 8, and 11. The SDQ is composed of 25 items comprising 5 scales: one positive (prosocial behaviours) and four negative (emotional symptoms, conduct problems, symptoms of hyperactivity/inattention, and peer relationship problems) (50). The questionnaire is identical from ages 5-11, however at the age of three, a modified age-appropriate version was administered that softens an item on reflectiveness and replaces two of the questions on antisocial behaviour with questions on oppositionality. For each of the items on the scale, caregivers responded whether the behaviour was 'not true,' 'somewhat true,' or 'certainly true' of their child. In line with scoring guidance (49), positively worded items in each scale were reverse-coded and the scores were scaled up pro-rata if at least 3 items in a scale were completed. For each of the 5 scales, the score could range from 0 to 10.

The Strengths and Difficulties Questionnaire yields high internal consistency, test-retest stability, and parent-youth agreement of the various SDQ scales. The French version of the survey has been validated by Shojaei *et al.* (51), who found the parent reported SDQ in France reliable and useful in epidemiological research. Capron, Thérond and Duyme (52) provide support for the real-world relevance of the SDQ by showing that difficulty scores at the top 10th percentile are associated with an increase in the number of at-risk youths (school failure and referrals for psychological care).

2.2.3. Covariates

Risk factors that met the theoretical criteria for confounding feature demographic measures such as centre of recruitment, parity (no prior births or at least one prior birth), family migration background (none, first generation and second generation) (53), maternal age, maternal and paternal education (years) (Cortes Hidalgo et al., 2020), maternal and paternal employment status (either employed or studying vs. not), family income (above or below 1500 euros/month corresponding to the lowest quartile in the sample) and family financial difficulties (reporting difficulties with clothing, feeding, utilities) (17).

A proxy for relationship status was whether the mother declared cohabiting with the father of the child, and social support was assessed at inclusion via four variables: support with practical problems from the partner, support with practical problems from someone else in their network, emotional support from the partner and emotional support from someone else in their network. The variables were not combined due to the psychological and social implications of different types of support from people at various proximities to the pregnancy

and child upbringing will have on both the mother's emotional wellbeing as well as the consecutive development of the child (54). Maternal history of depression (18) was considered via whether the mother reported any antidepressant use prior to pregnancy. Due to their association with (i) heritable child characteristics, (ii) the psychological status of the mother, and (iii) subsequent parenting behaviours, childhood behavioural problems and experienced adversity (any of the following experienced in childhood: material deprivation, circumstances leading up to placement in a public assistance program, needing educational assistance, parental conflict, conflict with or between parents, violent home environment, been a victim of beating) (17) were assessed as dichotomous variables. Childhood behavioural problems of the father were considered due to the potential implications for genetic influences, the partner relationship, and parenting behaviours.

Effect modifiers might improve predictive efficacy and lend vital explanatory power concerning the circumstances in which maternal stress can be more strongly associated with specific negative outcomes in children. Child sex was identified as a potential effect modifier, and thus a stratified analysis was conducted by male and female sex (39). Additionally, seeing a psychiatrist was considered an effect modifier as it may indicate self-efficacy of the mother, her ability to address her problems and additionally alleviate potential maladjustments in child development both during pregnancy and afterwards throughout childhood (55). Stratified analysis was presented based on whether the mother had reported any visits to a psychiatrist throughout pregnancy (assessed at inclusion and birth). Additional stratification was done depending on whether the mother has reported any psychiatrist visits postnatally between birth and 8 years after (assessed at 4 months, 8 months, 12 months, 2 years, 3 years, 4 years, 5 years, and 8 years). As the proportion of missingness was high in the variables included, the variables were dichotomised as 'known to have seen a psychiatrist' vs 'no known visit to a psychiatrist.'

2.3. Statistical methods

Group-based trajectory modelling (GBTM) and Joint trajectory modelling were executed via the Proc Traj package on SAS software (version 9.4; SAS Institute, Inc., Cary, NC). All other analyses were conducted using R Studio (version 4.1.2; R Core Team (56))

2.3.1. Descriptive statistics

Baseline characteristics of the sample are reported in Table 1 according to depression and anxiety status. Bivariate analyses are presented via p-values denoting the results of Fisher's Exact Tests, Independent samples t-tests or Unpaired Two-Sample Wilcoxon Tests depending on the variable type. A similar procedure was implemented to characterise the excluded individuals in Supplemental table 1.

2.3.2. Group-based trajectory modelling

Group-based trajectory modelling (GBTM) was used to classify individuals into meaningful subgroups that show statistically similar trajectories of emotional and behavioural characteristics between the ages of 3 and 11 years. GBTM is a specialised application of finite mixture modelling that uses maximum likelihood estimation (MLE) to identify groups of distinctive trajectories, which are summarised by a finite set of polynomial functions (57, 58). This is in opposition to standard ex-ante methods that use assignment rules based on subjective categorisation criteria, as GBTM allows the form and number of trajectories to emerge from the data itself. It additionally provides metrics to evaluate the precision of group assignment by estimating each individual's probability for membership in each trajectory and assigning them to the group they have the highest probability of belonging to. GBTM is a semi-parametric approach, and as such it does not assume a continuous distribution of trajectories within the population. This makes using a censored normal distribution in GBTM well-suited for phenomena such as behavioural symptoms, which are likely to be skewed (59). GBTM aims to identify subgroups of individuals who share optimally similar score trajectories within the group, and make the groups across as different as possible (60).

GBTM handles missing data by fitting a model using Maximum Likelihood Estimation (MLE). MLE assumes data are missing at random (MAR) and individuals with missing data are similarly assigned to the group they most likely belong to. In the present sample, 443 (39%) children had data available at all four timepoints, 408 (36%) had SDQ data at three timepoints while 284 (25%) had provided information at two timepoints. It should be noted individuals do not belong to a trajectory group but are rather assigned a probability of group membership. Thus, the model acts as a convenient statistical device to summarise groups of individuals following the same approximate developmental course, but it is not a concrete reflection of the reality. The number of trajectory groups can be altered, and individuals do not follow the group-level trajectory in lock step (61).

Multiple models were tested with different numbers of developmental trajectories and combinations of polynomial shapes (intercept, linear, quadratic, cubic). Bayesian information criterion (BIC) was used to guide model selection. However, a preference for an improvement of $2*\Delta BIC > 10$ (Bayes factor) between consecutive models was moderated by (a) a preference for a useful parsimonious model which fits the data well; (b) maximising the average posterior probability (App) value at >0.75 for each group; (d) adequate sample proportion in each group; (e) reasonably narrow confidence intervals; and (f) the odds of correct classification based on the posterior probabilities of group membership >5 for each group (Supplementary table 2 A-E). The trajectory membership was used as a dependent categorical variable for each of the SDQ subscales.

2.3.3. Joint trajectory analyses

Goodman, Lamping and Ploubidis (62) suggest that in low-risk and general population samples, a three-subscale division of the SDQ can be used by combining emotional symptoms and peer relationship problems into ‘internalising problems’ (10 items) and conduct problems and inattention-hyperactivity into ‘externalising problems’ (10 items). To assess the validity of this approach, joint trajectory modelling was used in the sample to probabilistically link trajectories of the subscales thought to be theoretically related (Nagin, 2010).

2.3.4. Multiple Imputation using Fully Conditional Specification

Multiple imputation (MI) using Fully Conditional Specification (FCS) implemented by the Multiple Imputation by Chained Equations (MICE) algorithm was used to impute data missing in covariates. MICE is a Monte-Carlo Markov Chain algorithm under the missing at random (MAR) hypothesis in which missing values are replaced in multiple versions of the dataset by simulating random draws from nonstandard distributions via Markov chains. MICE assumes that we can make an educated guess about missing data’s true value via complete data. The MAR assumption is mathematically convenient because it allows one to eschew an explicit probability model for nonresponse. In a longitudinal study, however, MAR may seem implausible as it is possible that subjects drop out for reasons related to current data values (63, 64). Nevertheless, MAR methods have been shown to perform well and even be more appropriate than alternatives in rich longitudinal studies even if data are missing not at random (MNAR) (65). A key feature of MI is that the imputation phase is operationally distinct from subsequent analyses. Following the imputation, each of the simulated complete datasets is analysed using standard methods. The results from each dataset are then pooled to produce estimates and confidence intervals that incorporate missing-data uncertainty.

MI was chosen over (i) exclusion of incomplete cases because this only leads to valid inferences when data are missing completely at random (MCAR), meaning probabilities of response do not depend on any other data values, present or unobserved. This assumption rarely holds in longitudinal studies. Case deletion results in bias when discarded cases differ systematically from the rest, and loss of power when the proportion of missingness is high. MI was chosen over (ii) single imputation as single imputation often overstates precision due to the omission of between-imputation variability. For joint inferences about multiple parameters, even small rates of missing information may impair a single-imputation procedure. In modern computing environments, the effort required to produce and analyse a multiply imputed dataset is often not substantially greater than what is required for good single imputation. MI was chosen over (iii) maximum likelihood estimation of missing covariates as real-world data is rarely fully parametric, which is a key assumption of the MLE approach. Additionally, by

imputing more than one value for each missing observation, uncertainty due to missingness is introduced into the analysis phase.

The five-iteration MI model included all variables included in the substantive analysis or predictive of missingness (outcome and exposure variables were used in the imputation model but were not themselves imputed) using binary or polytomous logistic regression for categorical covariates and linear regression for continuous covariates (66). In the present sample, on average, 1.6% of data in covariates were missing (with a maximum of 7.6% for paternal education). Altogether, 175 (15.4%) of the participants were missing any data in the covariates. Thus, in line with recommendations by Bodner (67) for minimum number of imputations given this proportion, 20 datasets were imputed. The relative efficiency of imputing 20 datasets was $\sqrt{1+\frac{\lambda}{m}} = \sqrt{1+\frac{0.154}{20}} = 1.0038$, meaning the standard deviation of the estimates was only 0.38% wider than if an infinite number of datasets were imputed (64).

2.3.5. Propensity score

Rosenbaum and Rubin (68) define the propensity score (PS) as the "probability of treatment assignment conditional on observed baseline covariates." The PS is a score assigned to each participant between 0 and 1 that reflects the likelihood of being in one of the exposure categories of interest conditional on a set of variables.

