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► **To cite this version:**

Nicolas Iv, Marie Herbein, Barbara Heude, Judith van Der Waerden, Maria Melchior, et al.. Children's Diet at 2 Years and Trajectories of Hyperactivity-Inattention Symptoms and Conduct Problems Between 3 and 8 Years: The EDEN Cohort. *Journal of Nutrition*, 2022, 152 (2), pp.484-491. 10.1093/jn/nxab398 . hal-03593602

HAL Id: hal-03593602

<https://hal.science/hal-03593602>

Submitted on 30 Jan 2023

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Children's diet at 2 years and trajectories of hyperactivity-inattention symptoms and conduct problems between 3 and 8 years: the EDEN cohort

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ABSTRACT

Background: Although the role of diet is increasingly acknowledged in psychiatry, data are still scarce regarding its early impact on the most significant behavioral disorders of childhood (i.e., hyperactivity-inattention and conduct problems). **Objectives:** The objective of this study was to explore the relation between children's dietary patterns at 2 years and developmental trajectories of hyperactivity-inattention and conduct problems between 3 and 8 years.

Methods: We recruited 1432 mother-child dyads from the French EDEN (étude sur les déterminants pré- et postnatals du développement et de la santé de l'enfant) mother-child cohort to conduct the analyses. Three dietary patterns, labeled guidelines, processed and fast foods, and baby foods, were identified using an FFQ in children aged 2 years in a previous study. The Strengths and Difficulties Questionnaire was used to assess hyperactivity-inattention and conduct problems at 3, 5, and 8 years of age and build related trajectories from 3 to 8 years. The relation between children's dietary patterns at 2 years and the worst developmental trajectories of hyperactivity-inattention and conduct problems were determined with multivariable logistic regressions adjusted for potential socioeconomic, maternal, and child confounders.

Results: The score on the guidelines dietary pattern was negatively associated with the risk of hyperactivity-inattention problems (OR: 0.75; 95% CI: 0.60–0.94), contrary to adherence to the baby foods dietary pattern (OR: 1.41; 95% CI: 1.16–1.71).

Conclusions: Distinct patterns of children's diet at 2 years were predictive of developmental trajectories of hyperactivity-inattention problems between 3 and 8 years. These results highlight the relevance of conducting further studies to clarify the mechanisms involved.

Keywords: hyperactivity-inattention problems, conduct problems, externalizing problems, dietary patterns, childhood

Introduction

The role of diet as a factor contributing to health and diseases is now well established, and various recommendations on appropriate dietary and nutritional interventions have been published to promote a healthy lifestyle throughout life (1–3). Systematic reviews and meta-analyses examining the associations between diet and common psychiatric disorders have shown that healthy eating habits are inversely associated with the risk of depression in adult males and females (4–6). These diets are characterized by a high intake of vegetables, fruits, whole grains, nuts, seeds, and fish, with limited amounts of processed foods. In contrast, unhealthy energy-dense and nutrient-poor diets rich in processed food and high in fats and sugars in adolescence and adulthood have been positively associated with common psychiatric disorders such as depression and anxiety (4, 7). Similar evidence exists in early childhood, where maternal and young child diets were associated with emotional and behavioral dysregulation in children, although this was based in part on cross-sectional studies (7–9). It is noteworthy that the longitudinal associations between children's diet early in life and externalizing behaviors in childhood have been far less investigated. However, externalizing problems represent the most frequent behavioral problems during childhood. Husky et al. (10) found that 10.4% of children were identified in France per their own evaluation as having an externalizing disorder including attention deficit disorder with or without hyperactivity (ADHD; 4.1%) and conduct problems (CP): that is, oppositional defiant disorder (5.3%) and conduct disorder (4.5%). Moreover, they are all associated with a wide range of negative outcomes during life, such as internalizing disorder, school failure, unemployment, and delinquency (11, 12). An association between a healthy diet and a lower risk of ADHD in children and adolescents was recently suggested in a meta-analysis, but this was based mostly on cross-sectional studies (13). Conduct problems have been associated with suboptimal eating habits, characterized by the intake of energy-dense foods (14). While there is a plausible biological hypothesis involving inflammatory systems, oxidative stress, and alterations of the intestinal microbiota, the role of environmental lifestyle factors also seems to be a major source of confusion bias in the diet–mental health relationship (15). Maternal age affects both the child's diet and the risk of ADHD or CP (16–18). Poor maternal eating habits shape

children's eating behavior (19). Socio-economic position plays an important role in the quality of a child's diet (20–22). Notably, maternal education level is known to influence a child's diet before and after 2 years of age (3, 23–28) and is negatively associated with the risk of ADHD and CP (29–31). In addition, a low family income is also associated with inadequate nutritional intake (32) and with a higher risk of ADHD and CP (31, 33). It is therefore essential to take these confounding factors into account when studying the potential effects of diet on the evolution of the developmental trajectories of these externalizing problems. Given the high socioeconomic costs of ADHD and CP and the significant comorbidities associated with these disorders, it seems relevant to study their relations with children's diets, as this could be a potentially modifiable behavior (34, 35). The objective of this study was to explore the longitudinal association between dietary patterns of 2-year-old children and the worst trajectories of symptoms of hyperactivity-inattention and CP in children between 3 and 8 years of age, accounting for relevant confounders.

Methods

Study design

The mother-child cohort EDEN (étude sur les déterminants pré- et postnatals du développement psychomoteur et de la santé de l'enfant) was designed to study the pre- and postnatal determinants that have a potential role in the child's psychological and social development and health (36). Pregnant women were recruited before 24 weeks of gestation during a prenatal appointment in the Obstetrics-Gynecology departments of Nancy and Poitiers university hospitals. Exclusion criteria included multiple pregnancies, a history of diabetes, an inability to speak or read French, and plans to move from the region within 3 years. Recruitment began in February 2003 in Poitiers and in September 2003 in Nancy, and lasted 27 months in each center. During pregnancy and after birth (2, 3, 5, and 8 years), socio- demographic and medical data on the mother and her child were collected from medical records, through interviews with the mother conducted between 24 and 28 weeks of gestational age at the university hospital maternity ward by dedicated investigators, and through self- administered questionnaires mailed to the mother during her

child's first year of life and at 2, 3, 5, and 8 years. Informed written consent from the parents was obtained at enrollment and consent for the child was obtained from both parents after the child's birth. The EDEN cohort received approval from the Bicêtre Hospital ethics committee and the Commission Nationale Informatique et Libertés, which oversees ethical aspects of data collection in France.

Participants

Of the 2002 pregnant women included in the EDEN cohort mother-child dyads were excluded for the following reasons: miscarriage (n=11) deaths in utero (n=7), medical termination of pregnancy (n=2), loss of sight (n=14), moving (n=8), withdrawal of consent (n=51), not meeting inclusion criteria (n=2). Data were obtained at birth for 1,899 mother-child dyads. Of these, 1527 children were still being followed at 3 years, 1255 at 5 years, and 883 at 8 years. For our analysis, we included 1432 mother-child respondents who had at least 1 measurement on the Strengths and Difficulties Questionnaire (SDQ). The characteristics of participants in the EDEN cohort were comparable to those of the national population in terms of the average age, proportion of unmarried couples, socio-demographic characteristics of parents, birth weight, and rate of prematurity, with the exception of a higher level of education among mothers in the cohort (36). During the follow-up period, the attrition rate was higher among families whose mothers were young, had lower levels of education and lower income, did not live with the child's father, smoked during pregnancy, had psychological difficulties during pregnancy, and had a child that was not of low birth weight (36).

Dependent variables: children's hyperactivity-inattention and CP trajectories from 3 to 8 years

Children's behavior at 3, 5, and 8 years of age was assessed using the SDQ, which was completed by their mothers (37, 38). This validated questionnaire includes 25 items related to 5 dimensions of children's behavior: emotions, CP, hyperactivity-inattention, peer relationships, and prosocial behavior (39). In this paper, we focused on the CP and hyperactivity-inattention subscales. The dimension of hyperactivity-inattention is composed of 5 items, 2 of which deal with hyperactivity ("restless, hyperactive, can't

stay still for long,” and “constantly fidgeting or squirming”), 2 with inattention [“easily distracted, concentration wanders,” “can stop and think things out before acting” (wave 3 years) or “think things out before acting” (waves 5 and 8 years)], and 1 with impulsivity (“good attention span, sees work through to the end”). The SDQ items are rated from 0 to 2 points (0 = never, 1 = sometime true, 2 = certainly true). The CP dimension is composed of 5 items that relate to temper tantrums (“often loses his/her temper”), obedience (“generally behaves well, obeys adults most of the time”), fights (“often fights with or bullies other children”), lying [“often fights with adults” (3 years old) or “often lies or cheats” (5 and 8 years old)], stealing [“can be mean to others” (wave 3 years old) or “steals at home, school or elsewhere” (waves 5 and 8 years old)]. All items corresponded to the prior 6 months or the current school year. The scores range from 0 to 10 for each dimension. The higher the score, the poorer the child’s functioning. Measurements of scores in each of the 2 dimensions at 3, 5, and 8 years of age were used to identify individual developmental trajectories of symptoms of hyperactivity-inattention and CP. Data on SDQ were available for 1308 children at 3 years, 1185 at 5 years, and 874 at 8 years.

