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Prenatal Diet and Children's Trajectories of Anxiety and Depression Symptoms from 3 to 8 Years: The EDEN Mother-Child Cohort

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ABSTRACT

Background: Maternal diet quality during pregnancy has been linked to offspring's physical and mental health outcomes across the lifespan. However, few studies have examined its association with subsequent offspring's anxiety and depression issues.

Objectives: The objective of the study was to examine the relationship between maternal prenatal dietary patterns and offspring's anxiety and depression symptoms from 3 to 8 years.

Methods: We used data from 1242 children enrolled in the French EDEN (Etude des déterminants pré- et postnatals précoces du développement et de la santé de l'enfant) birth cohort. Maternal third trimester dietary patterns—namely, "Healthy" (i.e., high intake in fruit, vegetables, fish, and whole-grain cereals) and "Western" (i.e., high intake in processed and snacking foods) patterns—were evaluated using a validated qualitative FFQ. Children's anxiety and depression symptoms (i.e., fears, worries, misery, nervousness, and somatic symptoms) were assessed by mothers using the Strengths and Difficulties Questionnaire at ages 3, 5, and 8 years, from which trajectories were derived using group-based trajectory modeling. We used logistic regressions to analyze the associations between maternal dietary patterns and children's anxiety and depression symptom trajectories.

Results: We identified 2 trajectories of anxiety and depression symptoms from 3 to 8 years of age: low to moderate ($n = 1058$; reference group) and moderately high ($n = 184$). Maternal low adherence to the Healthy dietary pattern in the third trimester was significantly associated with moderately high children's anxiety and depression symptom trajectories from 3 to 8 years (OR, 1.87; 95% CI, 1.40–2.51), in crude and adjusted analyses. The maternal Western dietary pattern was not significantly associated with anxiety and depression symptom trajectories.

Conclusions: High maternal prenatal adherence to a Healthy dietary pattern was negatively related to anxiety and depression symptoms in children. As maternal diet is a key lifestyle factor, further research should investigate its association with subsequent offspring anxiety and depression symptoms in aiming to later inform prevention strategies focusing on pregnancy. *J Nutr* 2021;151:162–169.

Keywords: diet, anxiety, depression, pregnancy, child, cohort studies, epidemiology

Introduction

The extensive research underpinning the Developmental Origins of Health and Disease hypothesis (1) suggests that fetal environmental exposures may have long-term effects on subsequent health outcomes in offspring (1–4).

Among environmental exposures, maternal prenatal nutrition has been highlighted for its potential impact on physical (5, 6) and mental health in offspring (3, 7–9). Indeed, maternal prenatal nutrient intake may affect offspring's brain development during critical or sensitive periods throughout pregnancy, sometimes resulting in long-lasting functional changes (4, 10–12). Notwithstanding the extreme situation of prenatal exposure to famine, which has been associated with affective psychosis and affective disorder (13, 14), epidemiological studies among humans have suggested a link between maternal diet and psychological development in offspring (3, 7–9, 15). These findings are strengthened by animal models which

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found that maternal increases in nutrient (i.e., fatty acids and glucose) intake during pregnancy influenced the development of neurotransmitter systems (i.e., serotonergic and dopaminergic systems) (16, 17), resulting in increased anxiety-like disorders in offspring (16). In addition, animal models have shown that maternal intake of such nutrients increased circulatory inflammatory cytokines in offspring, affecting neural development that is important for behavioral regulation (18, 19). Furthermore, when providing a favorable in-utero environment to brain development, some nutrients are important, such as iron, iodine, zinc, and long-chain PUFAs (LC-PUFAs) (15, 20, 21). Particularly, LC-PUFAs of the ω-3 series (mainly found in fish, vegetable oils, nuts, seeds, and breast milk) may reduce brain plasticity, a process that has been linked to anxiety-like disorders in animals (22) and mood disorders in humans (23).

It is increasingly recognized that separately investigating the impact of individual nutrients on health problems cannot fully account for the complex correlations and potential interactions between nutrients, even though they are consumed together in a diet. However, few studies have probed maternal dietary patterns (DPs) to assess the variety, combination, and frequency of foods consumed (1, 3, 7, 9, 10, 24). Furthermore, only 3 longitudinal population-based studies have investigated the association between prenatal DPs and subsequent anxiety and depression symptoms in offspring (3, 8, 9). In these studies, the estimated strength of the association was low (8) and the results may have been inconclusive, as they did not fully capture some important confounders, such as maternal anxiety during pregnancy (9). Indeed, maternal mental health is a well-established nonspecific predictor associated with subsequent mental health in offspring (25, 26). Specifically, through biological (27) and environmental (28, 29) mechanisms, maternal anxiety and depression have been shown to be associated with an increased risk for offspring anxiety and depression. Otherwise, it has been suggested that the dietary quality of mothers and children is associated (10, 30). Thereby, the effect of children's diet should be investigated when studying the relationship between maternal prenatal diet and outcomes in offspring.