In line with recommendations from Brookhart *et al.* (69) as well as Chesnaye *et al.* (70), all baseline covariates that could confound the relationship between the exposure and outcome were considered on the basis of the criteria for confounding (71). A prominent simulation study by Brookhart *et al.* (69) suggests variables that are statistically unrelated to the exposure but related to the outcome should always be included in a propensity score calculation as this acts to decrease variance without increasing bias. The inclusion of variables only associated with the exposure, however, should be avoided to prevent unnecessary increase in variance (70). Variables that are measured post-baseline should be avoided as they may be influenced or modified by the exposure (72). Following those recommendations, bivariate associations between each covariate and outcome subscale trajectory membership were calculated using Fisher's Exact Test, Analysis of Variance (ANOVA) and Kruskal-Wallis Test. Variables that were associated with the outcome at $p>0.20$ were used to calculate propensity scores for the observations independently in each subscale using binomial logistic regressions.

2.3.6. Inverse probability weighting (IPW)

The propensity scores were incorporated into the analysis via inverse probability weighting (IPW). IPW separates the design of the study from the analysis by creating a

pseudo-population different from that from which the data was collected (73). The new sample balances the distribution of measured baseline patient characteristics in the exposed and unexposed groups by weighting each individual unit in the analysis by the inverse probability of receiving their actual exposure, thus simulating a randomised control trial (74). In contrast to true randomization, it should be emphasized that the propensity score can only account for confounders that have been measured and are included in the analysis. However, a key benefit of propensity scores over standard regression analysis is their ability to sidestep issues with multicollinearity.

Following the application of the method, balance between exposed and unexposed groups was checked for all included baseline characteristics in each imputed dataset both before and after weighting via standardised mean differences (SMD) (75). As a rule of thumb, SMD below 0.1 can be considered negligible (70, 76). In cases where SMD remained above 0.1 in any of the twenty imputed datasets after application of IPW, supplementary regressions were run to check for residual confounding by adding the variable to the pooled multivariate regression model. If there was a change in the beta coefficient of the exposure above 10% (indicating residual confounding), a doubly-adjusted OR was presented in the final results (77). If a covariate is rare, extreme weights can increase the variability of the treatment effect, leading to biased results. To address this, weights were curtailed at the 99th percentile (78).

2.3.7. Multinomial logistic regression

Multinomial logistic regressions on multiply imputed and inverse probability weighted datasets were used to quantify the association between maternal prenatal anxiety and depression status with each of the SDQ subscale categories, taking the category with least problem characteristics (low trajectory for all four difficulties subscales and high trajectory for prosocial behaviours) as reference. Results were pooled from all MI datasets. Subsequent stratified analyses were conducted by the following variables (using the same methods): (i) child sex, (ii) whether the mother has reported seeing a psychiatrist during pregnancy (asked at enrolment and birth), and (iii) whether the mother has reported seeing a psychiatrist from childbirth up eight years after (asked at 4 months, 8 months, 12 months, 2 years, 3 years, 4 years, 5 years, and 8 years).

2.4. Ethical considerations

The longitudinal EDEN cohort received approval from the ethics committee of Kremlin Bicetre and from CNIL (Commission Nationale Informatique et Liberté), the French data privacy institution. Written consent was obtained from the mother for herself at inclusion and for her child after delivery (40).

3. Results

3.1. Description of the study population

The demographic characteristics of the sample are shown in Table 1. 21.8% of women were classified in the high depression symptomatology group and 17.5% in the high anxiety symptoms group. Of the 247 women with elevated levels of depression, 116 (47.0%) also belonged to the high anxiety levels category. 58.3% of the anxious women were simultaneously classified as depressed (Fisher's exact test OR = 8.56, 95% CI 6.04-12.20). 46.9% of the children were female. Overall, mothers classified as experiencing prenatal depression or anxiety were more likely to have less favourable profiles on key socioeconomic and social support characteristics associated with mental health status. They were more likely to live in a household with income below €1,500 per month, report financial difficulties meeting costs of clothing, food or utilities, report previous antidepressant use (indicating history of depression), and fewer years of education. Both exposures were associated with lower propensity to report presence of emotional support from partner and network, lower likelihood to live with the father of the child, having experienced adversity in childhood, reporting behavioural problems in their own childhood, and were near the threshold for significance in their association with the propensity to be unemployed (*p=0.054* for depression and *p=0.060* for anxiety). Additionally, women scoring high in the depression scale were more likely to be primiparous and be first- and second-generation migrants, while anxious women were more likely to have been recruited from Pompiers and be older. Women who scored higher on depression or anxiety were more likely to have visited a psychiatrist during pregnancy, and women with elevated levels of depression were more likely to have reported visiting one after pregnancy.

3.2. Trajectories

For all subscales, three-group models were chosen based on fit statistics, posterior probabilities, interpretability, and meaningful group sizes. Symptom trajectories between ages 3-11 are presented graphically along with 95% confidence intervals (CI) in Figure 2. Three-trajectory models for each of the subscales denote persistently low, intermediate, or high-level symptoms. Overall, 13.2% of the children were allocated to the trajectory indicating persistently high levels of emotional symptoms, 15% to the highest trajectory of conduct problems, 14.6% to high inattention-hyperactivity and 7.8% to high levels of peer relationship problems group. 7.6% followed the persistently low levels of prosocial behaviours trajectory. Supplemental table 2 (A-E) shows Bayesian Information Criterions (BIC) and Average Posterior Probabilities (App) for the best models based on 1-5 groups for each outcome.

Table 1. Characteristics of the study population (N=1135)											
Variables		**Depression**					**Anxiety**				
		High (n = 247)		**Low (n=888)**			**High (n = 199)**		**Low (n=936)**		
	N	**n**	**%**	**n**	**%**	**P-value[a]**	**n**	**%**	**n**	**%**	**P-value[a]**
Centre of recruitment (Nancy)	1135	114	46.15	421	47.41	*0.773*	79	39.70	456	48.72	*0.023**
Primiparous (yes)	1133	100	40.82	433	48.76	*0.03**	82	41.41	451	48.24	*0.085*
Mother unemployed and not studying	1127	52	21.22	139	15.76	*0.054*	43	21.72	148	15.93	*0.06*
Father unemployed and not studying	1114	11	4.62	37	4.22	*0.857*	10	5.24	38	4.12	*0.44*
Migrant background	1117					*0.033**					*0.465*
None		205	84.02	780	89.97		168	86.60	817	89.09	
Second generation		31	12.70	70	8.07		20	10.31	81	8.83	
First generation		8	3.28	17	1.96		6	3.09	19	2.07	
Household income <1500 €/month	1129	36	14.63	83	9.40	*0.025**	35	17.68	84	9.02	*<0.001**
At least one financial difficulty (clothing, feeding, utilities)	1127	29	11.84	36	4.08	*<0.001**	24	12.12	41	4.41	*<0.001**
Antidepressant use before pregnancy	1126	27	11.02	29	3.29	*<0.001**	24	12.18	32	3.44	*<0.001**
Practical support (partner)	1124	25	10.42	66	7.47	*0.143*	20	10.31	71	7.63	*0.246*
Practical support (someone else)	1130	48	19.59	140	15.82	*0.175*	36	18.27	152	16.29	*0.528*
Emotional support (partner)	1121	12	5.00	17	1.93	*0.019**	11	5.67	18	1.94	*0.01**

Emotional support (someone else)	1129	23	9.39	43	4.86	*0.013**	19	9.64	47	5.04	*0.018**
Living with father of the child	1128	18	7.35	19	2.15	*<0.001**	12	6.09	25	2.69	*0.025**
Childhood adversity (mother)	1117	90	37.50	195	22.23	*<0.001**	65	33.68	220	23.81	*0.006**
Childhood behaviour problems (mother)	1122	27	11.02	38	4.33	*<0.001**	18	9.09	47	5.09	*0.042**
Childhood behaviour problems (father)	1055	27	11.84	78	9.43	*0.317*	12	6.45	93	10.70	*0.081*
Child sex (female)	1135	132	53.44	400	45.04	*0.021*	96	48.24	436	46.58	*0.696*
Known visits to a psychologist during pregnancy	1135	44	17.81	54	6.08	*<0.001**	40	20.10	58	6.20	*<0.001**
Known psychologist visits after birth to 8 years	1135	54	21.86	106	11.94	*<0.001**	36	18.09	124	13.25	*0.092**
		Mean	**SD**	**Mean**	**SD**	**P-value[b]**	**Mean**	**SD**	**Mean**	**SD**	**P-value[b]**
Maternal age (years)	1109	30.94	5.06	30.56	4.6	*0.265*	31.39	4.93	30.49	4.64	*0.016**
		Median	**IQR**	**Median**	**IQR**	**P-value[c]**	**Median**	**IQR**	**Median**	**IQR**	**P-value[c]**
Maternal education (years)	1131	13	(12.0-17.0)	14	(11.0-17.0)	*<0.001**	14	(11.0-17.0)	14	(12.0-17.0)	*<0.001**
Paternal education (year)	1054	12	(11.0-14.0)	14	(11.0-17.0)	*0.156*	12	(11.0-14.75)	12	(11.0-17.0)	*0.217*

[a] Fisher's exact test; [b] independent samples t-test; [c] Unpaired Two-Samples Wilcoxon Test