Main exposure: child’s dietary patterns at 2 years old

Children’s dietary intake at the age of 2 years was collected using an FFQ, as previously described (28). A previous analysis of these data using principal component analysis (PCA) identified 3 dietary patterns, which accounted for 26.8% of the explained variance. The first pattern, labeled processed and fast foods, was mainly characterized by a high consumption of French fries, processed meat, carbonated soft drinks, crisps, biscuits, pizzas, fruit juices, dairy puddings and ice cream, legumes, and bread (in descending order of factor loadings) and by a low consumption of cooked vegetables (10.9% of explained variance). The second pattern, labeled guidelines, was mainly characterized by the frequent consumption of cooked vegetables, rice, fruits, raw vegetables, low-fat fish, potatoes, ham, compotes, meat, and bread (9.3% of explained variance). The third pattern, named baby foods, had high positive loadings for baby foods, breakfast cereals, and stewed fruit and negative loadings for raw vegetables and fresh fruit (6.6% of explained variance). Scores for each pattern were calculated at the individual level by summing the observed

standardized frequencies of consumption per food group, weighted according to the PCA loadings. The higher the score, the higher the child's adherence to the dietary pattern (28).

Covariates

The adjustment variables selected for the main analysis were based on a directed acyclic graph (DAG) constructed from the literature (**Supplemental Figures 1 and 2**). Children's characteristics included sex (male/female), birth weight (kg), gestational age (weeks), and mode of delivery (spontaneous vaginal delivery, surgical vaginal delivery, cesarean section). Parental characteristics included maternal education (school years), maternal age (years), maternal BMI (kg/m²), maternal smoking during pregnancy (cigarettes), maternal alcohol use during pregnancy (yes/no), maternal depression during pregnancy (Center for Epidemiologic Studies–Depression Scale, with scores ranging from 0 to 60), maternal anxiety (State-Trait Anxiety Inventory, with scores ranging from 20 to 80), any breastfeeding duration (month), maternal cannabis use (yes/no), maternal employment (“no, housewife”; “no maternity leave”; “no, parental leave”; “no, student”; “no, unemployed or looking for a job”; “no, other situation”; “yes”), paternal age (years), paternal employment (“no, student”; “no, unemployed or looking for a job”; “no, other situation”; “yes”), parental separation before birth assessment (biological father not living with the mother and child; yes/no), family income at age 2 (<450€/month, 450–800€/month, 800–1500€/month, 1500–2300€/month, 2300–3000€/month, 3000–3800€/month, 3800–4500€/month, >4500€/month), and 2 maternal dietary patterns during pregnancy, previously identified using PCA: healthy (i.e., characterized by a high intake of fruit, vegetables, fish, and whole-grain cereals) and Western (characterized by a high intake of processed and snacking foods).

Data on maternal age, maternal education, maternal smoking, maternal alcohol consumption, maternal depression, maternal anxiety, paternal age, and parental separation were assessed during pregnancy. Data on the child's sex, birth weight, gestational age, mode of delivery, and maternal dietary patterns during pregnancy were collected at birth. Data on the breastfeeding duration were collected between birth and 1 year. Data on the maternal BMI, maternal cannabis use, maternal employment, and family income were assessed at 2 years.

Statistical analyses

The identification of developmental trajectories of symptoms of hyperactivity-inattention and CP was based on latent process mixed modeling. This approach divides the structural linear mixed model that describes the quantity of interest (a latent process) according to time and covariates from the measurement model that link the quantity of interest to the observations (details are available in the **Supplemental Statistical Methods**) (40). The best models were selected based on the Bayesian information criterion and Akaike information criterion, and by maximizing the posterior probability of membership in the class of highest developmental trajectory. The data on SDQ were available for 1308 children at 3 years, 1185 at 5 years, and 874 at 8 years. Trajectories from 3 to 8 years were identified for 1432 subjects. A descriptive analysis of the study population was conducted in terms of means and SDs for quantitative variables and percentages for qualitative variables based on the LPMM (latent process mixed model) grouping (the worst trajectory compared with other trajectories). Then, a comparison of the characteristics of these groups was made using a Student's test or Wilcoxon's nonparametric test for quantitative variables and a chi-squared test or Fisher's exact test for qualitative variables, depending on the application conditions. A descriptive analysis of the excluded and included populations was conducted following the same procedure.

The relationships between child dietary patterns at 2 years and the highest trajectories of externalized problems (hyperactivity-inattention and CP) were studied using logistic regression, adjusted for covariates selected by the DAG (Supplemental Figures 1 and 2) after multiple imputation of the main exposure and covariates, assuming that data were missing at random. The chained equation process comprised 5 cycles, and 10 data sets were created. Three sensitivity analyses were performed. The first analysis used complete data and the original set of confounding variables (hyperactivity-inattention: $n = 580$; CP: $n = 650$). The second sensitivity analysis was adjusted with additional covariates (including paternal age, mode of delivery, gestational age, maternal smoking during pregnancy, maternal alcohol use during pregnancy, maternal depression, maternal anxiety during pregnancy, maternal cannabis use at 2 years, and employment of the mother and the father at 2 years), and used complete data (hyperactivity-inattention: $n = 444$; CP: $n = 500$).

The last sensitivity analysis consisted of logistic models fitted with cofounders selected according to the augmented backward elimination procedure, which combined significance criteria with the change in the estimate and used complete data (hyperactivity-inattention: $n = 476$; CP: $n = 547$) (41). Finally, the linearity of the quantitative variables used in the logistic regression models was verified. The analyses were performed using R v4.0.2 (R core team) and the LCMM and MICE packages.

Results

Data of 1432 mother-child dyads from the French mother-child cohort were analyzed (a flowchart is available in Figure 1).

Compared to children excluded from the present analyses, included children were breastfed for longer durations. They scored lower and higher on the processed and fast foods and guidelines dietary patterns, respectively. They were born to older mothers, with a higher level of education and with higher score on the Western dietary pattern during pregnancy. Their mothers were also less likely to be separated from their fathers and had a higher family income (further details available in **Supplemental Table 1**).

Trajectories of hyperactivity-inattention symptoms (the worst trajectory, $n = 132$; other trajectories, $n = 300$) and CP (highest, $n = 217$; other trajectories, $n = 1215$) were identified (**Supplemental Figures 3–6**). The characteristics of the total study population, according to children's hyperactivity-inattention and CP trajectories from 3 to 8 years, are summarized in Tables 1 and 2. Compared to others, children in the worst trajectory (i.e., the highest trajectory) of hyperactivity-inattention scored lower on the guidelines dietary pattern (mean SD: -0.2 ± 0.9 compared with 0.1 ± 1.0 in other children; $P = 0.003$), while their score was higher on the baby foods dietary pattern (0.3 ± 1.0 compared with 0.0 ± 1.0 in other children; $P < 0.001$).

Table 3 shows the associations between children's dietary patterns at 2 years of age and hyperactivity-inattention and CP between 3 and 8 years, before and after adjusting for covariates. Children who scored higher on the guidelines and the baby foods dietary patterns were less and more likely, respectively, to belong to the worst trajectory of

hyperactivity- inattention symptoms, in both the unadjusted [guidelines: OR: 0.77 (95% CI: 0.62–0.97); baby foods: OR: 1.36 (95% CI:1.10–1.67)] and adjusted [guidelines: OR: 0.75 (95% CI: 0.60–0.94); baby foods: OR: 1.41 (95% CI: 1.16–1.71)] models. No significant associations were found between any of the 3 dietary patterns and CP. These results were confirmed in the sensitivity analysis using only complete data adjusted with the original set of confounding variables [guidelines: OR: 0.49 (95% CI: 0.34–0.71); baby foods: OR: 1.79 (95% CI: 1.30–2.47)], with additional covariates [guidelines: OR: 0.42 (95%CI: 0.26–0.67); baby foods: OR: 1.63 (95% CI: 1.12–2.37)], and with cofounders selected according to the augmented backward elimination procedure [guidelines: OR: 0.47 (95%CI: 0.31–0.71); baby foods: OR: 1.66 (95% CI: 1.17–2.35); **Supplemental Tables 2 and 3**].