Considering the increasing incidence of anxiety and depression symptoms in children (31), clarifying whether the perinatal diet (i.e., a modifiable risk factor) is associated with these symptoms could offer important avenues for early prevention. Therefore, we investigated the association between DPs during pregnancy and children's trajectories of anxiety and depression symptoms from 3 to 8 years of age.

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Supplemental Tables 1–10 and Supplemental Figures 1 and 2 are available from the "Supplementary Data" link in the online posting of the article and from the same link in the online table of contents at https://academic.oup.com/jn.
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Abbreviations used: DAG, directed acyclic graphs; DP, maternal dietary patterns; LC-PUFAs, long-chain polyunsaturated fatty acids; PCA, principal component analysis; SDQ, Strengths and Difficulties Questionnaire.

Methods

Study design and participants

The EDEN (Etude des déterminants pré- et postnatals précoces du développement et de la santé de l'enfant) mother-child cohort study was designed to investigate pre- and postnatal determinants of child development and health. The cohort recruited pregnant women (before 24 weeks of amenorrhea) in 2 French university hospitals (Nancy and Poitiers, 2003–2005) during prenatal visits to the Department of Obstetrics and Gynecology. The exclusion criteria included multiple pregnancy, prepregnancy diabetes, illiteracy in French, and plans to leave the area within 3 years. The EDEN cohort was approved by the Bicêtre Hospital ethics committee and the Commission Nationale Informatique et Libertés. Informed written consent was obtained from both parents at enrollment and after the child's birth. Data collection was conducted in multiple waves from medical records (during pregnancy and at child's birth), by trained interviewers (during pregnancy, at birth, and at 3, 5, and 8 years), and from mothers' self-reports at all study points. Detailed information about the study design and data is available in the EDEN cohort profile paper (32). In total, 2002 mothers were included in the cohort (**Supplemental Figure 1**). Compared with a nationally representative sample of pregnant women in France in 2003, the EDEN cohort participants had similar parental sociodemographic characteristics except for educational attainment, which was higher in EDEN (32). Among these, 1717, 1611, 1527, 1255, and 883 mother-child pairs participated at child ages 1, 2, 3, 5, and 8 years, respectively. Finally, 1242 mother-child pairs presented available information on maternal diet during pregnancy and at least 1 assessment of the child's anxiety and depression symptoms, and were included in our study. These participants differed from the original sample in terms of maternal age, education level, family income, children's birth order, prepregnancy BMI, depressive symptoms during pregnancy, cigarette consumption during pregnancy, gestational diabetes, breastfeeding duration, and children's dietary patterns at age 2 years (**Table 1**).

Measures

Children's anxiety and depression symptoms.

We used the French version of the Strengths and Difficulties Questionnaire (SDQ), completed by mothers, to assess children's anxiety and depression symptoms when the children were 3, 5, and 8 years of age (33, 34). This validated instrument includes a scale for anxiety and depression symptoms comprising the following 5 items: "often unhappy, depressed or tearful," "nervous or clingy in new situations, easily loses confidence," "many fears, easily scared," "often complains of headaches, stomach-aches or sickness," and "many worries or often seems worried" [α range: 0.60 (5 years)]. All items refer to the past 6 months or the current school year and were scored 0 (never), 1 (sometimes true), or 2 (certainly true). At each time point, a quantitative score ranging from 0 to 10 was obtained by summing items.

DPs during pregnancy.

Maternal diet in the last trimester of pregnancy was assessed retrospectively during the maternity stay after delivery for 1599 mothers. We used a qualitative FFQ slightly adapted from a questionnaire developed and validated in another French study (35). It comprised 137 items answered on a 7-point scale ranging from never to more than once a day. These items were grouped into 44 food groups (e.g., fruity vegetables, other vegetables, high-fat dairy products, pods and peas, condiments, eggs, refined-grain cereals, snack, blue fish). We used principal component analysis (PCA) to identify DPs during pregnancy and identified 2 DPs: Healthy (i.e., characterized by a high intake of high nutrient–dense foods such as fruit, vegetables, fish, and whole-grain cereals) and

TABLE 1 Comparison of participants versus nonparticipants on key variables in the EDEN study