* p<0.05

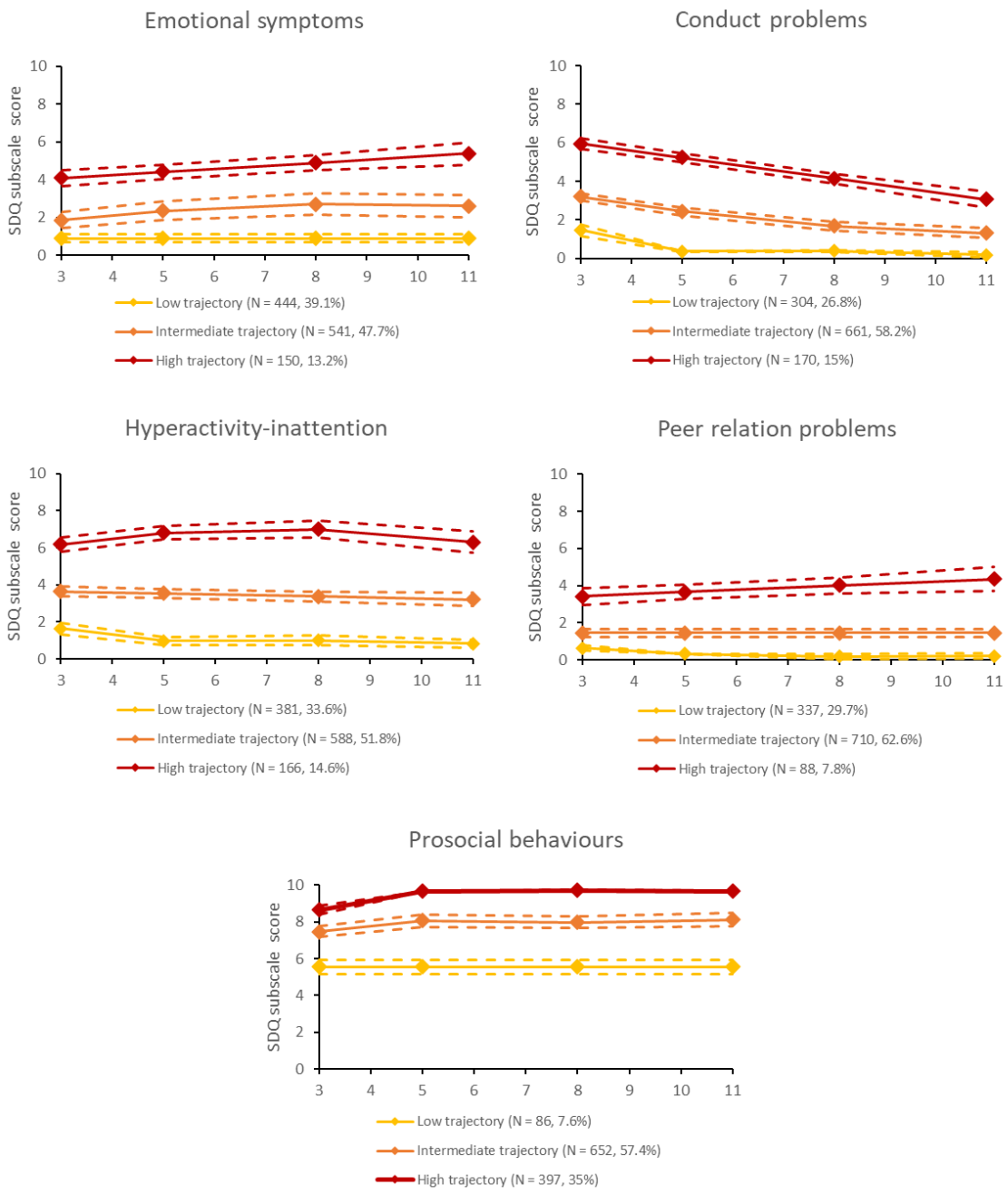

Figure 2. *Trajectories of children's emotional and behavioural symptom scores (max 10 in each subscale) measured through parent-report of the Strengths and Difficulty Questionnaires from ages 3 to 11 years (EDEN cohort study, n=1135).*

3.3. Joint trajectory analyses

3.3.1. Internalising symptoms (emotional symptoms, peer relationship problems)

The highest joint probability in the internalising symptom scales (Supplemental table 3) involved intermediate trajectories on both emotional symptoms and peer relationship problems (32%), followed by low symptom trajectories in both categories (28%). Examination of conditional probabilities indicated those following the low trajectory in emotional symptoms

were most likely (62.7%, SE = 6.2%) to be in the low trajectory of peer relationship problems (for the intermediate category, 36.9%, SE = 6.1%; for the high trajectory, 0.4%, SE = 0.7%). Those in the intermediate emotional symptoms trajectory were highly likely to place in the intermediate (72.1%, SE = 4.5%), and less likely to be in the low (19.5%, SE = 4.8%) or high (8.3%, SE = 2.5%) peer relationship problems category. Those in the high trajectory of emotional symptoms most likely placed in the intermediate peer relationship problem (63.5%, SE = 8.3%) trajectory, while 36.4% (SE = 8.0%) were in the high and almost none 0.13% (SE = 3.1%) in the low trajectory. Cross-classification results suggested that emotional and peer relation trajectories were significantly associated (χ^2 = 112.82, df = 4, *p<0.001*).

3.3.2. Externalising symptoms (conduct problems, inattention-hyperactivity)

In the externalising symptom scales (Supplemental table 4), placing in the intermediate category in both conduct problems and hyperactivity-inattention was associated with the highest joint probability (38%). Following a low inattention-hyperactivity trajectory presented a conditional joint probability of 74.1% (SE = 4.6%) to be in the low and 25.9% (SE = 4.6%) of being in the intermediate trajectory of conduct problems. The probability of following a high conduct problem trajectory was 0% (SE = 0%). Those following the intermediate inattention-hyperactivity trajectory were most likely to place in the intermediate (69%, SE = 3.1%) conduct problems trajectory (17.4%, SE = 3.2% for the low and 12.8%, SE = 2.2% for the high trajectory). Those following the high trajectory had a probability of 2.4% (SE = 1.9%) of classifying in the low, 25.0% (SE = 6.0%) in the intermediate and 72.6% (SE = 5.9%) of being the high trajectory of conduct problems. Cross-classification results suggested that emotional and peer relation trajectories were significantly associated (χ^2 = 310.22, df = 4, *p<0.001*).

3.4. Regression analyses

In bivariate analyses (Table 2), children of mothers who experienced elevated levels of depression or anxiety symptomatology at the timepoint of reference in pregnancy were more likely to present with persistently high levels emotional symptoms, conduct problems, inattention-hyperactivity, and peer relationship problems as well as to have persistently low levels of prosocial behaviours in comparison to the reference categories. Following adjustment for baseline child and family characteristics via inverse probability weighting (IPW), associations remained significant between prenatal maternal depression status and high symptom trajectories of emotional symptoms (OR_{IPW} = 1.90, 95% CI 1.21-2.99), conduct problems (OR_{IPW} = 1.68, 95% CI 1.06-2.64), inattention-hyperactivity (OR_{IPW} = 1.66, 95% CI 1.06-2.61) and peer relationship problems (OR_{IPW} = 1.94, 95% CI 1.11-3.39). Children exposed to prenatal maternal depression additionally had higher odds of following the intermediate emotional symptoms trajectory (OR_{IPW} = 1.41 95% CI 1.01-1.98) compared to the reference category (low levels of difficulties)

Table 2. Depression and anxiety and children's trajectories of emotional and behavioural development from ages 3 to 11 (low, intermediate, high) (n=1135)													
SDQ subscales		**Depression**						**Anxiety**					
		Bivariate analysis			**IPW**			**Bivariate analysis**			**IPW**		
		OR	**95% CI**	**P-value**	**OR**	**95% CI**	**P-value**	**OR**	**95% CI**	**P-value**	**OR**	**95% CI**	**P-value**
Emotional symptoms	L	Ref			Ref			Ref			Ref		
	I	**1.43**	(1.04-1.97)	*0.026**	**1.41**	(1.01-1.98)	*0.046**	**1.35**	(0.96-1.91)	*0.084*	**1.35**	(0.94-1.95)	*0.107*
	H	**2.04**	(1.33-3.13)	*0.001**	**1.90**	(1.21-2.99)	*0.006**	**1.98**	(1.25-3.12)	*0.003**	**1.96**	(1.21-3.16)	*0.007**
Conduct problems	L	Ref			Ref			Ref			Ref		
	I	**1.16**	(0.82-1.65)	*0.398*	**0.98**	(0.68-1.41)	*0.917*	**1.22**	(0.83-1.78)	*0.306*	**1.09**	(0.73-1.63)	*0.682*
	H	**2.28**	(1.48-3.52)	*<0.001**	**1.68**	(1.06-2.64)	*0.026**	**1.94**	(1.21-3.11)	*0.006**	**1.64**	(0.99-2.72)	*0.054*
Inattention-hyperactivity	L	Ref			Ref			Ref			Ref		
	I	**1.38**	(0.99-1.91)	*0.053*	**1.25**	(0.88-1.76)	*0.210*	**1.28**	(0.90-1.82)	*0.176*	**1.19**	(0.82-1.74)	*0.366*
	H	**2.00**	(1.31-3.06)	*0.001**	**1.66**	(1.06-2.61)	*0.028**	**1.66**	(1.05-2.64)	*0.031**	**1.59**	(0.97-2.62)	*0.067*
Peer relation problems	L	Ref			Ref			Ref			Ref		
	I	**1.41**	(1.01-1.97)	*0.042**	**1.27**	(0.89-1.81)	*0.190*	**1.16**	(0.81-1.65)	*0.411*	**1.02**	(0.70-1.48)	*0.913*
	H	**2.24**	(1.32-3.81)	*0.003**	**1.90**	(1.08-3.34)	*0.025**	**1.94**	(1.11-3.39)	*0.02**	**1.57**	(0.87-2.83)	*0.135*
Prosocial behaviours	L	**1.68**	(1.00-2.81)	*0.048**	**1.49**	(0.87-2.56)	*0.145*	**2.13**	1.22-3.75)	*0.008**	**1.82**	(1.00-3.30)	*0.050**
	I	**0.96**	(0.71-1.30)	*0.785*	**0.88**	(0.64-1.21)	*0.434*	**1.43**	(1.01-2.02)	*0.042**	**1.24**	(0.87-1.79)	*0.236*
	H	Ref			Ref			Ref			Ref		

Bivariate and IPW- adjusted multinomial regressions (95% CI).
H, high-level symptoms; I, intermediate-level symptoms; L, low-level symptoms; SDQ, Strengths and Difficulties Questionnaire; *Ref, reference.*
Odds Ratios in bold and p values in italics.
* *p<0.05;*

High prenatal maternal anxiety symptoms were significantly associated with higher odds of following the high trajectory of emotional symptoms (OR_{IPW} = 1.95, 95% CI 1.21-3.16) and low trajectory of prosocial behaviours (OR_{IPW} = 1.82, 95% CI 1.00-3.3) compared to the reference categories. Associations with high levels of conduct problems (OR_{IPW} = 1.64, 95% CI 0.99-2.74) and inattention-hyperactivity (OR_{IPW} = 1.59, 95% CI 0.97-2.62), were no longer significant at p<0.05, but remain close to the margin.