Discussion

Main findings

This study, based on the longitudinal follow-up of children of the EDEN cohort, shows that toddlers' diet at 2 years predicts hyperactivity-inattention symptoms trajectories between 3 and 8 years. Even after accounting for covariates, lower adherence to the guidelines dietary pattern and higher scores on the baby foods dietary pattern were predictive of taking the worst trajectory of hyperactivity-inattention. No association was observed between children's dietary patterns and CP. Our results, based on a longitudinal design, are consistent with a meta-analysis mostly based on cross-sectional studies, suggesting that energy-dense and nutrient-poor diets mostly based on the high consumption of processed foods can enhance the risk of ADHD symptoms, while healthier diets rich in fruits and vegetables would seem to protect against ADHD symptoms (13). Previously, Lioret et al. (28) showed that the baby foods dietary pattern at 2 years that was used in our analyses was positively correlated with the processed and fast foods component (high loadings for chips, carbonated soft drinks, cookies, chocolate, dairy desserts, ice cream, and processed meat and low amounts of cooked and raw vegetables and fresh fruits) measured at 5 years of age, while the guidelines component at 2 years of age was positively correlated with the protein-rich and diversified component (foods of animal origin, starchy foods, raw and

cooked vegetables, fresh fruit, and pizza) at 5 years of age. The absence of a correlation between toddlers' dietary patterns and children's CP could correspond to a real absence, as found by Kohlboeck et al. (42), or could be the consequence of underrepresentation in the EDEN cohort of the most socially disadvantaged families, and therefore underrepresentation of unhealthy foods, leading to a lack of statistical power. However, the scientific literature concerning the relationship between children's dietary patterns and CP is less abundant, and the results are heterogeneous.

Interpretation

Several hypotheses can explain why children with high scores on the guidelines dietary pattern and low scores on the baby foods dietary pattern—that is, those with a healthier and more balanced diet—are less likely to take the worst trajectory of hyperactivity-inattention. Healthy diets like the Mediterranean diet are rich in omega-3 [$n-3$ ($\omega-3$)] PUFAs. A meta-analysis showed that $n-3$ PUFA supplementation improves ADHD clinical symptom scores and cognitive performance in children with ADHD, and that children and adolescents with ADHD have lower levels of DHA, EPA, and total $n-3$ PUFAs (43). The potential role of trace elements has also been investigated (44). A meta-analysis conducted by Tseng et al. (45) showed that peripheral serum ferritin levels were significantly lower in children with ADHD. Moreover, ADHD was significantly associated with iron deficiency, and the severity of ADHD was significantly higher in iron-deficient children than those without iron deficiency. Associations between zinc and ADHD were found, although 1 meta-analysis showed no association (46–48). Magnesium was also investigated, with lower serum magnesium levels among subjects with ADHD (49). Other mechanisms have been hypothesized. A systematic review reported that a diet without additives and food coloring was associated with a reduction in symptoms of hyperactivity-inattention in children, although the causal relationship could not be proven (50). The current study did not find an association between the processed and fast foods dietary pattern, which is presumably richer in additives, and a high trajectory of hyperactivity-inattention symptoms. However, the baby foods dietary pattern at 2 years is correlated with the processed and fast foods at 3 and 5 years. It is possible that food additives and coloring play a later role in developmental trajectories of inattention-

hyperactivity (28). Finally, a noncausal relationship between children's dietary patterns and trajectories of hyperactivity-inattention problems is possible. Indeed, parental educational practices are likely to influence the types of food consumed by the child. A cross-sectional study examining children aged 2 to 5 years and their parents showed that children of parents who overreacted and had restrictive eating practices had reduced consumption of fruits and vegetables (51). In addition, children consumed more fruits and vegetables if the parents were authoritarian and if family members dined together. Parental overreaction and laxity were also associated with higher intakes of nonessential foods (rich in fat and sugar) (51). Low parental coping skills and a lack of authority are linked to the exacerbation of ADHD symptoms (52). It is therefore conceivable that parenting practices may act as a confounding factor. However, the current study could not take this into account.

Strengths and weaknesses

This study presents several strengths: externalizing symptoms measured using SDQ, a validated questionnaire; the temporal precedence of diet on behavioral evaluations; the determination of developmental trajectories of externalizing behaviors based on latent process mixed modeling; and a global and multidimensional approach to diet. However, it also has limitations. There is selection bias related to an attrition rate higher among mothers with an adverse socioeconomic context and those whose children did not have a low birth weight in the EDEN cohort. Moreover, the dyads excluded from this study due to the lack of SDQ measurements are characterized by the same adverse socioeconomic context and by children who scored higher on the processed and fast foods and the guidelines dietary patterns. Information bias may also have been generated, as toddlers' diet was assessed using a short FFQ that did not allow for an extensive evaluation of the intake of different foods or of the quantity consumed. However, this questionnaire is appropriate for a global approach to diet. In addition, to maximize the number of individuals in the determination of the developmental trajectories of externalizing behaviors, subjects who had only 1 in 3 SDQ measures were included. An approach to diet based on an a priori analysis, where dietary patterns are based on existing knowledge about the relationships between food, nutrients, and disease, would have made it possible to study more specifically the potential value of diets that are currently recognized as healthy.

However, the guidelines dietary pattern is close enough to a diet considered healthy and could pave the way for new hypotheses concerning foods not taken into account in the a priori approach. Finally, we accounted for the main potential confounders in our main results but could not exclude residual confounding, such as parenting style, which is a cause of aggravation of ADHD and a risk factor of CP, or parents' physical issues, child care issues, medical care, insurance coverage, family support, and children's screen time, which may also be important to consider. However, the inclusion of different sets of additional covariates used for sensitivity analyses limited the confounding bias and underlines the robustness of the results.

Implications

In a previous publication using data from the EDEN cohort, Galera et al. (53) found that prenatal maternal dietary patterns were also associated with a high trajectory of hyperactivity-inattention symptoms in children. Altogether, the results of the current study are an additional argument in favor of preventive approaches that should combine the healthy eating habits of mothers and their children. Such preventive strategies involve the promotion of a healthy diet by making healthy foods more accessible, reducing the promotion of unhealthy foods, and promoting healthy food in different contexts, while taking the lifestyles of families into account. The findings are also an additional argument in favor of this type of preventive approach, and focus on healthy eating that goes beyond mothers and places the emphasis on their children. The promotion to parents of healthy diets in children from an early age could be facilitated through pediatricians or maternal and child welfare organizations. However, additional longitudinal studies are needed to replicate these results, while at the same time taking the complexity of the family environment in these associations into account. A better understanding of the mechanisms that explain the effects of healthy diets on mental health outcomes is necessary in order to develop effective interventions.

Conclusions

This study, which was based on a longitudinal design allowing the determination of developmental trajectories of externalizing behaviors and on a global and multidimensional

approach to diet, found an association between toddlers' diet at 2 years and hyperactivity-inattention symptom trajectories between 3 and 8 years. Further studies are needed to clarify the mechanisms involved in order to promote a healthier diet from an early age, especially among the least advantaged populations, who are also the most vulnerable and are therefore likely to adopt a diet dictated by economic imperatives (21). The growing evidence of the importance of diet as a factor influencing mental health is adding to the extensive scientific literature that supports healthy food as early as possible in life for better health outcomes.