	Participants, $n = 1242$	Nonparticipants, $n = 760$	Effect size[1]	P[2]
Parental characteristics at baseline				
Maternal education, y	14.0 ± 2.6	12.7 ± 2.7	−0.47	<0.001
Maternal age, y	29.3 ± 4.7	28.4 ± 5.3	−0.20	<0.001
Maternal prepregnancy BMI, *n* (%)	—	—	0.01	0.03
≤18.5 kg/m^2	97 (7.8)	70 (9.2)	—	
>18.5–25 kg/m^2	827 (66.6)	418 (55.0)	—	
>26–30 kg/m^2	220 (17.7)	120 (15.8)	—	
≥30 kg/m^2	98 (7.9)	74 (9.7)	—	
Pregnancy characteristics				
Maternal depressive symptoms	11.0 ± 7.4	13.1 ± 9.1	0.27	<0.001
Maternal anxiety	9.8 ± 9.5	11.5 ± 10.8	0.18	0.08
Maternal alcohol drinking, *n* (%)	101 (8.1)	36 (4.7)	−0.03	0.03
Maternal smoking, *n* (%)	—	—	0.12	<0.001
0 cigarettes/day	956 (77.0)	448 (59.0)	—	
>0–5 cigarettes/day	149 (11.8)	93 (12.2)	—	
>5–10 cigarettes/day	86 (6.9)	70 (9.2)	—	
>10 cigarettes/day	34 (2.7)	52 (6.8)	—	
Gestational diabetes, *n* (%)	84 (6.8)	39 (5.1)	−0.01	0.52
Child characteristics				
Male sex, *n* (%)	651 (52.4)	349 (45.9)	−0.01	0.91
Birth order >first child, *n* (%)	584 (47.0)	397 (52.2)	0.07	0.01
Birth weight, kg	3.3 ± 0.5	3.3 ± 0.6	−0.09	0.07
Gestational age, wk	39.3 ± 1.7	39.1 ± 1.9	−0.08	0.15
Postnatal characteristics				
Family income, euros/mo[3]	5.0 ± 1.3	4.4 ± 1.5	−0.43	<0.001
Parental separation, *n* (%)	138 (11.1)	53 (7.0)	0.16	<0.001
Maternal depressive symptoms[4]	4.4 ± 4.6	5.3 ± 5.0	0.18	0.01
Breastfeeding duration, *n* (%)	—	—	−0.06	0.09
None	314 (25.3)	190 (25.0)	—	
>0–6 mo	680 (54.8)	351 (46.2)	—	
>6 mo	248 (20.0)	109 (14.3)	—	

Values are means ± SDs for continuous variables and numbers (%) for categorical variables; $n = 2002$. Abbreviation: EDEN, Etude des déterminants pré- et postnatals précoces du développement et de la santé de l'enfant.
[1] Calculated as Cohen's d effect size or success rate difference.
[2] Based on unpaired t-test or Mann-Whitney test for continuous variables and χ^2 test for categorical variables.
[3] Family income from pregnancy to age 1 year (mean range in euros per month in each of 8 categories: *1*) ≤450; *2*) 451–800; *3*) 801–1500; *4*) 1501–2300; *5*) 2301–3000; *6*) 3001–3800; *7*) 3801–4500; and *8*) ≥4501).
[4] Maternal depressive symptoms, measured at child age 1 year.

Western (i.e., characterized by a high intake of fats and sugar from processed and snacking foods; **Supplemental Table 1**) (36). These 2 DPs corresponded to the first and second components of the PCA and explained 10.8% and 6.8% of the total variance, respectively [see Yuan et al. for further details (36)]. A score for each DP was calculated at the individual level by summing the observed standardized frequencies of consumption per food group, weighted according to the PCA loadings (36). In further analyses, we then used both quantitative PCA scores and their quartiles on each DP (i.e., low quartile vs. others for the Healthy DP and high quartile vs. others for the Western DP; **Supplemental Table 2**). By construction, patterns derived from PCA analyses were considered as independent.

Covariates.