3.5. Stratified analyses

3.5.1. Stratification by sex

Stratification by sex revealed differences in sex distribution across symptom subscales in emotional symptoms (*p=0.009)*, inattention-hyperactivity (*p<0.001)*, conduct problems (*p<0.001)* and prosocial behaviours (*p<0.001)* (Table 4). Further subgroup analyses (Figure 3 (A-B); Supplemental table 5) revealed that following stratification by sex, females exposed to prenatal depression (OR_{IPW} = 1.89, 95% CI 1.00-3.58) or anxiety (OR_{IPW} = 2.41, 95% CI 1.26-4.63) symptomatology had higher odds of following the high emotional symptoms trajectory compared to the reference category (low symptom trajectory).

Table 4. SDQ subscale trajectory membership by child sex (n=1135).

	Male (n = 603)		**Female (n = 532)**		
	n	**%**	**n**	**%**	**P-value[a]**
Emotional symptoms					*0.009**
Low trajectory (N = 444, 39.1%)	260	43.12	184	34.59	
Intermediate trajectory (N = 541, 47.7%)	273	45.27	268	50.38	
High trajectory (N = 150, 13.2%)	70	11.61	80	15.04	
Conduct problems					*<0.001**
Low trajectory (N = 304, 26.8%)	133	22.06	171	32.14	
Intermediate trajectory (N = 661, 58.2%)	352	58.37	309	58.08	
High trajectory (N = 170, 15%)	118	19.57	52	9.77	
Inattention-hyperactivity					*<0.001**
Low trajectory (N = 381, 33.6%)	174	28.86	207	38.91	
Intermediate trajectory (N = 588, 51.8%)	313	51.91	275	51.69	
High trajectory (N = 166, 14.6%)	116	19.24	50	9.40	
Peer relationship problems					*0.073*
Low trajectory (29.7%)	174	28.86	163	30.64	
Intermediate trajectory (62.6%)	372	61.69	338	63.53	
High trajectory (7.8%)	57	9.45	31	5.83	
Prosocial behaviours					*<0.001**
Low trajectory (N = 86, 7.6%)	61	10.12	25	4.70	
Intermediate trajectory (N = 652, 57.4%)	365	60.53	287	53.95	
High trajectory (N = 397, 35%)	177	29.35	220	41.35	

[a] Fisher's exact test; * *p<0.05*

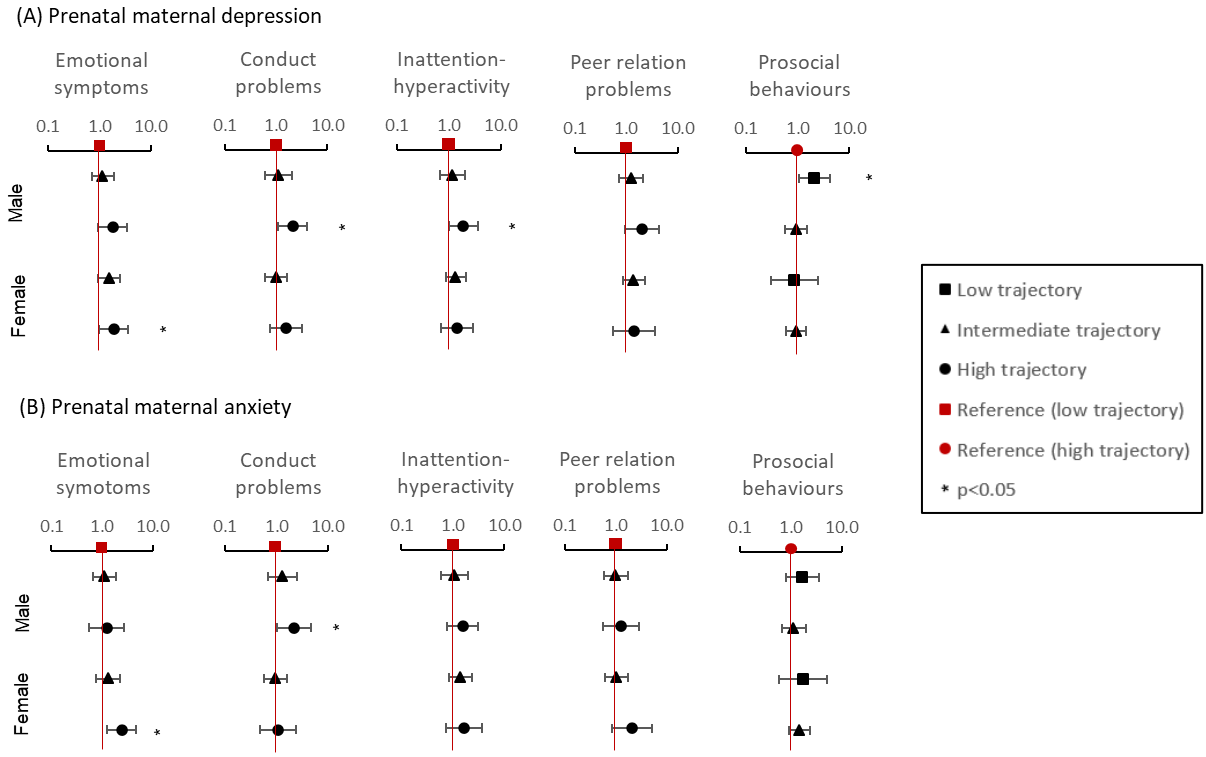

Figure 3 (A-B). *Maternal prenatal (A) depression and (B) anxiety and children's emotional and behavioural difficulties (ages 3-11) stratified by child sex. IPW-adjusted multinomial regression models with odds ratios (95% CI) presented in log scale in relation to the reference category. EDEN cohort study (n=1135).*

Males exposed to prenatal depression (OR_{IPW} = 2.11, 95% CI 1.09-4.10) and anxiety (OR_{IPW} = 2.23, 95% CI 1.03-4.70) had higher odds of classification in the high trajectory of conduct problems. Males exposed to prenatal depression were additionally more likely to display high levels of inattention-hyperactivity (OR_{IPW} = 1.88, 95% CI 1.00-3.53) and low levels of prosocial behaviours (OR_{IPW} = 2.08, 95% CI 1.05-4.13), and were close to the conventional *p<0.05* threshold of significance for increased odds for following high level trajectories of emotional symptoms (OR_{IPW} = 1.81, 95% CI 0.94-3.48; *p = 0.077*) and peer relationship problems (OR_{IPW} = 2.02, 95% CI 0.96-4.26; *p=0.063*) compared to the reference categories.

3.5.2. Stratification by visits to a psychologist

Table 5 shows the distribution in each SDQ subscale by whether it is known the mother visited a psychiatrist during pregnancy, and up to eight years after child was born. No significant differences were identified. It should be noted that 48% of the mothers who accessed care during pregnancy reported also doing so after birth. 29.3% of the mothers who accessed care postnatally reported having done so prenatally as well (Fisher's Exact OR =

7.51, 95% CI 4.71 – 11.98). Figure 4 (A-B) shows OR (95% CI) on log scale in each subscale in relation to the reference categories (exact results available in Supplemental tables 6-7).

In the group that reported visiting a psychiatrist during pregnancy (n=98), exposure to prenatal anxiety was associated with a lower likelihood of following a high symptom trajectory of inattention-hyperactivity (OR_{IPW} = 0.13, 95% CI 0.02-0.73) in comparison to the reference group. However, it should be noted that there were only eleven individuals in the high symptoms group. The association with exposure to prenatal depressive symptoms was marginally close to the level of significance in having lower odds of following the high trajectory of conduct problems (OR_{IPW} = 0.24, 95% CI 0.05-1.06) and the intermediate level trajectory of inattention-hyperactivity (OR_{IPW} = 0.41, 95% CI 0.17-1.01). In the group that reported no visits during pregnancy, depressive classification was associated with higher odds of following high trajectories of emotional symptoms (OR_{IPW} = 2.20, 95% CI 1.36-3.58), conduct problems (OR_{IPW} = 2.11, 95% CI 1.28-3.46), inattention-hyperactivity (OR_{IPW} = 2.06, 95% CI 1.26-3.38), peer relationship problems (OR_{IPW} = 2.28, 95% CI 1.24-4.20) and was close to the threshold of significance of increased likelihood for persistently low levels of prosocial behaviours (OR_{IPW} = 1.70, 95% CI 0.96-3.00). Exposure to prenatal anxiety was associated with to elevated odds of high levels of emotional symptoms (OR_{IPW} = 2.10, 95% CI 1.26-3.52), conduct problems (OR_{IPW} = 2.08, 95% CI 1.19-3.63), inattention-hyperactivity (OR_{IPW} = 2.22, 95% CI 1.29-3.82) and both intermediate (OR_{IPW} = 1.68, 95% CI 1.09-2.58) and low levels of prosocial behaviours (OR_{IPW} = 2.89, 95% CI 1.51-5.50) in comparison to the reference groups.

Following stratification on known visits after pregnancy, no associations were significant in the group who reported any visits (n=160). In the group that did not report visits, depressive classification was associated with higher odds of following a high trajectory of emotional symptoms (OR_{IPW} = 2.03, 95% CI 1.21-3.39), conduct problems (OR_{IPW} = 1.77, 95% CI 1.06-2.97), peer relationship problems (OR_{IPW} = 2.23, 95% CI 1.18-4.22) and was close to the level of significance of increasing the likelihood of following the high symptom trajectory of inattention-hyperactivity (OR_{IPW} = 1.65, 95% CI 0.98-2.77) compared to the reference groups. Anxious classification led to higher odds of high levels of emotional problems (OR_{IPW} = 2.15, 95% CI 1.26-3.69), inattention-hyperactivity (OR_{IPW} = 1.90, 95% CI 1.11-3.26). It was marginally close to level of significance for conduct problems (OR_{IPW} = 1.73, 95% CI 0.99-3.01) and low levels of prosocial behaviours (OR_{IPW} = 1.91, 95% CI 0.99-3.70).

In the group that visited a psychiatrist during pregnancy, continuation of care (inferred by reporting psychiatrist visits both during and after pregnancy) was not significantly associated with group membership on the inattention-hyperactivity (χ^2 = 3.27, $p = 0.195$) nor conduct problems (χ^2 = 0.33, $p=0.849$) subscale (where anxiety may have been protective).