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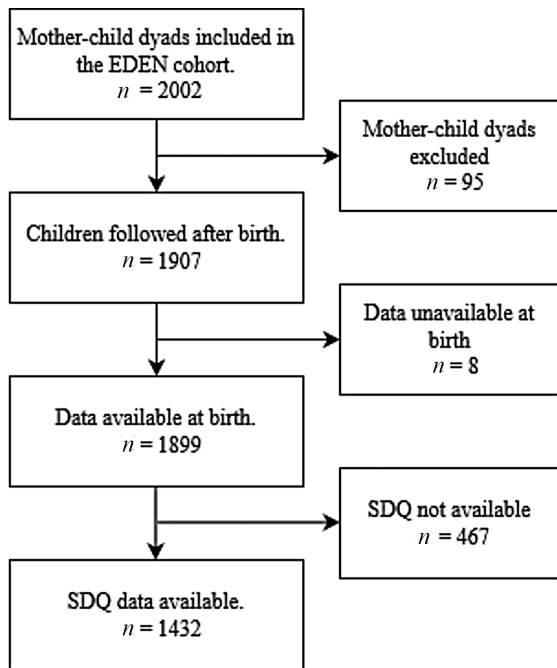


FIGURE 1 Flow chart of the EDEN Cohort, France, 2005–2011. Abbreviations: EDEN, étude sur les déterminants pré- et postnatals du développement psychomoteur et de la santé de l'enfant; SDQ, Strengths and Difficulties Questionnaire

TABLE 1 Children's characteristics of the study population according to children's hyperactivity-inattention and conduct problems trajectories from 3 to 8 years

	All participants	Hyperactivity-inattention			Conduct problems		
		Other trajectories (<i>n</i> = 1300)	Worst trajectory (<i>n</i> = 132)	<i>P</i>	Other trajectories (<i>n</i> = 1215)	Worst trajectory (<i>n</i> = 217)	<i>P</i>
Children's characteristics							
Male sex	746 (52.1)	656 (50.5)	90 (68.2)	<0.001 ¹	608 (50.0)	138 (63.6)	<0.001
Birth weight (kg)	3.3 ± 0.5	3.3 ± 0.5	3.2 ± 0.5	0.080	3.3 ± 0.5	3.3 ± 0.6	0.741
Gestational age (weeks)	39.3 ± 1.7	39.3 ± 1.7	39.3 ± 1.8	0.656	39.3 ± 1.7	39.2 ± 1.7	0.840
Mode of delivery							
spontaneous vaginal delivery	1058 (74.2)	965 (74.6)	93 (71.0)	0.657	897 (74.2)	161 (74.5)	0.679
surgical vaginal delivery	160 (11.2)	144 (11.1)	16 (12.2)		139 (11.5)	21 (9.7)	
cesarean section	207 (14.5)	185 (14.3)	22 (16.8)		173 (14.3)	34 (15.7)	
Any breast-feeding duration							
No	366 (25.6)	333 (25.6)	33 (25.0)	0.819	311 (25.6)	55 ± 25.3	0.891
[0-6] months	780 (54.5)	705 (54.2)	75 (56.8)		659 (54.2)	121 ± 55.8	
>6 months	286 (20.0)	262 (20.2)	24 (18.2)		245 (20.2)	41 ± 18.9	
Children's dietary patterns¹							
Processed and fast foods	0.0 ± 1.0	0.0 ± 1.0	0.1 ± 1.1	0.272	0.0 ± 1.0	0.0 ± 1.0	0.323
Guidelines	0.0 ± 1.0	0.1 ± 1.0	-0.2 ± 0.9	0.003	0.0 ± 1.0	0.0 ± 1.0	0.802
Baby foods	0.0 ± 1.0	0.0 ± 1.0	0.3 ± 1.0	<0.001	0.0 ± 1.0	0.2 ± 1.1	0.041

Data are from the EDEN cohort, France, 2005–2011. Values are *n* (%) or mean (SD). Abbreviation: EDEN, etude sur les déterminants pré- et postnatals du développement psychomoteur et de la santé de l'enfant.

¹ Data were obtained when the child was 2 years old.

TABLE 2 Parental characteristics of the study population according to children’s hyperactivity-inattention and conduct problems trajectories from 3 to 8 years

	All participants	Hyperactivity-inattention			Conduct problems		
		Other trajectories (n = 1300)	Worst trajectory (n = 132)	<i>P</i>	Other trajectories (n = 1215)	Worst trajectory (n = 217)	<i>P</i>
Parental characteristics							
Maternal age (years) ²	29.5 ± 4.7	29.5 ± 4.7	28.8 ± 4.6	0.087	29.5 ± 4.7	29.2 ± 5.0	0.307
Maternal BMI (kg/m ²) ¹							
≤18.5	47 (7.0)	40 (6.6)	7 (10.9)	0.639	38 (63.7)	9 (8.6)	0.813
18.5–25	421 (62.9)	382 (63.1)	39 (60.9)				
25–30	131 (19.6)	119 (19.7)	12 (18.8)		109 (19.3)	22 (21.0)	
≥30	70 (10.5)	60 (10.6)	6 (9.4)		58 (10.3)	12 (11.4)	
Maternal education (years)	13.9 ± 2.6	14.0 ± 2.6	13.4 ± 2.5	0.008	14.0 ± 2.6	13.4 ± 2.7	0.003
Maternal dietary patterns ²							
Healthy	0.0 ± 0.9	0.0 ± 0.9	-0.1 ± 1.0	0.563	0.0 ± 0.9	-0.1 ± 1.0	0.195
Western	0.0 ± 0.9	-0.1 ± 0.9	0.1 ± 1.1	0.137	0.1 ± 0.9	0.1 ± 1.1	0.005
Maternal smoking (cigarettes) ²	1.1 ± 2.7	1.0 ± 2.7	1.4 ± 3.0	0.200	1.0 ± 2.6	1.5 ± 3.3	0.032
Maternal alcohol consumption ²	108 (7.6)	91 (7.0)	17 (12.9)	0.015	87 (7.2)	21 (9.7)	0.201
Maternal depression (CES-D) ²	11.0 ± 7.7	10.8 ± 7.7	13.3 ± 7.6	<0.001	10.8 ± 7.8	12.5 ± 7.5	<0.001
Maternal anxiety (STAI) ²	30.0 ± 9.7	29.8 ± 9.5	32.3 ± 10.7	0.006	29.7 ± 9.6	31.6 ± 9.9	0.018
Maternal cannabis use ¹	38 (3.0)	34 (2.9)	4 (3.4)	1.000	33 (3.0)	5 (2.6)	0.766
Maternal employment ¹							
no, housewife	91 (7.2)	81 (7.0)	10 (8.4)	0.113	70 (6.5)	21 (11.1)	<0.001

no, maternity leave	56 (4.4)	51 (4.4)	5 (4.2)		53 (4.9)	3 (1.6)	
no, parental leave	159 (12.5)	145 (12.6)	14 (11.8)		128 (11.9)	31 (16.4)	
no, student	19 (1.5)	15 (1.3)	4 (3.4)		18 (1.7)	1 (0.5)	
no, unemployed or looking for a job	59 (4.7)	48 (4.2)	11 (9.2)		42 (3.9)	17 (9.0)	
no, other situation (disability, pension)	2 (0.2)	2 (0.2)	0 (0.0)		2 (0.2)	0 (0.0)	
yes	882 (69.6)	807 (70.2)	75 (63.0)		766 (71.0)	116 (61.4)	
Paternal age (years) ²	34.8 ± 87.8	35.1 ± 92.1	31.9 ± 5.3	0.235	35.3 ± 95.0	31.2 ± 5.0	0.242
Paternal employment ¹							
no, student	1 (0.1)	1 (0.1)	0 (0.0)	0.768	1 (0.1)	0 (0.0)	0.302
no, unemployed or looking for a job	45 (3.6)	42 (3.7)	3 (2.5)		34 (3.2)	11 (5.8)	
no, other situation (disability, pension)	15 (1.2)	13 (1.1)	2 (1.7)		13 (1.2)	2 (1.1)	
yes	1206 (95.2)	1092 (95.1)	114 (95.8)		1030 (95.5)	176 (93.1)	
Parental separation ²	57 (4.0)	49 (3.8)	8 (6.1)	0.303	42 (3.5)	15 (6.9)	0.029
Family income per month ¹							
<450 euros	1 (0.1)	1 (0.1)	0 (0.0)	0.029	1 (0.1)	0 (0.0)	0.076
451-800 euros	25 (2.0)	23 (2.0)	2 (1.7)		20 (1.9)	5 (2.7)	
801-1500 euros	92 (7.3)	75 (6.6)	17 (14.4)		71 (6.7)	21 (11.2)	
1501-2300 euros	304 (24.3)	266 (23.5)	38 (32.2)		250 (23.5)	54 (28.9)	
2301-3000 euros	356 (28.4)	329 (29.0)	27 (22.9)		306 (28.7)	50 (26.7)	
3000-3800 euros	248 (19.8)	230 (20.3)	18 (15.3)		218 (20.5)	30 (16.0)	
3801-4500 euros	121 (9.7)	113 (10.0)	8 (6.8)		110 (10.3)	11 (5.9)	
>4500 euros	105 (8.4)	97 (8.6)	8 (6.8)		89 (8.4)	16 (8.6)	

Values are *n* (%) or mean ± SD. Abbreviations: CES-D, Center for Epidemiologic Studies-Depression Scale; EDEN, etude sur les déterminants pré- et postnataux du développement psychomoteur et de la santé de l'enfant; STAI, State-Trait Anxiety Inventory.