Potential covariates were considered in our analyses based on existing literature. We used the directed acyclic graphs (DAG) approach to identify an optimal subset of covariates for inclusion in the analysis (**Supplemental Figure 2**). The identified covariates included child sex (male/female), child birth order (oldest vs. other), maternal prepregnancy BMI (kg/m^2), maternal age at inclusion (years), maternal educational level (years of study), maternal alcohol intake throughout pregnancy (>2 units/week vs. no or ≤2 units/week), smoking throughout pregnancy (0, 1–5, 5–10, or 10+ cigarettes/day), maternal anxiety during pregnancy (mean score on the State-Trait Anxiety Inventory) (37), and depression during pregnancy (mean score on the Center for Epidemiologic Studies Depression Scale Revised) (38). The DAG identified 3 intermediate variables on the causal pathway between third-trimester DPs and children's anxiety and depression symptoms: diagnosed gestational diabetes (yes/no), gestational age (weeks of amenorrhea), and child birth weight (kg). These variables were included in a further model to avoid an over-adjustment. Additional variables collected after the child's birth (i.e., postnatal variables) were included in a subsequent model to estimate the direct influence of third-trimester DPs on children's anxiety and depression symptoms. It included breastfeeding duration (none, <6 months, or ≥6 months), family income reported at age 1 year (mean range in euros per month in each of 8 categories: *1*) ≤450; 2) 451–800; *3*) 801–1500; *4*) 1501–2300; *5*) 2301–3000; *6*) 3001–3800; *7*) 3801–4500; and *8*) ≥4501), postnatal maternal depression at age 1 year (mean score on the Edinburgh Postnatal Depression Scale) (39), and child's dietary pattern at 2 years. Children's dietary patterns at 2 years were derived by PCA from a FFQ and included 3 patterns (40): *1*) Processed and fast foods (i.e., high intake of French fries, processed meat, carbonated soft drinks, chocolate, chips, cookies, pizza, fruit juice, meat, dairy desserts, and ice cream; highest quartile vs. others); 2) Guidelines (i.e., high intake of cooked vegetables, rice, fresh fruit, raw vegetables, low-fat fish,

potatoes, ham, stewed fruit, and meat; lowest quartile vs. others); and *3*) Baby foods (high intake of baby foods, breakfast cereals, and stewed fruit and low intake of raw vegetables and fresh fruit; highest quartile vs. others).

Statistical analysis

Descriptive statistics.

Participant and nonparticipant characteristics are presented as means ± SDs or *n* (%). To compare them, Cohen's d effect size or the success rate difference were computed (very small, <0.20; small, 0.20–0.50; medium, 0.50–0.80; large, 0.80–1.20; very large, 1.20–2.0; huge, >2.0). We used a Student's *t* test or Mann-Whitney test for continuous variables and a χ^2 test for categorical variables to compare participants and nonparticipants and to further describe participants according to maternal third-trimester diet.

Identifying childhood trajectories of anxiety and depression symptoms.

We identified developmental anxiety and depression symptom trajectories from 3 to 8 years by using group-based trajectory modeling with semi-parametric mixture models and censored-normal distribution (41, 42), implemented on Stata. The method permits the identification of clusters of individuals having similar trajectories of anxiety and depression symptoms. Full information maximum likelihood was used to account for missing data. The best model was identified in terms of the number of groups, and the polynomial order of the trajectories was determined on the Bayesian information criteria. The best model was also identified using parsimony criteria and previous knowledge about anxiety and depression symptom development during childhood (43). Each participant was assigned to the group he or she had the highest posterior probability of belonging to.

Longitudinal associations between childhood trajectories of anxiety and depression symptoms and DP during pregnancy.

Sample weighting. We used weighting to handle sample attrition to approximate the initial target population for sociodemographic characteristics. Thus, a weight inversely proportional to the probability of being lost to follow-up was given to each individual based on his or her sociodemographic characteristics. Weights permitted each subject included in the analyses (i.e., participants) to account for himself or herself and for nonparticipants who presented the same sociodemographic characteristics. It also permitted us to take into account selective nonresponses on the SDQ questionnaire.

Data imputation. To prevent the loss of further participants due to missing data on covariates, we conducted multiple imputed analyses. The imputation model used the Multivariate Imputation by Chained Equations method (on 20 data sets) (44) and included the outcome, DPs during pregnancy, and all other covariates. Covariates presented, on average, 9.2% of missing data (with a maximum of 17.6% for maternal anxiety during pregnancy).

Logistic regressions. We conducted logistic regressions to estimate the odds of presenting a moderately high trajectory of anxiety and depression symptoms for each of the DPs during pregnancy, compared with the profile presenting low to moderate anxiety and depression symptom trajectories. The 2 DPs were simultaneously included in models. We provided the following estimates: *1*) unadjusted; *2*) adjusted for covariates; *3*) adjusted for covariates and intermediate covariates; and *4*) adjusted for covariates, intermediate covariates, and postnatal variables. Furthermore, the interaction between the Healthy and Western DPs was tested.