Table 5. SDQ subscale trajectory membership by visits to a psychiatrist during pregnancy and after child's birth up to the age of 8.

	During pregnancy					After pregnancy				
	Known psychiatric visit(n=98)		No known visit (n=1037)			Known psychiatric visit (n=160)		No known visit (n=975)		
	n	%	n	%	P-values[a]	n	%	n	%	P-values[a]
Emotional symptoms					*0.884*					*0.077*
Low trajectory (N = 444, 39.1%)	36	36.73	408	39.34		53	33.13	391	40.10	
Intermediate trajectory (N = 541, 47.7%)	49	50.00	492	47.44		78	48.75	463	47.49	
High trajectory (N = 150, 13.2%)	13	13.27	137	13.21		29	18.13	121	12.41	
Conduct problems					*0.336*					*0.410*
Low trajectory (N = 304, 26.8%)	22	22.45	282	27.19		37	23.13	267	27.38	
Intermediate trajectory (N = 661, 58.2%)	57	58.16	604	58.24		95	59.38	566	58.05	
High trajectory (N = 170, 15%)	19	19.39	151	14.56		28	17.50	142	14.56	
Inattention - hyperactivity					*0.628*					*0.878*
Low trajectory (N = 381, 33.6%)	34	34.69	347	33.46		56	35.00	325	33.33	
Intermediate trajectory (N = 588, 51.8%)	53	54.08	535	51.59		80	50.00	508	52.10	
High trajectory (N = 166, 14.6%)	11	11.22	155	14.95		24	15.00	142	14.56	
Peer relationship problems					*0.310*					*0.261*
Low trajectory (29.7%)	35	35.71	302	29.12		39	24.38	298	30.56	
Intermediate trajectory (62.6%)	58	59.18	652	62.87		109	68.13	601	61.64	
High trajectory (7.8%)	5	5.10	83	8.00		12	7.50	76	7.79	
Prosocial behaviours					*0.316*					*0.885*
Low trajectory (N = 86, 7.6%)	7	7.14	79	7.62		11	6.88	75	7.69	
Intermediate trajectory (N = 652, 57.4%)	50	51.02	602	58.05		95	59.38	557	57.13	
High trajectory (N = 397, 35%)	41	41.84	356	34.33		54	33.75	343	35.18	

[a] Fisher's exact test, * *p<0.05*

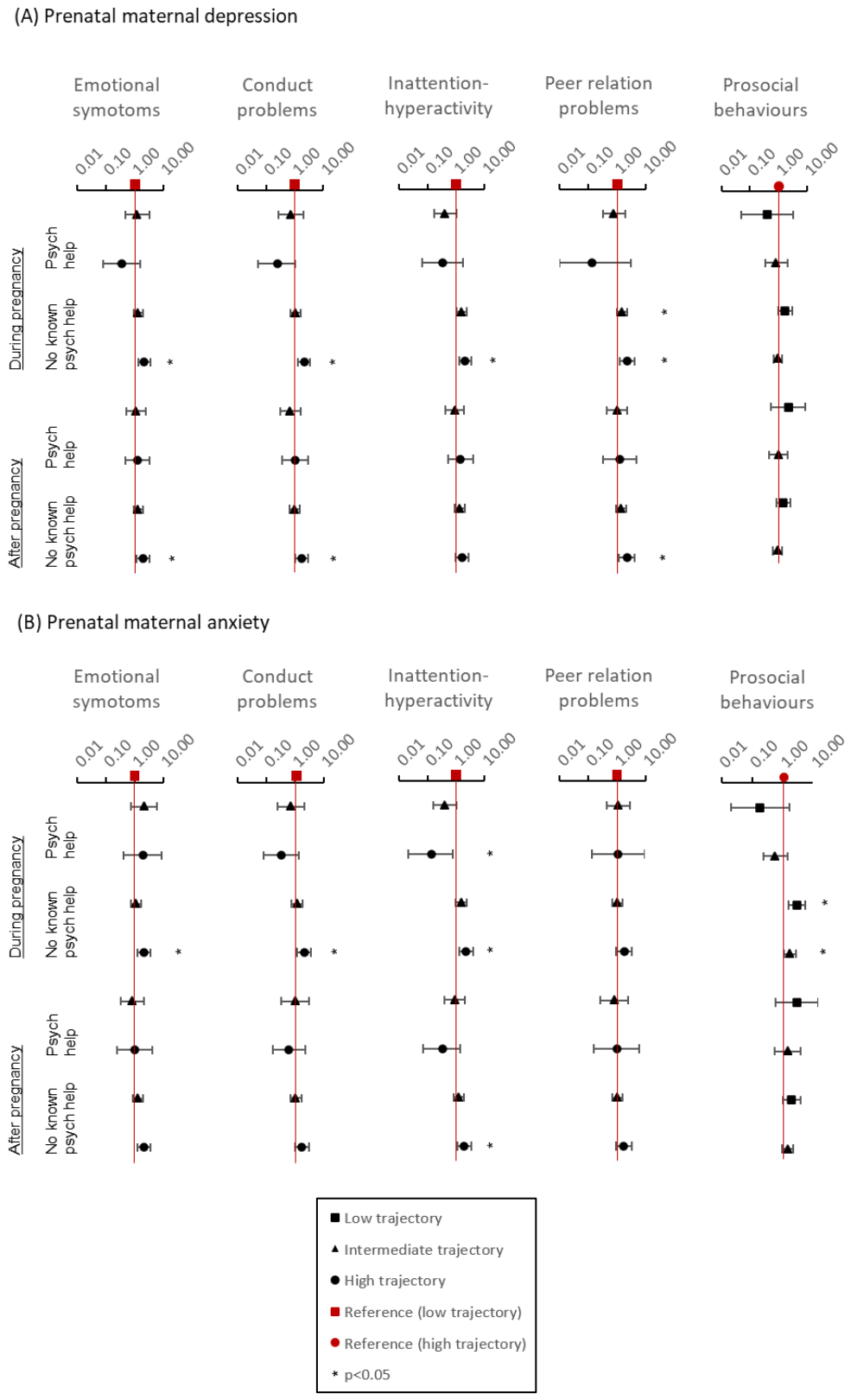

Figure 4 (A-B). *Maternal prenatal depression (A) and anxiety (B) and children's emotional and behavioural difficulties (ages 3-11), stratified by whether mother is reported having accessed psychiatric services during pregnancy, and up to 8 years after pregnancy. Odds ratios (95% CI) obtained from inverse probability weight (IPW)-adjusted multinomial regression models in relation to the reference category presented on the log scale. EDEN cohort study (n=1135).*

4. Discussion

4.1. Summary

4.1.1. Main results

This study conducted among a community sample in two French cities found a point prevalence of depressive symptomatology of 21.76%, similar to the prevalence found by Giardinelli *et al.* (79) in an Italian sample, but higher than estimates for clinical depression derived from reviews (12-15%) (8, 80). The proportion classified as anxious (17.53%) is close to the prevalence of self-reported anxiety symptoms in first and second trimester found in a systematic review by Dennis *et al.* (81). The key differences in the socioeconomic and social support profiles of the women classified as anxious or depressed are in line with key risk factors for adverse mental health reported in the literature (14).

For each of the Strengths and Difficulties Questionnaire (SDQ) subscales, the sample split into persistently high-, intermediate-, and low-level symptom trajectories. For each of the difficulties subscales, the majority of children followed either low or intermediate trajectories. For prosocial behaviours, most children followed the high or intermediate symptom trajectories. The proportion of children belonging to the trajectories indicating higher levels of difficulties or lower levels of strengths (7.6%-15%) is considered empirically relevant because belonging to the top 90th percentile of SDQ scores is associated with an increase of the proportion of at-risk youths (52). A 2001 WHO report indicated that 10-20% of all children present one or more mental or behavioural problems, which can be considered a public health issue with high morbidity (82) that warrants specific policy and economic considerations. The joint trajectory analysis in the present study revealed that the subscales indicating internalising problems (emotional symptoms and peer relationship problems), and externalising problems (inattention-hyperactivity and conduct problems) were related. This is similar to previous findings (62) and allows for consideration of the findings in light of the literature discussing internalisation and externalisation problems.

Prenatal depressive symptoms increased the risk of the child following the high-level trajectories of emotional symptoms, conduct problems, inattention-hyperactivity, and peer relationship problems throughout childhood to early adolescence – thus significantly increasing the risk for both internalising and externalising problems, but not low prosocial behaviours. Significantly higher internalising and externalising problems following depressive symptomatology during pregnancy were similarly found in a Finnish birth cohort (29). Wolford *et al.* (83) used repeated measurements of depressive symptomatology and found that without interventions, women's point measured depressive symptoms stayed highly stable throughout the pregnancy and led to high levels of attention-deficit disorder symptomatology. In the

literature, the association between depressive symptoms during pregnancy and psychiatric problems among children was independent of, but partially mediated by postnatal depression (29, 83). The highest risk of psychiatric problems was found in children whose mothers reported clinically significant depressive symptoms across pregnancy trimesters and during and after pregnancy.

Prenatal maternal anxiety was associated with following the high trajectory of emotional symptoms and the low trajectory of prosocial behaviours. The risk of following high symptom trajectories for both of the externalising problems (conduct problems and inattention-hyperactivity) were close to the margin of significance. Similarly, Tuovinen *et al.* (5) found evidence that both depressive and anxiety symptoms are strongly associated with clinically diagnosed disorders by the WHO ICD-10 (84) in childhood. Ibanez *et al.* (32) considered depression and anxiety in the same cohort as the present study, and found that comorbidity of both adverse mental health symptoms led to worse neonatal outcomes than having only one of them. This is concerning as depressive and anxiety classification overlapped significantly in the present study as well. Ibanez *et al.* (85) consecutively assessed cognitive development in the EDEN cohort and found strong associations between maternal antenatal anxiety and poorer cognitive development at 2-3 years. Lower cognitive development in childhood is frequently associated with more subsequent parent and teacher reports of behavioural problems (86).