¹Data were obtained during pregnancy.

²Data were obtained when the child was 2 years old.

TABLE 3 Association between children’s dietary patterns at 2 years old and developmental trajectories of inattention-hyperactivity and conduct problems

	Unadjusted model (<i>n</i> = 1432)		Adjusted model* (<i>n</i> = 1432)	
	OR	95% CI	OR	95% CI
Hyperactivity-inattention				
Processed and fast foods, per SD	1.06	0.89–1.27	0.99	0.82–1.20
Guidelines, per SD	0.77	0.62–0.97	0.75	0.60–0.94
Baby foods, per SD	1.36	1.10–1.67	1.41	1.16–1.71
Conduct problems				
Processed and fast foods, per SD	1.06	0.92–1.22	1.00	0.85–1.18
Guidelines, per SD	0.97	0.83–1.14	1.03	0.87–1.21
Baby foods, per SD	1.14	0.98–1.34	1.15	0.97–1.35

Data are from the EDEN cohort, France, 2005–2011.

Abbreviation: EDEN, etude sur les déterminants pré- et postnatals du développement psychomoteur et de la santé de l’enfant.

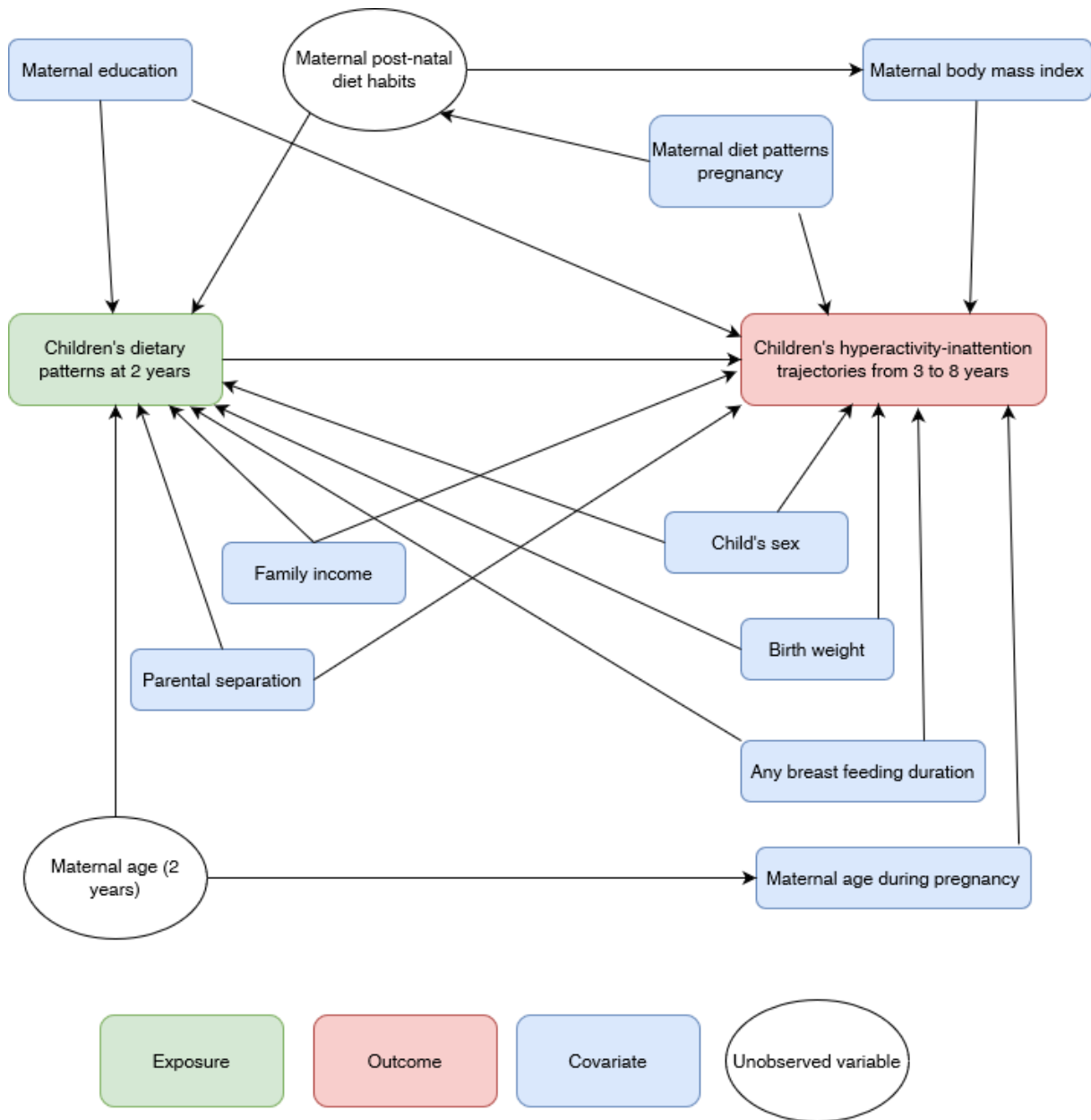
* Common adjustments for inattention-hyperactivity and conduct problems include: children’s sex, maternal education, maternal BMI, parental separation, family income, mother’s age at pregnancy, and any breastfeeding duration. Additional adjustments for inattention-hyperactivity include: birth weight, prenatal maternal dietary patterns.

Children's diet at 2 years and trajectories of hyperactivity-inattention symptoms and conduct problems between 3 and 8 years: the EDEN cohort

Nicolas IV

Online Supplementary Material

Supplementary figure 1. Directed acyclic graph illustrating relationships between developmental trajectories of hyperactivity-inattention and dietary patterns of children at 2 years old.



- Maternal education → Children's dietary patterns at 2 years (1–6)
- Maternal education → Children's hyperactivity-inattention trajectory from 3 to 8 years (7,8)
- Maternal age → Children's dietary patterns at 2 years (9)
- Maternal age → Children's hyperactivity-inattention trajectory from 3 to 8 years (10)
- Maternal BMI → Children's hyperactivity-inattention trajectory from 3 to 8 years (11)
- Maternal diet during pregnancy → Maternal post-natal dietary habits → Children's dietary patterns at 2 years (12)
- Children's sex → Children's dietary patterns at 2 years (13)
- Children's sex → Children's hyperactivity-inattention trajectory from 3 to 8 years (14–18)
- Birth weight → Children's dietary patterns at 2 years (19)
- Birth weight → Children's hyperactivity-inattention trajectory from 3 to 8 years (20)
- Breast feeding duration → Children's dietary patterns at 2 years (21)

- Breast feeding duration → Children's hyperactivity-inattention trajectory from 3 to 8 years (22)
- Family income → Children's dietary patterns at 2 years (23)
- Family income → Children's hyperactivity-inattention trajectory from 3 to 8 years (24)
- Parental separation → Children's dietary patterns at 2 years (25)
- Parental separation → Children's hyperactivity-inattention trajectory from 3 to 8 years (26)
- Maternal diet during pregnancy → Children's hyperactivity-inattention trajectory from 3 to 8 years (27)

Supplementary figure 2. Directed acyclic graph illustrating relationships between developmental trajectories of conduct problems and dietary patterns of children at 2 years.