Sensitivity analyses. To investigate the effect of maternal mental health [i.e., a nonspecific predictor of mental health in offspring (25, 26)] on our finding, sensitivity analyses were conducted by restricting analyses to *1*) nonanxious mothers during pregnancy; *2*) nondepressed mothers during pregnancy; *3*) nonanxious and nondepressed mothers during pregnancy; *4*) nondepressed mothers during pregnancy and up to child age 1 year; and *5*) nonanxious and nondepressed mothers during pregnancy and up to child age 1 year. In addition, to assess the impact of missing data, sensitivity analyses were conducted by rerunning the logistic regression models after removing the inverse probability weights. Finally, we used maternal third-trimester DP quartiles to test a potential dose-response relationship with offspring's anxiety and depression symptom trajectories from 3 to 8 years of age.

Statistical significance was set at $P < 0.05$. Statistical analyses were performed using R (version 3.5.1).

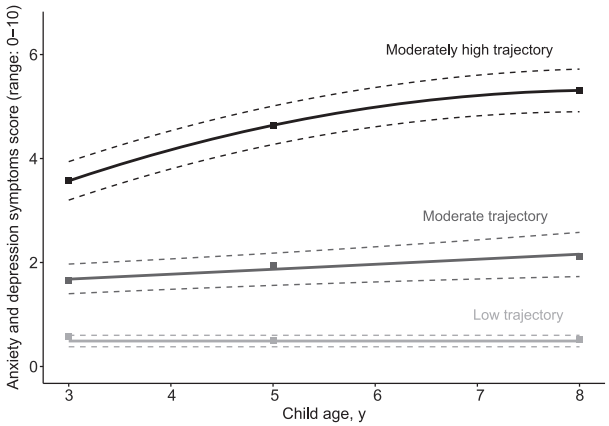

FIGURE 1 Anxiety and depression symptom trajectories from 3 to 8 years for EDEN (Etude des déterminants pré- et postnatals précoces du développement et de la santé de l'enfant) children. The boxes represent observed values, the solid lines represent fitted regression slopes, and the dashed lines represent their 95% confidence intervals. Fit indices of model include log-likelihood, −5504.96; Bayesian information criterion, −5537.02; entropy, 0.791 (i.e., quality of classification; adequate if >0.70); and mean odds of correct classification, 14.8 (i.e., the model classifies participants 14.8 times better than classification by chance; adequate if >5.0).

Results

When identifying childhood anxiety and depression symptom trajectories, the best model identified 3 groups (**Supplemental Table 3**): low (20.21%), moderate (64.98%), and moderately high (14.81%; **Figure 1**). The mean probabilities of being in each trajectory group were 0.71 (SD = 0.17) for the low group, 0.82 (SD = 0.13) for the moderate group, and 0.85 (SD = 0.14) for the moderately high group (**Supplemental Table 4** presents SDQ scores within the selected model). Nevertheless, the aim of the study was to identify a group of children presenting moderately high trajectories of anxiety and depression symptoms (i.e., different from others). Thus, the low and moderate symptom trajectory groups were combined and used as the reference group in subsequent analyses. Characteristics of the sample according to anxiety and depression trajectories are presented in **Supplemental Table 5**.

Table 2 shows the characteristics of the sample according to DP during pregnancy. In brief, mothers more likely to score high on the Healthy DP had higher educational levels and family incomes, were older, and were more likely to have breastfed their child. Conversely, the Western DP was negatively associated with maternal age, educational level, and family income.

Crude and adjusted associations between pregnancy DPs and children's anxiety and depression symptom trajectories

TABLE 2 Characteristics of participants in the EDEN study according to maternal diet patterns during pregnancy