The present study adds to the literature documenting the strong effects of prenatal depressive and anxiety symptoms on child development; however, it does not fully characterize the mechanisms of transmission. For instance, Hentges *et al.* (19) found that the pathway from prenatal stress to internalising and externalising problems was fully mediated by postnatal stress and child temperament. In contrast, Mackinnon *et al.* (4) found that stress measured through stressful life events during pregnancy increased the risk of externalising symptoms (conduct problems and hyperactivity) even after adjustment for postnatal stress, and identified a positive dose-response relationship. Ibanez *et al.* (85) found that postnatal maternal depression mediated 26.5% of the effect on children's cognitive scores, while parental stimulation mediated 13.2%. Considering the high proportion of women who go onto experience postnatal depression following prenatal stress (35), further analyses of the present sample is needed to characterise the potential mechanisms of transmission.

4.1.2. Stratification by sex

The sex distribution between trajectories differed in each SDQ subscale except peer relationship problems. Fewer females followed the high trajectories of both externalising problems and the low trajectory of prosocial behaviours, while fewer males were followed the

high trajectory of emotional symptoms. This study does not provide information on gender, however given the social context, insufficient sample size and lack of information in the dataset on gender, the findings will be discussed in relation to the gender/sex binary. Even as scientific practise and understanding evolve, the gender binary still influences individuals' thinking and behaviour, and thus the binary frameworks can in some instances be treated as empirically relevant (87). However, further studies would benefit from taking a wider approach.

Exposure to both depression and anxiety symptomatology was significantly associated with a higher likelihood of following the trajectory of high levels of emotional symptoms in females and conduct problems in males. Males exposed to prenatal depression were additionally more likely to display persistently elevated levels of inattention-hyperactivity and persistently low levels of prosocial behaviours. Additionally, males exposed to prenatal maternal depression were close to the margin of significance of a higher likelihood of following a high trajectory of emotional symptoms and peer relationship problems, altogether suggesting males may have been more affected by the exposure. The evidence in the literature on gender differences in problem manifestation is mixed, as some studies found boys more vulnerable to the effects of maternal stress during pregnancy (88), whereas others have found girls to be more vulnerable, particularly to emotional problems (23). Gerardin *et al.* (88) suggest that higher vulnerability to prenatal stress may be key to understanding the higher prevalence of child psychiatric disorders in males.

The differences by sex may in part arise from differential embryonic and foetal development. It has been suggested that male foetuses expend more energy on growth and less on resilience, rendering them on average more vulnerable to the total effects of stress. However, females may be more vulnerable to less severe but lasting health complications in the emotional domains such as anxiety and depression (39). Leadbeater *et al.* (89) propose a social model for the differences in emotional problems, whereby the gender difference may also be due to higher interpersonal vulnerabilities in girls and stronger links between girls' social relationships and internalizing problems. Boys' greater vulnerability to self-criticism may partly explain higher rates of externalising problems. Kohlhoff and Barnett (90) identified male infant gender as a risk factor for lower maternal parental self-efficacy, meaning mothers were less likely to apply positive parenting practises with boys than girls.

4.1.3. Stratification by known psychiatric visits

The division into trajectory groups in each subscale was not significantly different depending on whether the mother reported accessing psychiatric services during and after pregnancy or not. However, reporting utilisation of services was significantly dependent on depression and anxiety status at inclusion (Table 1). In the group that reported visiting a

psychiatrist during pregnancy, higher scores on the anxiety scale were associated with a lower likelihood of following the high trajectory of inattention-hyperactivity symptoms, meaning in this group, anxiety appeared to be a protective factor. The analysis of the full sample did not find a significant association, whereas following stratification, the odds of allocation to the high trajectory compared to the reference were significantly higher in the group without known visits in pregnancy, meaning anxiety was a risk factor. This finding is surprising but should be interpreted in light of the small number of children in the group with known visitations (98 mother-child dyads) who were assigned to the high symptoms trajectory (11 dyads). Although not statistically significant, similar tendencies were observed in the analysis of conduct problems whereby depression appeared to decrease the risk of from high conduct problems in the psychiatrist-visiting group (based on 19 dyads in the high symptoms group) but increase in the non-visiting group. Thus, the results indicate that depression may have had a protective association with externalising problems in the group that actively sought out psychiatric care.

The potential protective effect of stress is puzzling and should be interpreted with caution, however it is possible psychiatric care during pregnancy reduced feelings of stress and thus made the stress exposure acute and less impactful. Irwin *et al.* (91) found that increasing, but not decreasing anxiety during pregnancy led to adverse developmental outcomes (pertaining to lower receptive language and motor skills) while Lahti *et al.* (29) found that psychiatric problems were most prevalent in children whose mothers reported clinically significant depressive symptoms across pregnancy trimesters and during and after pregnancy. Additionally, utilisation of services during pregnancy may indicate a degree of self-efficacy, which will continue to influence parenting practises and maternal mental health throughout the child's development. A possible mechanism of protectiveness could be that the mothers who experienced negative mood symptoms during pregnancy and actively sought out care may have found their symptoms to be a cause for concern. Searching for help could have indicated self-efficacy and awareness (92) which allowed the mothers to actively prioritise the development of their coping skills, which may have indirectly made the initial adverse mental health status protective. However, given that the number of women who reported visits was low and the frequency and quality of psychological care were not assessed, the finding may have been due to chance.

In the group that reported psychiatrist visits at any point after the birth, no significant nor marginally significant protective or risk associations were identified in any of the symptom subscales, while associations remained positive and around or above the margin of significance in the group without known visitations. Despite a statistically significant overlap between the two groups, it should be noted that less than half of the women who reported seeing a psychiatrist during pregnancy also reported doing so after. Visiting a psychiatrist

regardless of stress status at enrolment may in fact be associated with characteristics of the mother, in which case the variable serves as a proxy. Parental self-efficacy is linked to parental competence and parental psychological functioning, which can protect against child problem behaviours and aid psychological adjustment (92). Clayborne *et al.* (93) found that maternal self-efficacy was a moderating factor for internalising, but not externalising symptoms. Higher levels of positive maternal mental health (self-esteem and self-efficacy) during pregnancy may buffer the associations between prenatal maternal stress and child internalising and externalising symptoms (93). In the current study, psychiatric visits moderated both internalising and externalising symptoms and led to the opposite protective effects in inattention-hyperactivity traits. Self-efficacy is additionally associated with positive parenting practices (94), which promote child socioemotional functioning. Previous research demonstrates that mother–offspring attachment (95), dyadic affect regulation (96) and parenting (19) moderate the association between prenatal stress and offspring neurodevelopment, suggesting that the negative effects of prenatal stress may be mitigated by early interventions aimed at increasing attachment and self-efficacy. However, meta-analyses have revealed positive psychological interventions themselves can have an effect on increasing well-being and reducing depressive symptoms (97). A Finnish cohort study revealed that the associations between maternal depression and internalising/externalising problems were partially mediated by maternal depressive symptoms after pregnancy (29). The stratification by visits to a psychiatrist in this sample provides support for the continuation of stress and interpersonal stress transmission model (19). Assuming the visit was effective, and the mother was no longer stressed during the development of the child, the effect of prenatal depression and anxiety disappeared.

4.2. Strengths and limitations

The findings should be interpreted in consideration of several limitations. Firstly, the EDEN cohort is derived from two distinct cities in France and is thus neither nationally nor globally representative. The study sample has on average higher educational attainment and higher income than the national average in France. Thus, further investigation is warranted in more diverse populations to represent the full socioeconomic and ethnic diversity of the French population. The final study sample is likely even less representative, as significant attrition occurred over the follow-up period and the excluded participants differed from the included in nearly all socioeconomic and psychological characteristics measured (Supplemental table 1).

Secondly, measures for both exposure and outcome were derived from responses to self-report questionnaires. Self-assessment of psychological stress is highly subjective in nature, and there are numerous individual and cultural differences in reporting and recognising mental states. Additionally, despite some studies reporting consistency of symptoms of

distress throughout pregnancy (83), there is no information on this as the questionnaires were administered to the women at one specific time point amenorrhea, and thus represented a snapshot of momentary stress rather than persistent symptoms. This difference leads to a failure to consider the persistence of mood problems, can bias the study and lead to misrepresentation of the effects on the foetus. Liou *et al.* (98) describe that correlations between depression, stress and anxiety can be moderate to low as the different types of maternal distress follow distinct developmental trajectories through pregnancy – indicating that anxiety and depression symptomatology may not be the best approach to quantify stress. Although mothers on average report higher levels of problem behaviour than teachers (99), both sources of assessment are generally consistent and valid in the SDQ (100). Nevertheless, variations in reporting style cannot be ruled out and parents may differ in their expectations and report of child behaviour as a function of sex.

Finally, the variables pertaining to known visits to a psychiatrist are problematic as the majority of participants have not provided information on this at every time point possible, making misclassification likely. It is assumed the individuals who did not respond to whether they sought psychiatric help at any of the time points did not do it, which is not a valid inference. Additionally, the number of individuals in the subsamples with known visitations were small, meaning associations identified may have been due to chance. Information was missing on paternal mental health (101), genetic confounding (on factors other than self-reported childhood behaviour issues), and this study did not conduct a mediation analysis to separate potential foetal programming effects from the effects mediated through smoking, birthweight, postnatal mental health, mother-child attachment, and parenting style.

The strengths of this study are that it is based on repeated measures and longitudinal assessments of the children's emotional and behavioural development up to the age of eleven. Information was collected on a large number of factors, allowing for adjustment on numerous confounders. Propensity scores were applied through inverse probability weighting to render exposure groups strictly comparable (102) and account for selection and confounding factors. This does not rule out the possibility of unmeasured confounders, however it is unlikely the associations observed can be fully explained by these. Finally, the use of validated and recommended questionnaires with overall good psychometric properties was a key strength.

4.3. Future directions

Further analyses are needed to characterise the full developmental cascade while maintaining awareness of its complexity and difficulties analysing it using rigid methods. Key hypotheses for the mechanisms of intergenerational transmission of stress effects include the foetal programming hypothesis, interpersonal stress transmission and continuation of stress

models (19). This study characterised the total impact of stress and partially considered interpersonal stress transmission and continuation of stress models through stratification on the known psychiatrist visit variables. Additional mediation analyses are warranted to consider postnatal maternal depression, early parental care, parenting characteristics, substance abuse and adverse birth outcomes (4). Future research would benefit from separating objective and subjective stress, as well as stress itself from symptoms of depression and anxiety when studying child outcomes (33) as evidence indicates these may be a different concepts that exert different effects on the child and warrant the development of different interventions. Furthermore, the associations need to be validated in diverse populations, and larger samples may be needed to fully characterise the sex differences in vulnerability and investigate the full effects of perinatal psychiatric interventions to improve maternal mental health. Specialised studies may be needed to take the full gender spectrum (87) into account.