Maternal education → Children's dietary patterns at 2 years (1–6)

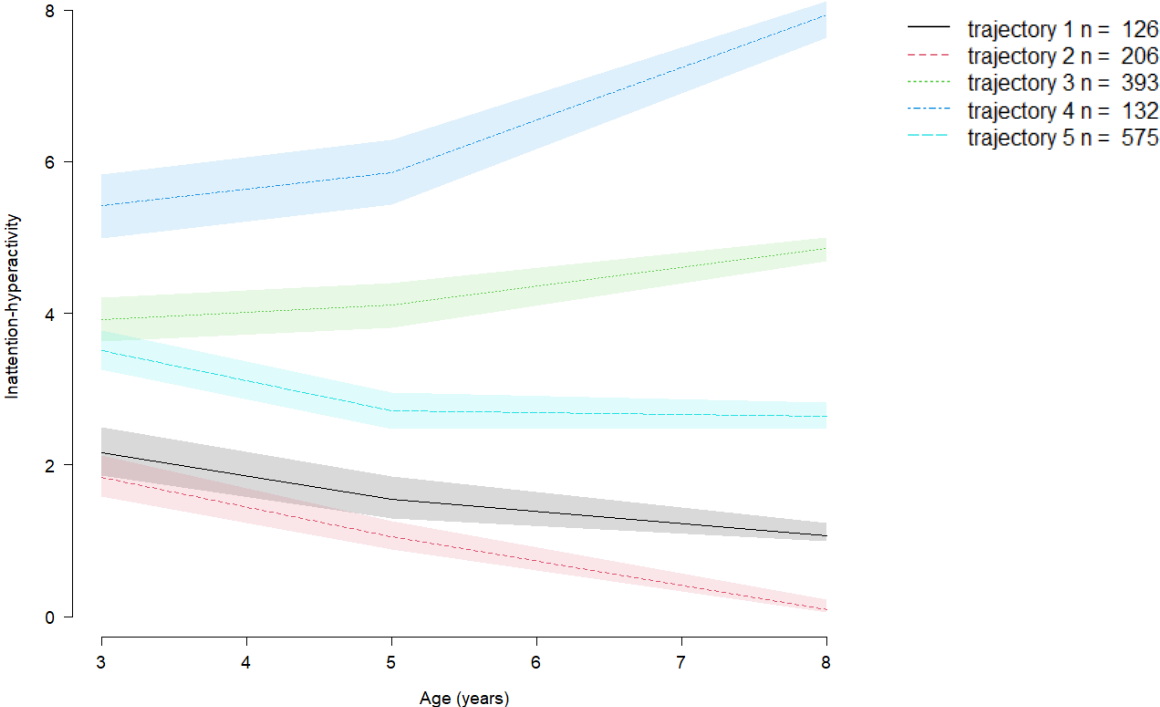
Maternal education → Children's conduct problem trajectories from 3 to 8 years (28)
 Maternal age → Children's dietary patterns at 2 years (9)
 Maternal age → Children's conduct problems trajectories from 3 to 8 years (29)
 Maternal BMI → Children's conduct problems trajectories from 3 to 8 years (30)
 Maternal post-natal dietary habits → Children's dietary patterns at 2 years (12)
 Maternal post-natal dietary habits → Maternal BMI (31)
 Children's sex → Children's dietary patterns at 2 years (13)
 Children's sex → Children's conduct problems trajectories from 3 to 8 years (32,33)
 Breast feeding duration → Children's dietary patterns at 2 years (21)
 Breast feeding duration → Children's conduct problems trajectories from 3 to 8 years (34)
 Family income → Children's dietary patterns at 2 years (23)
 Family income → Children's conduct problems trajectory from 3 to 8 years (28)
 Parental separation → Children's dietary patterns at 2 years (25)
 Parental separation → Children's conduct problems trajectories from 3 to 8 years (35)

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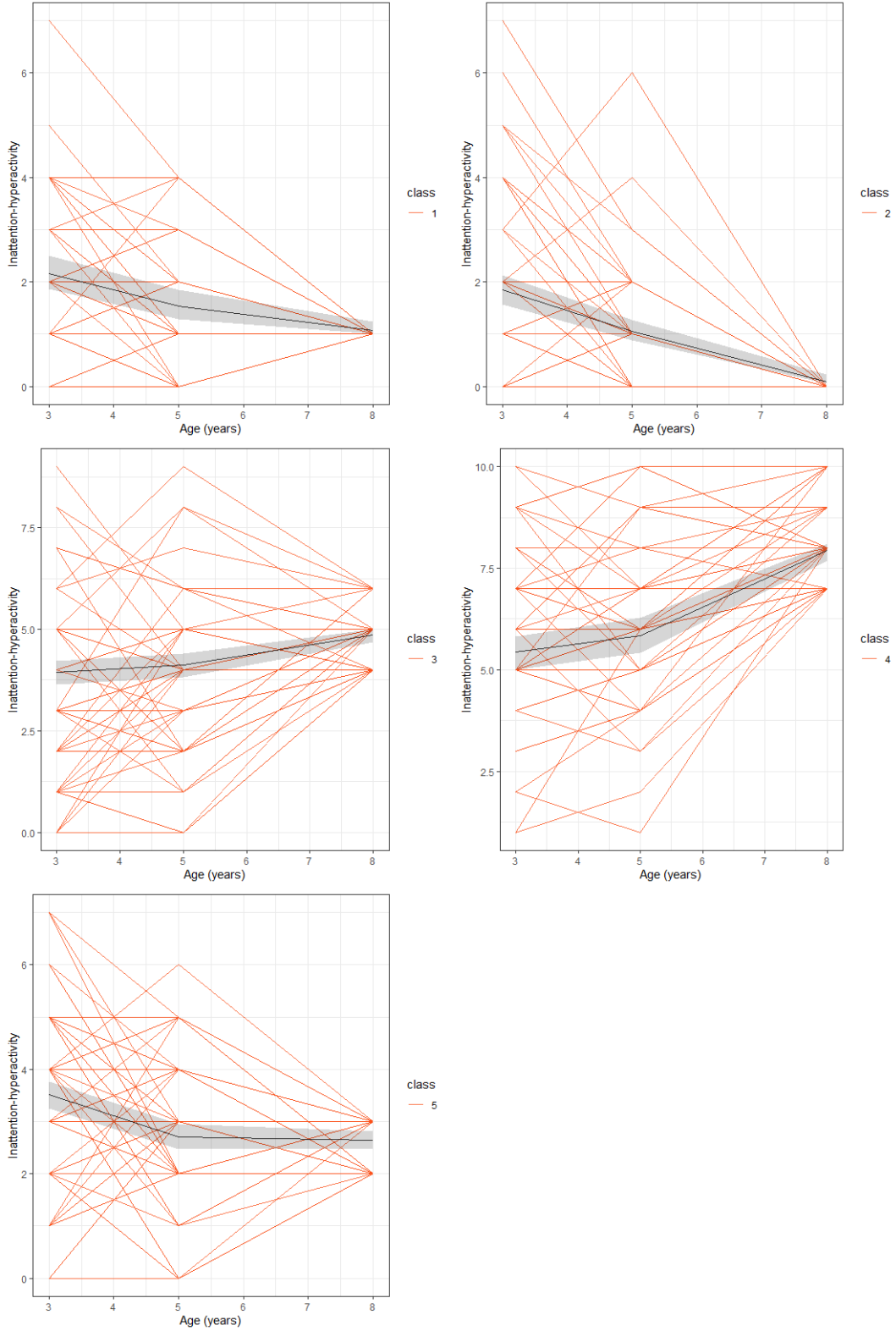
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Supplementary figure 3. Mean developmental trajectories of inattention-hyperactivity in children between 3 and 8 years old. EDEN Cohort, France, 2005-2011.