		Maternal dietary pattern during pregnancy					
		Healthy pattern			Western pattern		
	n	Lowest quartile, $n = 309$	Others, $n = 933$	*P* value	Highest quartile, $n = 310$	Others, $n = 932$	*P* value[1]
Moderately high child's anxiety/depression symptoms trajectory	1242	60 (19.4)	124 (13.3)	0.01	43 (13.9)	141 (15.1)	0.65
Prenatal characteristics							
Male sex, *n* (%)	1242	151 (48.9)	500 (53.6)	0.15	164 (52.9)	487 (52.3)	0.84
Birth order > first child, *n* (%)	1242	138 (44.7)	520 (55.7)	0.001	180 (58.1)	478 (51.3)	0.04
Maternal education, y	1146	12.9 ± 2.1	14.0 ± 2.3	<0.001	13.0 ± 2.2	13.9 ± 2.2	<0.001
Maternal age, y	1242	27.6 ± 4.9	29.9 ± 4.5	<0.001	28.4 ± 4.7	29.7 ± 4.7	<0.001
Parental separation, *n* (%)	1026	40 (12.9)	98 (10.5)	0.26	37 (11.9)	101 (10.8)	0.33
Maternal alcohol-drinking during pregnancy, *n* (%)	1242	20 (6.5)	81 (8.7)	0.22	30 (9.7)	71 (7.6)	0.25
Maternal smoking during pregnancy, *n* (%)	1225	—	—	0.06	—	—	<0.001
0 cigarettes/day	—	222 (71.8)	734 (78.7)		212 (68.4)	744 (79.8)	
>0–5 cigarettes/day	—	40 (12.9)	109 (11.7)		38 (12.3)	111 (11.9)	
>5–10 cigarettes/day	—	30 (9.7)	56 (6.0)		34 (11.0)	52 (5.6)	
>10 cigarettes/day	—	11 (3.6)	23 (2.5)		22 (7.2)	12 (1.3)	
Maternal prepregnancy BMI, *n* (%)	1242	—	—	0.17	—	—	0.0003
≤18.5 kg/m^2	—	21 (6.8)	76 (8.1)		41 (13.2)	56 (6.0)	
>18.5–25 kg/m^2	—	196 (63.4)	631 (67.6)		199 (64.2)	628 (67.4)	
>26–30 kg/m^2	—	60 (19.4)	160 (17.2)		44 (14.2)	176 (18.9)	
≥30 kg/m^2	—	32 (10.4)	66 (7.1)		26 (8.4)	72 (7.7)	
Gestational diabetes, *n* (%)	1242	13 (4.2)	71 (7.6)	0.04	6 (1.9)	78 (8.4)	<0.001
Maternal depressive symptoms during pregnancy	1235	10.7 ± 6.8	11.0 ± 7.6	0.45	11.7 ± 7.7	10.7 ± 7.3	0.05
Maternal anxiety during pregnancy	1024	9.4 ± 9.1	10.0 ± 9.6	0.43	9.9 ± 9.4	9.8 ± 9.5	0.87
Characteristics at birth							
Gestational age, wk	1242	39.3 ± 1.6	39.3 ± 1.7	0.44	39.2 ± 1.7	39.3 ± 1.6	0.48
Birth weight, kg	1242	3.27 ± 0.5	3.30 ± 0.5	0.31	3.28 ± 0.5	3.30 ± 0.5	0.62
Postnatal characteristics							
Breastfeeding duration, *n* (%)	1242	—	—	<0.001	—	—	0.002
None	—	97 (31.4)	217 (23.3)		101 (32.6)	213 (22.9)	
>0–6 mo	—	177 (57.3)	503 (53.9)		159 (51.3)	521 (55.9)	
>6 mo	—	35 (11.3)	213 (22.8)		50 (16.1)	198 (21.2)	
Family income (euro/mo)[2]	1241	4.6 ± 1.2	5.1 ± 1.3	<0.001	4.7 ± 1.3	5.1 ± 1.3	<0.001
Maternal depressive symptoms[3]	1161	4.4 ± 4.4	4.4 ± 4.7	0.98	4.8 ± 5.0	4.3 ± 4.5	0.09
Children dietary patterns at 2 y, *n* (%)							
Processed and fast foods, highest quartile	1115	72 (23.3)	207 (22.2)	0.58	118 (38.1)	161 (17.3)	<0.001
Guidelines, lowest quartile	1115	106 (34.3)	173 (18.5)	<0.001	94 (30.3)	185 (19.8)	<0.001
Baby foods, highest quartile	1115	83 (26.9)	196 (21.0)	0.02	74 (23.9)	205 (22.0)	0.45

Values are means ± SDs for continuous variables and numbers (%) for categorical variables; $n = 1242$. Abbreviations: EDEN, Etude des déterminants pré- et postnatals précoces du développement et de la santé de l'enfant.

[1] Based on unpaired t-test or Mann-Whitney test for continuous variables and χ^2 test for categorical variables.

[2] Family income from pregnancy to age 1 year (mean range in euros per month in each of 8 categories: *1*) ≤450; *2*) 451–800; *3*) 801–1500; *4*) 1501–2300; *5*) 2301–3000; *6*) 3001–3800; *7*) 3801–4500; and *8*) ≥4501).