5. Conclusion and recommendations

Taken together, these results support the existing literature by showing that prenatal maternal depression and anxiety symptoms are associated with increased risk of many childhood emotional and behavioural problems (4, 5, 19, 24, 29, 30). The effect on specific developmental outcomes differs by sex and there may be significant effect modification by visits to a psychiatrist. Considering the high prevalence of prenatal stress symptoms, the fact that they frequently go unnoticed in routine care (103), and the potentially life-altering consequences of prenatal maternal stress for the offspring, this study provides further evidence that failure to address maternal stress during pregnancy would be a missed opportunity to intervene and ensure optimal outcomes and support for each individual. Even a modest association would in its absolute impact present a significant public health problem, especially in lower-income countries with a high prevalence of antenatal depression and poor access to quality mental health services (14). There is an urgent need to incorporate comprehensive measures to optimise women's psychological well-being into routine antenatal care. To facilitate conversations around sensitive issues, routine standardised screening should be considered and clear referral pathways to psychiatric services need to be in place to address adverse mental health symptoms, which could be vital to support the family through the vulnerable times (103). Findings additionally highlight the potential effectiveness of tailored prenatal preventative programs that continue into the postnatal period, potentially targeting self-efficacy, maternal postnatal stress, mother–offspring attachment (95), and parenting behaviours (19). This study adds to a body of evidence hoped to warrant investment in evidence-based services and programmes, as well as further research into the causes, prevention, impact, and treatment of adverse perinatal mental health.

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Appendices

Supplemental table 1. Characteristics of the EDEN cohort by whether they were included in the present study.

	Denominator	Included (n=1135)		Excluded (n=867)		
		n	%	n	%	*P-value*[a]
Centre of recruitment (Nancy)	2002	535	47.14	498	57.44	*<0.001**
Primiparous (yes)	1903	533	47.04	315	40.91	*0.009**
Mother unemployed and not studying	1908	191	16.95	235	30.09	*<0.001**
Father unemployed and not studying	1864	48	4.31	76	10.13	*<0.001**
Migrant background	1887					*<0.001**
None		985	88.66	629	81.06	
Second generation		101	9.09	95	12.24	
First generation		25	2.25	52	6.70	
Household income <1500 €/month	1919	119	10.48	208	26.53	*<0.001**
At least one financial difficulty (clothing, feeding, utilities)	1908	65	5.77	105	13.44	*<0.001**
Antidepressant use before pregnancy	1904	56	4.97	67	8.61	*0.002**
Practical support (partner)	1900	91	8.10	102	13.14	*<0.001**
Practical support (someone else)	1914	188	16.64	137	17.47	*0.66*
Emotional support (partner)	1897	29	2.59	63	8.12	*<0.001**
Emotional support (someone else)	1913	66	5.85	94	11.99	*<0.001**
Living with father of the child	1912	37	3.28	85	10.84	*<0.001*
Childhood adversity (mother)	1890	285	25.51	283	36.61	*<0.001**
Childhood behaviour problems (mother)	1904	65	5.79	77	9.85	*0.001**
Childhood behaviour problems (father)	1753	105	9.95	99	14.18	*0.008**
Child sex (Female)	1903	532	46.87	371	42.79	*0.543*
Known visits to a psychiatrist during pregnancy	2002	98	8.63	83	9.57	*0.480*
Known visits to a psychiatrist from birth to 8 years after	2002	160	14.09	61	7.03	*<0.001**

		Mean	***SD***	***Mean***	***SD***	***P-value[b]***
Maternal age (years)	1668	30.64	4.70	29.42	4.91	*<0.001**
		Median	***IQR***	***Median***	***IQR***	***P-value[c]***
Maternal education (years)	1910	14	12.0 – 17.0	12	11.0-14.0	*<0.001**
Paternal education (years)	1745	14	11 – 17.0	12	11.0-14.0	*<0.001**

[a] Fisher's exact test; [b] Independent samples t-test; [c] Unpaired Two-Samples Wilcoxon Test
* p<0.05

Supplemental table 2 (A-E). Comparison of model parameters for one-, two-, three-, four- and five-group trajectory models. Bayesian Information Criterions (BIC) and average posterior probabilities (App).

(A) Trajectories of emotional symptoms

Model	**BIC**	App group 1	App group 2	App group 3	App group 4	App group 5
1-group	-7054.05	1				
2-group	-6791.36	0.918	0.874			
3-group	-6752.94	0.807	0.764	0.810		
4-group	-6747.23	0.804	0.734	0.661	0.733	
5-group	-6739.71	0.688	0.775	0.662	0.638	0.792

(B) Trajectories of inattention-hyperactivity

Model	**BIC**	App group 1	App group 2	App group 3	App group 4	App group 5
1-group	-7946.89	1				
2-group	-7523.02	0.928	0.896			
3-group	-7383.14	0.884	0.861	0.883		
4-group	-7260.47	0.781	0.794	0.796	0.865	
5-group	-7372.88	0.779	0.773	0.754	0.717	0.795

(C) Trajectories of peer relation problems

Model	**BIC**	App group 1	App group 2	App group 3	App group 4	App group 5
1-group	-6058.31	1				
2-group	-5883.52	0.892	0.825			
3-group	-5825.60	0.785	0.846	0.831		
4-group	-5815.20	0.753	0.598	0.846	0.830	
5-group	-5808.39	0.621	0.648	0.770	0.813	0.781

(D) Trajectories of conduct problems

Model	**BIC**	App group 1	App group 2	App group 3	App group 4	App group 5
1-group	-7017.98	1				
2-group	-6707.20	0.910	0.864			
3-group	-6579.45	0.846	0.890	0.890		
4-group	-6650.91	0.801	0.631	0.852	0.846	
5-group	-6640.51	0.831	0.784	0.605	0.768	0.805

(E) Trajectories of prosocial behaviours

Model	**BIC**	App group 1	App group 2	App group 3	App group 4	App group 5
1-group	-6615.77	1				
2-group	-6344.70	0.874	0.886			
3-group	-6277.06	0.822	0.853	0.851		
4-group	-6297.90	0.812	0.738	0.761	0.773	
5-group	-6299.46	0.900	0.776	0.754	0.758	0.580

Supplemental table 3. Joint probability classification in emotional symptom and peer relationship problem SDQ subscale trajectories.

		Emotion trajectories		
		High trajectory (13.2%)	Intermediate trajectory (47.7%)	Low trajectory (39.1%)
Peer relationship problems	High trajectory (7.8%)	4.0	3.7	0.2
	Intermediate trajectory (62.6%)	6.9	32.0	16.5
	Low trajectory (29.7%)	0	8.7	28.0

Supplemental table 4. Joint probability classification in conduct problem and inattention-hyperactivity SDQ subscale trajectories.

		Conduct problems		
		High trajectory (15.0%)	Intermediate trajectory (58.2%)	Low trajectory (26.8%)
Hyperactivity/ inattention	High trajectory (14.6%)	10.7	6.9	0
	Intermediate trajectory (51.8%)	3.7	38	8
	Low trajectory (33.6%)	0.3	9.5	22.9

Supplemental table 5. Stratified by sex: Depression and anxiety and children's trajectories of emotional and behavioural development from ages 3 to 11 (low, intermediate, high) (n=1135).

SDQ subscales		Depression						Anxiety					
		Males			Females			Males			Females		
		OR	95% CI	P-value	OR	95% CI	P-value	OR	95% CI	P-value	OR	95% CI	P-value
Emotional symptoms	L	Ref			Ref			Ref			Ref		
	I	**1.17**	(0.73-1.89)	*0.515*	**1.56**	(0.96-2.52)	*0.072*	**1.11**	(0.66-1.87)	*0.690*	**1.31**	(0.77-2.22)	*0.322*
	H	**1.81**	(0.94-3.48)	*0.077*	**1.89**	(1.00-3.58)	*0.049**	**1.22**	(0.56-2.65)	*0.609*	**2.41**	(1.26-4.63)	*0.008**
Conduct problems	L	Ref			Ref			Ref			Ref		
	I	**1.12**	(0.62-2.03)	*0.700*	**1.01**	(0.62-1.63)	*0.976*	**1.31**	(0.68-2.53)	*0.421*	**0.95**	(0.57-1.59)	*0.844*
	H	**2.11**	(1.09-4.10)	*0.027**	**1.55**	(0.75-3.16)	*0.230*	**2.23**	(1.03-4.70)	*0.030**	**1.09**	(0.49-2.44)	*0.831*
Inattention-hyperactivity	L	Ref			Ref			Ref			Ref		
	I	**1.17**	(0.67-2.02)	*0.581*	**1.33**	(0.85-2.09)	*0.212*	**1.08**	(0.60-1.93)	*0.802*	**1.40**	(0.84-2.34)	*0.191*
	H	**1.88**	(1.00-3.53)	*0.048**	**1.41**	(0.69-2.91)	*0.349*	**1.56**	(0.78-3.11)	*0.209*	**1.65**	(0.74-3.67)	*0.221*
Peer relation problems	L	Ref			Ref			Ref			Ref		
	I	**1.24**	(0.73-2.11)	*0.429*	**1.39**	(0.86-2.25)	*0.185*	**0.98**	(0.57-1.71)	*0.956*	**1.02**	(0.61-1.71)	*0.933*
	H	**2.02**	(0.96-4.26)	*0.063*	**1.41**	(0.56-3.56)	*0.464*	**1.26**	(0.56-2.81)	*0.580*	**2.04**	(0.83-5.03)	*0.121*
Prosocial behaviours	L	**2.08**	(1.05-4.13)	*0.036**	**0.87**	(0.30-2.49)	*0.792*	**1.67**	(0.79-3.54)	*0.666*	**1.72**	(0.58-5.05)	*0.115*
	I	**0.93**	(0.56-1.52)	*0.761*	**0.93**	(0.60-1.43)	*0.738*	**1.13**	(0.65-1.95)	*0.182*	**1.48**	(0.91-2.40)	*0.325*
	H	Ref			Ref			Ref			Ref		

IPW- adjusted multinomial regressions (95% CI).
H, high-level symptoms; I, intermediate-level symptoms; L, low-level symptoms; SDQ, Strengths and Difficulties Questionnaire; Ref, reference.
Odds Ratios in bold and p values in italics.
* <0.05

Supplemental table 6. Stratified by whether mother reports visiting a psychiatrist during pregnancy: Depression and anxiety and children's trajectories of emotional and behavioural development from ages 3 to 11 (low, intermediate, high) (n=1135).