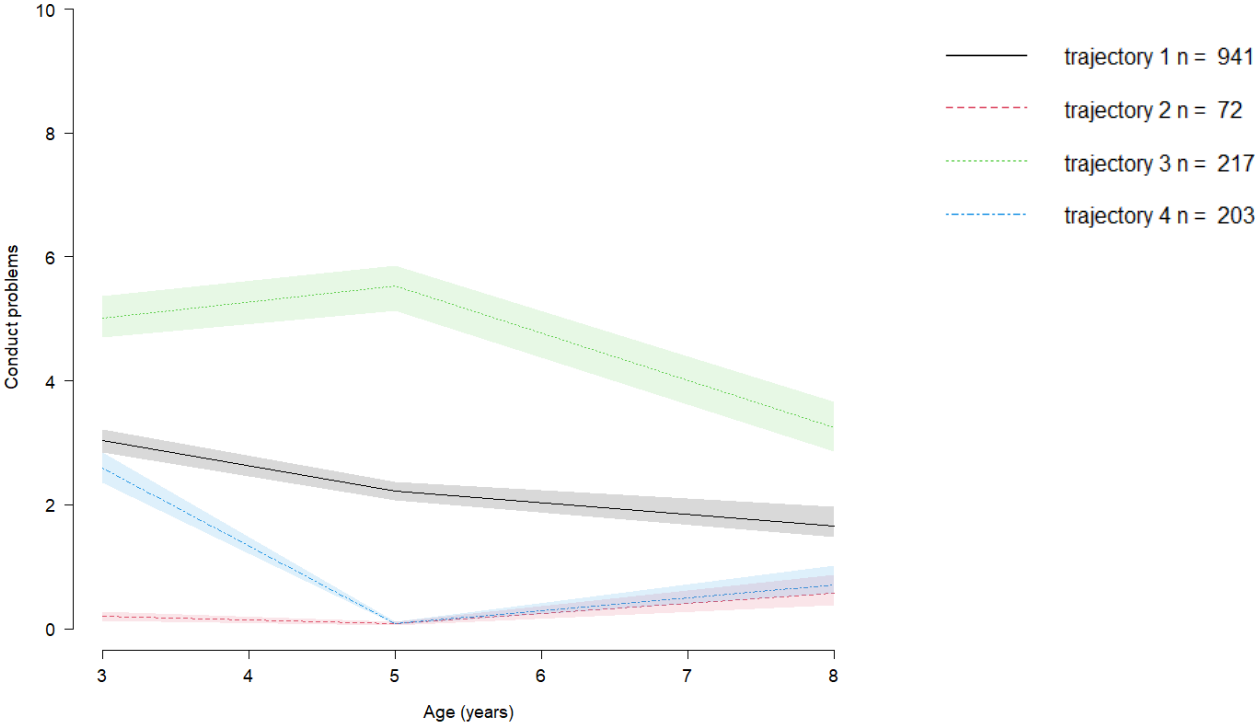


Five trajectories of hyperactivity-inattention symptoms were identified. BIC and AIC were equal to 13773.09 and 13620.35, respectively. The mean posterior probability of belonging to the highest trajectory was 0.87. 75.8 % of individuals in this group had a posterior probability greater than 0.7 and 0.9.

Supplementary figure 4. Individual trajectories within each developmental trajectory class of inattention-hyperactivity. EDEN Cohort, France, 2005-2011.

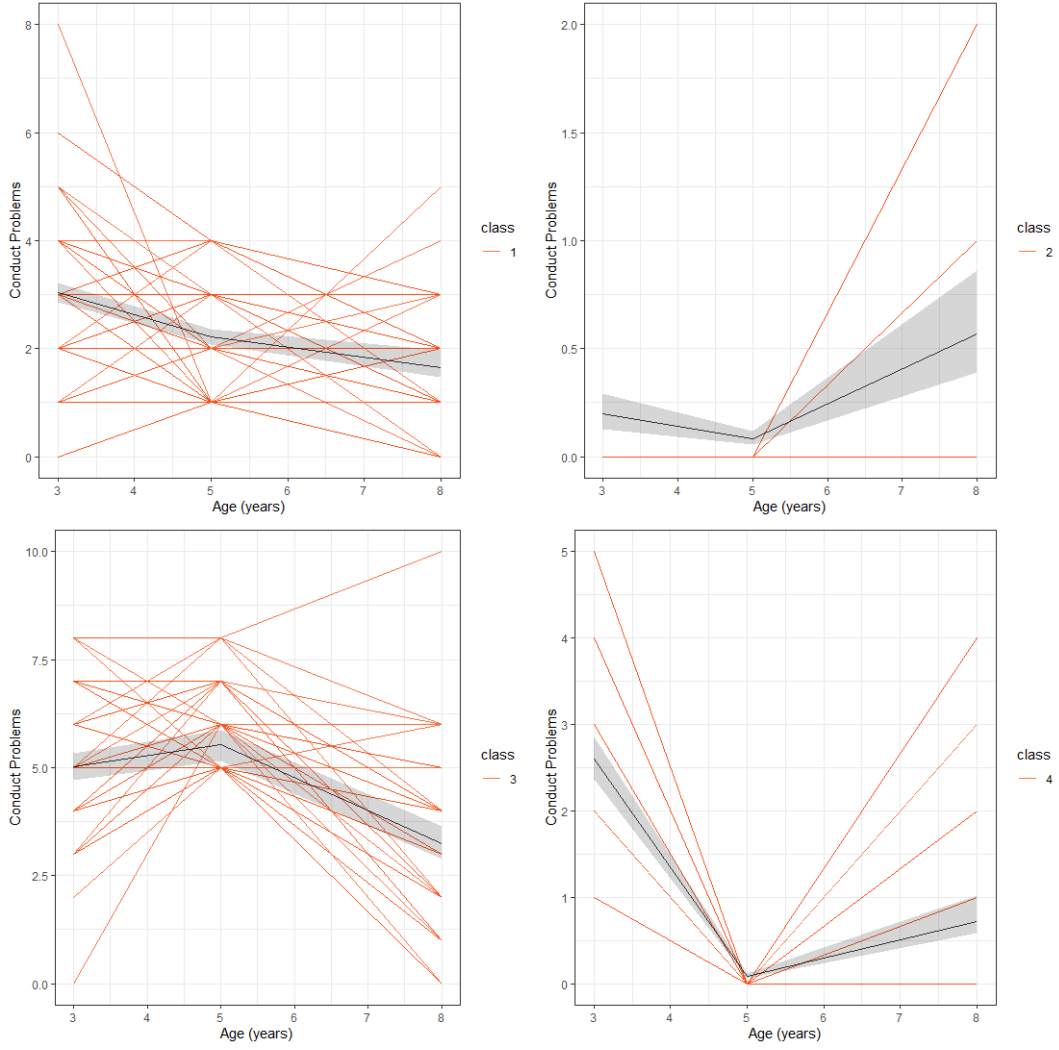


Supplementary figure 5. Mean developmental trajectories of conduct problems in children between 3 and 8 years old. EDEN Cohort, France, 2005-2011



Four conduct problems trajectories were identified. BIC and AIC were equal to 12243.02 and 12111.33, respectively. The mean posterior probability of belonging to the highest trajectory was 0.90. 86.6% and 83.4% of individuals in this group had a posterior probability greater than 0.7 and 0.9, respectively.

Supplementary figure 6. Individual trajectories within each developmental trajectory class of conduct problems. EDEN Cohort, France, 2005-2011.



Supplementary table 1. Characteristics of excluded and included populations. EDEN cohort, France, 2005-2011.

	All	Excluded (n=570)	Included (n=1432)	<i>p</i>
Child characteristics				
Male sex	1000 (52.5)	254 (53.9)	746 (52.1)	0.490
Birth weight (kg)	3.3 ± 0.5	3.2 ± 0.5	3.3 ± 0.5	0.114
Gestational age (weeks)	39.2 ± 1.8	39.1 ± 1.9	39.3 ± 1.7	0.689
Mode of delivery				
spontaneous vaginal delivery	1405 (74.0)	343 (73.0)	1062 (74.3)	0.004
surgical vaginal delivery	195 (10.3)	35 (7.4)	160 (11.2)	
cesarean section	299 (15.7)	92 (19.6)	207 (14.5)	
Any breast-feeding duration				
No	504 (26.6)	138 (30.0)	366 (25.6)	0.041
[0-6] months	1031 (54.5)	251 (54.6)	780 (54.5)	
>6 months	357 (18.9)	71 (15.4)	286 (20.0)	
Children's dietary patterns ¹				
Processed and fast foods	0.0 ± 1.0	0.2 (1.1)	0.0 ± 1.0	0.030
Guidelines	0.0 ± 1.0	-0.2 (1.0)	0.0 ± 1.0	0.003
Baby foods	0.0 ± 1.0	0.0 (1.0)	0.0 ± 1.0	0.780
Parental characteristics				
Maternal age (years) ²	29.0 ± 5.0	27.7 ± 5.3	29.5 ± 4.7	<0.001
Maternal BMI (kg/m ²) ¹				
≤18.5	56 (7.4)	9 (9.8)	47 (7.0)	0.672
18.5–25	478 (62.8)	57 (62.0)	421 (62.9)	
25–30	150 (19.7)	19 (20.7)	131 (19.6)	
≥30	77 (10.1)	7 (7.6)	70 (10.5)	
Maternal education (years)	13.6 ± 2.7	12.6 ± 2.7	13.9 ± 2.6	<0.001
Maternal dietary patterns ²				
Healthy	0.0 ± 1.0	0.0 ± 1.2	0.0 ± 0.9	0.789
Western	0.0 ± 1.0	0.0 ± 1.1	0.0 ± 0.9	0.001
Maternal smoking (cigarettes) ²	1.5 ± 3.4	2.6 ± 4.8	1.1 ± 2.7	<0.001
Maternal alcohol consumption ²	137 (7.1)	29 (5.9)	108 (7.5)	0.220
Maternal depression (CES-D) ²	11.0 ± 7.8	NA	11.0 ± 7.8	NA
Maternal anxiety (STAI) ²	30.0 ± 9.7	NA	30.0 ± 9.7	NA
Maternal cannabis use ¹	47 (3.3)	9 (6.0)	38 (3.0)	0.087
Maternal employment ¹				
no, housewife	111 (7.8)	20 (13.5)	91 (7.2)	0.002
no, maternity leave	66 (4.7)	10 (6.8)	56 (4.4)	
no, parental leave	182 (12.9)	23 (15.5)	159 (12.5)	
no, student	22 (1.6)	3 (2.0)	19 (1.5)	
no, unemployed or looking for a job	71 (5.0)	12 (8.1)	59 (4.7)	
no, other situation (disability, pension)	3 (0.2)	1 (0.7)	2 (0.2)	
yes	961 (67.9)	79 (53.4)	882 (69.6)	
Paternal age (years) ²	33.9 ± 76.2	31.1 ± 6.3	34.8 ± 87.7	0.125
Paternal employment ¹				
no, student	1 (0.1)	0 (0.0)	1 (0.1)	<0.001
no, unemployed or looking for a job	62 (4.4)	17 (12.1)	45 (3.6)	
no, other situation (disability, pension)	17 (1.2)	2 (1.4)	15 (1.2)	
yes	1328 (94.3)	122 (86.5)	1206 (95.2)	
Parental separation ²	122 (6.4)	65 (13.3)	57 (4.0)	<0.001
Family income per month ¹				
<450 euros	1 (0.1)	0 (0.0)	1 (0.1)	
451-800 euros	40 (2.9)	15 (10.3)	25 (2.0)	
801-1500 euros	114 (8.2)	22 (15.1)	92 (7.3)	
1501-2300 euros	345 (24.7)	41 (28.1)	304 (24.3)	
2301-3000 euros	387 (27.7)	31 (21.2)	356 (28.4)	
3000-3800 euros	270 (19.3)	22 (15.1)	248 (19.8)	
3801-4500 euros	131 (9.4)	10 (6.8)	121 (9.7)	
>4500 euros	110 (7.9)	5 (3.4)	105 (8.4)	