[3] Maternal depressive symptoms, measured at child age 1 year.

between 3 and 8 years of age are presented in Table 3. In unadjusted analyses, children of mothers presenting a low adherence to a Healthy DP during pregnancy were significantly more likely to present moderately high anxiety and depression symptom trajectories from 3 to 8 years (OR, 1.70; 95% CI, 1.30–2.22). After adjustments, the ORs remained stable and showed that maternal Healthy DP exposure was related to children's anxiety and depression symptoms independently from the children DPs at age 2 years. The Western DP was not significantly associated with subsequent anxiety and depression symptoms, either in crude or adjusted analyses. The interaction term between Healthy and Western DPs was not statistically significant ($P = 0.08$). Associations were similar in all sensitivity analyses (**Supplemental Tables 6, 7, 8, 9,** and **10**).

Discussion

This population-based representative and prospective study revealed that low adherence of mothers to a third-trimester Healthy DP was associated with a higher subsequent likelihood that their offspring would show moderately high anxiety and depression symptoms between 3 and 8 years of age. These findings were robust to a range of potential confounders (including child sex and birth order, maternal prepregnancy BMI, maternal age and educational level, and maternal alcohol intake and smoking during pregnancy). By adjusting the analyses for covariates not considered in previous studies, our findings extend previous research (3, 9, 10) and present the association between third-trimester maternal diet and child anxiety and depression trajectories independently of

TABLE 3 Weighted logistic regression models examining maternal dietary patterns during pregnancy and children's anxiety and depression symptoms between 3 and 8 years of age in the EDEN study

	Unadjusted model OR (95% CI)	Adjusted model for covariates[1] OR (95% CI)	Adjusted model for covariates[1], intermediate variables[2] OR (95% CI)	Adjusted model for covariates[1], intermediate variables[2], and postnatal variables[3] OR (95% CI)
Trajectories of anxiety/depression symptoms, moderately high vs. low to moderate				
Maternal dietary pattern during pregnancy, PCA scores				
Healthy pattern	0.79 (0.68–0.92)	0.74 (0.63–0.87)	0.74 (0.63–0.88)	0.74 (0.62–0.88)
Western pattern	1.05 (0.92–1.19)	1.12 (0.97–1.30)	1.11 (0.96–1.29)	1.12 (0.96–1.31)
Maternal dietary pattern during pregnancy				
Healthy pattern, low quartile vs. others	1.70 (1.30–2.22)	1.87 (1.40–2.51)	1.87 (1.39–2.51)	1.88 (1.39–2.55)
Western pattern, high quartile vs. others	0.96 (0.72–1.27)	1.15 (0.84–1.57)	1.13 (0.82–1.55)	1.15 (0.83–1.61)

n = 1242. Abbreviations: EDEN, Etude des déterminants pré- et postnatals précoces du développement et de la santé de l'enfant; PCA, principal component analysis
[1]Adjusted for child gender, child birth order, maternal prepregnancy BMI, maternal age at inclusion, maternal alcohol intake, maternal smoking, prenatal maternal anxiety, prenatal maternal depressive symptoms, and maternal education.
[2]Adjusted for intermediate variables: diagnosed gestational diabetes, gestational age, and birth weight.
[3]Adjusted for postnatal variables: breastfeeding, family income, postnatal maternal depressive symptoms, and children dietary patterns at 2 years (Processed and fast foods, Guidelines, and Baby food).

children's dietary patterns. Indeed, our results were in line with recent evidence from animal studies suggesting that nutritional exposure in early life may be associated with anxiety and depression symptoms in offspring (16, 22). These results were also consistent with previous observational studies using maternal dietary patterns as exposure variables and showing that DPs are related to anxiety and depression symptoms in the offspring in middle childhood (9). However, the direction of the association was different. This might be due to a confounding effect, as important covariates such as maternal anxiety during pregnancy were not accounted for in the previous study (9). Importantly, we did not find any evidence supporting a relationship between the Western DP and anxiety and depression symptoms in children, similarly to other studies (3, 9). Thus, further research would be needed to further investigate this association.

Several potential mechanisms can be put forward to interpret these findings. A first causal explanation could be based on the Developmental Origins of Health and Disease hypothesis (1) and the neurodevelopmental origin of psychiatric disorders (3, 4). It posits that although the brain continues to develop throughout childhood, prenatal alterations in brain structure and function might have a strong impact on later psychiatric disorders (23, 45). Thus, inadequate macro- and micronutrient intake during pregnancy has been shown to be associated with impaired psychological development in children (15). Moreover, a lack of adequate macro- and micronutrient intake during pregnancy has been shown to be associated with impaired psychological development in children (15). For example, extensive research found evidence that maternal fish and seafood consumption during pregnancy (i.e., important loading factors of the Healthy maternal third-trimester DP) was associated with better neurocognitive development in offspring by providing LC-PUFAs of the ω-3 series (15, 46). These fatty acids are involved in the brain cells' membrane structure and neuronal signaling functions (22, 47). After delivery, breast milk (whose composition depends on fatty acid intake and reserves during pregnancy) is also a good source of LC-PUFAs that may participate in brain growth, suggesting another possible pathway by which maternal diet may influence the mental health of children. Therefore, diet during pregnancy could play a role both before birth and later in childhood. Likewise, within the neurodevelopmental origin of psychiatric disorders hypothesis, links have been shown between prenatal diet and the immunological system, oxidative stress, and the microbiota. These may play a role in modulating early vulnerability factors for later mental symptoms (3, 30).