		Depression						**Anxiety**					
SDQ subscales		**Known visit to a psychiatrist (n=98)**			**No known visit (n=1037)**			**Known visit to a psychiatrist (n=98)**			**No known visit (n=1037)**		
		OR	**95% CI**	**P-value**	**OR**	**95% CI**	**P-value**	**OR**	**95% CI**	**P-value**	**OR**	**95% CI**	**P-value**
Emotional symptoms	L	Ref			Ref			Ref			Ref		
	I	**1.27**	(0.49-3.33)	*0.617*	**1.33**	(0.91-1.93)	*0.140*	**2.15**	(0.75-6.18)	*0.154*	**1.16**	(0.77-1.74)	*0.474*
	H	**0.37**	(0.08-1.61)	*0.183*	**2.20**	(1.36-3.58)	*0.001**	**1.94**	(0.42-8.96)	*0.395*	**2.10**	(1.26-3.52)	*0.005**
Conduct problems	L	Ref			Ref			Ref			Ref		
	I	**0.71**	(0.26-1.98)	*0.513*	**1.08**	(0.72-1.62)	*0.716*	**0.74**	(0.25-2.17)	*0.584*	**1.19**	0.75-1.88)	*0.452*
	H	**0.24**	(0.05-1.06)	*0.060*	**2.11**	(1.28-3.46)	*0.003**	**0.33**	(0.08-1.33)	*0.118*	**2.08**	1.19-3.63)	*0.010**
Inattention-hyperactivity	L	Ref			Ref			Ref			Ref		
	I	**0.41**	(0.17-1.01)	*0.052*	**1.57**	(1.06-2.33)	*0.025**	**0.40**	(0.16-1.01)	*0.053*	**1.52**	(0.98-2.35)	*0.059*
	H	**0.33**	(0.07-1.68)	*0.183*	**2.06**	(1.26-3.38)	*0.004**	**0.13**	(0.02-0.73)	*0.020**	**2.22**	(1.29-3.82)	*0.004**
Peer relation problems	L	Ref			Ref			Ref			Ref		
	I	**0.79**	(0.32-1.95)	*0.604*	**1.51**	(1.01-2.26)	*0.045*	**1.12**	(0.43-2.95)	*0.813*	**1.06**	(0.70-1.62)	*0.780*
	H	**0.13**	(0.01-3.23)	*0.215*	**2.28**	(1.24-4.20)	*0.008**	**1.12**	(0.13-9.48)	*0.916*	**1.77**	(0.93-3.36)	*0.080*
Prosocial behaviours	L	**0.39**	(0.05-3.17)	*0.377*	**1.70**	(0.96-3.00)	*0.070*	**0.17**	(0.02-1.68)	*0.131*	**2.89**	(1.51-5.50)	*0.001**
	I	**0.85**	(0.34-2.13)	*0.729*	**0.97**	(0.68-1.37)	*0.859*	**0.57**	(0.23-1.40)	*0.217*	**1.68**	(1.09-2.58)	*0.018**
	H	Ref			Ref			Ref			Ref		

IPW- adjusted multinomial regressions (95% CI).
H, high-level symptoms; I, intermediate-level symptoms; L, low-level symptoms; SDQ, Strengths and Difficulties Questionnaire; Ref, reference.
Odds Ratios in bold and p values in italics.
* <0.05

Supplemental table 7. Stratified by whether mother reports having visited a psychiatrist after child's birth up to the age of 8: Depression and anxiety and children's trajectories of emotional and behavioural development from ages 3 to 11 (low, intermediate, high) (n=1135).

SDQ subscales		Depression						Anxiety					
		Known visit to a psychiatrist (n=160)			No known visit (n=975)			Known visit to a psychiatrist (n=160)			No known visit (n=975)		
		OR	**95% CI**	**P-value**	**OR**	**95% CI**	**P-value**	**OR**	**95% CI**	**P-value**	**OR**	**95% CI**	**P-value**
Emotional symptoms	L	Ref			Ref			Ref			Ref		
	I	**1.15**	(0.53-2.47)	*0.725*	**1.37**	(0.93-2.00)	*0.107*	**0.83**	(0.32-2.13)	*0.698*	**1.33**	(0.89-2.00)	*0.164*
	H	**1.29**	(0.48-3.47)	*0.609*	**2.03**	(1.21-3.39)	*0.007**	**1.01**	(0.25-4.06)	*0.991*	**2.15**	(1.26-3.69)	*0.005**
Conduct problems	L	Ref			Ref			Ref			Ref		
	I	**0.70**	(0.30-1.62)	*0.401*	**1.00**	(0.66-1.52)	*0.982*	**1.02**	(0.34-3.08)	*0.971*	**1.08**	(0.70-1.67)	*0.733*
	H	**1.03**	(0.36-2.99)	*0.953*	**1.77**	(1.06-2.97)	*0.030**	**0.61**	(0.17-2.23)	*0.456*	**1.73**	(0.99-3.01)	*0.052*
Inattention-hyperactivity	L	Ref			Ref			Ref			Ref		
	I	**0.90**	(0.42-1.91)	*0.779*	**1.35**	(0.91-2.02)	*0.136*	**0.88**	(0.38-2.01)	*0.754*	**1.26**	(0.83-1.92)	*0.286*
	H	**1.41**	(0.51-3.91)	*0.512*	**1.65**	(0.98-2.77)	*0.060*	**0.32**	(0.07-1.36)	*0.123*	**1.90**	(1.11-3.26)	*0.020**
Peer relation problems	L	Ref			Ref			Ref			Ref		
	I	**1.02**	(0.46-2.27)	*0.960*	**1.46**	(0.97-2.21)	*0.069*	**0.82**	(0.27-2.49)	*0.723*	**1.03**	(0.69-1.56)	*0.872*
	H	**1.26**	(0.32-4.99)	*0.737*	**2.23**	(1.18-4.22)	*0.013**	**1.00**	(0.16-6.17)	*0.998*	**1.71**	(0.91-3.21)	*0.094*
Prosocial behaviours	L	**2.19**	(0.53-8.99)	*0.277*	**1.47**	(0.65-1.33)	*0.194*	**2.79**	(0.56-13.80)	*0.208*	**1.91**	(0.99-3.70)	*0.055*
	I	**1.02**	(0.48-2.17)	*0.963*	**0.93**	(0.82-2.65)	*0.679*	**1.43**	(0.55-3.73)	*0.460*	**1.43**	(0.95-2.14)	*0.086*
	H	Ref			Ref			Ref			Ref		

IPW- adjusted multinomial regressions (95% CI).

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

Odds Ratios in bold and p values in italics.

** <0.05*

Résume (Français)

Titre : Enceinte et stressée : L'impact de la dépression prénatale et de la symptomatologie anxieuse de la mère sur les trajectoires de développement émotionnel et comportemental de l'enfant dans la cohorte EDEN.

Contexte : L'exposition *in utero* au stress maternel prénatal, mesurée par la symptomatologie de la dépression et de l'anxiété, a été associée à des caractéristiques émotionnelles et comportementales défavorables jusqu'à la moyenne enfance. Cette étude visait à quantifier et à caractériser cette association dans la population française. **Méthodes :** 1135 enfants de la cohorte mère-enfant EDEN mise en place en France ont été suivis depuis la grossesse jusqu'à l'âge de 11 ans. La modélisation de trajectoire basée sur le groupe a été utilisée pour modéliser leurs trajectoires de caractéristiques comportementales et émotionnelles déterminées à 4 points dans le temps via un questionnaire sur les forces et les difficultés administré aux les parents. En utilisant des scores de propension et des poids de probabilité inverse (IPW) pour tenir compte des facteurs de sélection et de confusion, des régressions logistiques multinomiales ont été utilisées pour quantifier les associations. Des analyses supplémentaires ont été effectuées stratifiées en fonction du sexe, des visites connues chez le psychiatre pendant la grossesse et enfin des visites de la naissance à 8 ans. **Résultats :** Comparativement aux enfants qui n'ont pas été exposés à des niveaux élevés de symptômes dépressifs maternels in utero, ceux qui l'ont été avaient une probabilité plus élevée des niveaux élevés de symptômes émotionnels (OR_{IPW} = 1,90 ; IC 95% 1,21-2,99), de problèmes de comportement (OR_{IPW} = 1,68 ; IC 95% 1,06-2,64), d'inattention-hyperactivité (OR_{IPW} = 1,66 ; IC 95% 1,06-2,61) et de problèmes de relations avec les autres (OR_{IPW} = 1,94 ; IC 95% 1,11-3,39). L'anxiété maternelle prénatale était associée à des niveaux élevés de symptômes émotionnels (OR_{IPW} = 1,95, IC 95% 1,21-3,16) et à de faibles niveaux de comportements prosociaux (OR_{IPW} = 1,82, IC 95% 1,00-3,3). Les enfants de sexe féminin exposés à la dépression (OR_{IPW} = 1,89, IC 95% 1,00-3,58) ou à l'anxiété (ORI_{PW} = 2,41, IC 95% 1,26-4,63) maternelle prénatale étaient plus susceptibles de suivre une trajectoire élevée de symptômes émotionnels. Les enfants de sexe masculin exposés à la dépression (OR_{IPW} = 2,11, IC 95% 1,09-4,10) et à l'anxiété (OR_{IPW} = 2,23, IC 95% 1,03-4,70) maternelle prénatale étaient plus susceptibles d'être classés dans la trajectoire élevée des problèmes de comportement. Aucun risque accru par l'exposition à la dépression et à l'anxiété prénatales n'a été identifié chez les enfants de mères qui avaient déclaré avoir consulté un psychiatre ni pendant ni après la grossesse jusqu'à l'âge de 8 ans. **Conclusion :** La dépression et l'anxiété maternelles prénatales sont associées à des risques accrus de résultats émotionnels et comportementaux défavorables chez les enfants. Les associations avec des résultats spécifiques diffèrent selon le sexe et sont modifiées par l'accès aux soins psychiatriques.