Furthermore, the observed association might be subject to confounding. There was evidence that maternal social background influenced the DPs that described the maternal third-trimester diet in the study. Specifically, an unfavorable third-trimester maternal diet was associated with social (e.g., poor educational attainment, low family income), health-related (e.g., smoking), and biological (e.g., diabetes and high BMI) factors. Moreover, the EDEN cohort has a higher overall income than the general French population, and attrition rates over the follow-up period were highest in families from less advantaged sociodemographic backgrounds (32). Thus, residual confounding due to unmeasured factors related to selective attrition might still be present in our analyses despite the use of sample weighting. Furthermore, the nonsignificant association between a Western DP and subsequent anxiety and depression symptom trajectories in children may be due to the lack of representativeness of the study sample. Further longitudinal studies including larger sample sizes should be conducted to limit statistical power loss.

Strengths and limitations

This study has several strengths, including its large, community-based sample; the longitudinal measures of maternal diet; and the repeated assessments of children's anxiety and depression symptoms, limiting reverse causality and recall bias. Moreover, consideration of the whole diet through a DP analysis allowed the study of a mixture of eating patterns, which is more realistic than the attribution of preconceived Healthy and Western score profiles based on theoretical grounds. In addition, the percentage of variance explained by both DPs in the study (17.6%) is moderate and is similar to those estimated in the broader literature focusing on DP (48–50). Also, albeit population-specific, the DPs obtained through PCA have been shown to be fairly reproducible across populations (49).

Despite these strengths, the study has limitations. The selective attrition among children with less favorable socioeconomic backgrounds may have introduced a selection bias. To handle it, analyses were conducted using sample weighting. This bias might be rather low, as suggested by repeated analyses

without sample weighting, which provided similar results. However, some factors associated with attrition may have been unmeasured, leaving a persistent selection bias. Another limitation is the subjectivity of the measures, as they both relied exclusively on maternal reports. This may have created a bias due to shared method variance. Although mothers are mainly the primary caregivers of young children and arguably are the most aware of their offspring's symptoms, the exclusive reliance on maternal reports for children's anxiety and depression symptoms may have introduced a measurement bias. Nevertheless, the SDQ presents satisfactory psychometric properties and good external validity (51). Otherwise, the self-reported nature of maternal dietary intake may have introduced an information bias. Indeed, pregnancy is a time when women are more likely to adapt their dietary habits out of concern for the developing fetus (52, 53). In addition, it has been pointed out that anxious pregnant women are more likely to report weight-restrictive behavior during pregnancy than those who are not anxious (54). Thus, mothers with and without mental health problems may have answered questions about diet differently. This potential misclassification was limited, however, by the use of a validated FFQ (35), and sensitivity analyses amongst nonanxious mothers showed comparable results. Future studies should seek to establish whether the present findings are confirmed when data are collected from multiple informants. Therewith, mothers' diets during pregnancy were related to breastfeeding and to children's diets at 2 years. This suggests that the third-trimester diet may constitute a proxy for lifestyle factors and act in combination with them. Thus, unmeasured lifestyle factors might confound the association between third-trimester diet and anxiety and depression symptoms. Likewise, residual confounding, notably due to unmeasured variables of home environment quality or family composition, may also be present in this study. However, the inclusion of a thorough list of covariates, used for successive adjustments, limited confounding bias and illustrated the robustness of the results.

In conclusion, our study found a significant association between maternal diet during pregnancy and subsequent offspring's anxiety and depression symptoms. However, research in nationally representative samples and focusing on a wide range of individual variables from multiple informants is now needed to further investigate this association. Emotional problems are established early markers of subsequent mental health problems (30). In addition, diet is a key lifestyle factor. Thus, it could be later investigated in prevention strategies focusing on pregnancy and aiming at improving mental health among children. Particularly, pregnancy is a time when women are more likely to adapt their nutritional habits owing to their concern for the developing fetus (52, 53). Furthermore, promoting a quality diet amongst expecting parents could have a beneficial knock-on effect on the health of the whole family, including the child.

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