¹ data obtained when child was 2 years old; ² data obtained during pregnancy; BMI, body mass index; CES-D, Center for Epidemiologic Studies-Depression Scale; STAI, State-Trait Anxiety Inventory; NA, not available

Supplementary table 2. Association between children's dietary patterns at 2 years old and developmental trajectories of inattention-hyperactivity and conduct problems. Sensitivity analysis on complete data. EDEN cohort, France, 2005-2011.

	Unadjusted model (N=1252)		Adjusted model * (N ₁ =572; N ₂ =641)	
	OR	95% CI	OR	95% CI
Hyperactivity-inattention				
Processed and fast foods	1.07	0.90 - 1.28	1.13	0.82 - 1.56
Guidelines	0.73	0.60 - 0.90	0.49	0.34 - 0.71
Baby foods	1.46	1.20 - 1.76	1.79	1.30 - 2.47
Conduct problems				
Processed and fast foods	1.08	0.93 - 1.25	1.18	0.95 - 1.46
Guidelines	0.98	0.84 - 1.14	0.93	0.74 - 1.17
Baby foods	1.19	1.02 - 1.38	1.43	0.88 - 1.37

OR, odds ratio; CI, confidence interval;

*Common adjustments for inattention-hyperactivity and conduct problems:

Children's sex, maternal education, maternal BMI, parental separation, family income, mother's age at pregnancy, breastfeeding duration. Additional adjustment for inattention-hyperactivity: birth weight, prenatal maternal nutrition;

N₁, number of subjects for hyperactivity-inattention;

N₂, number of subjects for conduct problems.

Supplementary table 3. Association between children's dietary patterns at 2 years old and developmental trajectories of inattention-hyperactivity and conduct problems. Sensitivity analysis with additional confounders and confounders selected according to the augmented backward elimination procedure. EDEN cohort, France, 2005-2011.

	Ajusted model ¹ (N ₁ =444; N ₂ =500)		Adjusted model ² (N ₁ =476; N ₂ =547)	
	OR	95% CI	OR	95% CI
Hyperactivity-inattention				
Processed and fast foods (per SD)	1.37	0.90 - 2.1	1.36	0.92 - 2.00
Guidelines (per SD)	0.42	0.26 - 0.67	0.47	0.31 - 0.71
Baby foods (per SD)	1.63	1.12 - 2.37	1.66	1.17 - 2.35
Conduct problems				
Processed and fast foods (per SD)	1.26	0.96 - 1.65	1.22	0.97 - 1.55
Guidelines (per SD)	1.07	0.81 - 1.41	1.00	0.79 - 1.29
Baby foods (per SD)	1.17	0.90 - 1.51	1.12	0.88 - 1.42

OR, odds ratio; CI, confidence interval; SD, standard deviation

¹Common adjustments with additional confounders for inattention-hyperactivity and conduct problems: Children's sex, maternal education, maternal BMI at 2 years, parental separation, family income, mother's age at pregnancy, any breast feeding duration, gestational age, paternal age, mode of delivery, maternal alcohol consumption during pregnancy, maternal smoking during pregnancy, maternal depression during pregnancy, maternal anxiety during pregnancy, maternal cannabis use at 2 years, maternal employment at 2 years, and paternal employment at 2 years. Additional adjustment for inattention-hyperactivity: birth weight, prenatal maternal nutrition;

²Adjustments selected according to the augmented backward elimination procedure.

Adjustments for hyperactivity-inattention: Maternal dietary patterns during pregnancy, maternal BMI, birth weight, family income, children's sex, gestational age, maternal depression during pregnancy, maternal employment at 2 years, paternal employment at 2 years. Adjustments for conduct problems: maternal BMI at 2 years, family income, children's sex, maternal alcohol consumption during pregnancy, maternal anxiety during pregnancy;

N₁, number of subjects for hyperactivity-inattention;

N₂, number of subjects for conduct problems

How to estimate a latent process mixed model using lcmm function (Proust-Lima) (1,2)

Each dynamic phenomenon can be characterized by a latent process ($\Lambda(t)$) which evolves in continuous time t . When modeling repeated measures of marker, it is usually not conceived as a latent process measured with error. Yet this is the underlying assumption made by the mixed model theory. Function `lcmm` exploits this framework to extend the linear mixed model theory to any type of outcome (ordinal, binary, continuous with any distribution).

The latent process mixed model

The quantity of interest defined as a latent process is modeled according to time using a linear mixed model:

$$\Lambda(t) = X(t)\beta + Z(t)u_i + w_i(t)$$

where:

- $X(t)$ and $Z(t)$ are vectors of covariates ($Z(t)$ is included in $X(t)$);
- β are the fixed effects (i.e., population mean effects);
- u_i are the random effects (i.e., individual effects); they are distributed according to a zero-mean multivariate normal distribution with covariance matrix B ;
- $(w_i(t))$ is a Gaussian process that might be added in the model to relax the intra-subject correlation structure.

The relationship between the latent process of interest and the observations of the marker Y_{ij} (for subject i and occasion j) is simultaneously defined in an equation of observation:

$$Y_{ij} = H(\Lambda(t_{ij}) + \varepsilon_{ij}; \eta)$$

where:

- t_{ij} is the time of measurement for subject i and occasion j ;
- ε_{ij} is an independent zero-mean Gaussian error;
- H is the link function (parameterized by η) that transforms the latent process into the scale and metric of the marker.

Different parametric families are used. When the marker is continuous, H^{-1} is a parametric family of increasing monotonic functions among:

- the linear transformation: this reduces to the linear mixed model (2 parameters)
- the Beta cumulative distribution family rescaled (4 parameters)
- the basis of quadratic I-splines with m knots ($m+2$ parameters)

Steps to determine trajectories of hyperactivity-inattention and conduct problems.

Only time (Children's age) was used to determine latent processes. There were no other covariates involved in the models.

First, we fitted latent process mixed models without and with random effect to test if quadratic and cubic terms of time (Children's age) had a significant fixed effect and random effect. We found that there were significant quadratic effects for fixed and random effects for both outcome trajectories.

Second, we fitted different latent process mixed model with quadratic effect of time in fixed and random effects, and with different numbers of groups (ranging from 2 to 5 groups) and different quadratic I-splines link functions. To select the most appropriate link function, we compared the different models based on the Bayesian information criterion, the Akaike information criterion, the mean posterior probability of belonging to the worst trajectory, the percentage of individuals of the

worst trajectory who had a posterior probability greater than 0.7 and 0.9 of belonging to their trajectory. We selected a model with five trajectories and an I-splines link function with five nodes located at the quantiles of the SDQ hyperactivity-inattention subscale score distribution for the hyperactivity-inattention trajectories, and a model with four trajectories and an I-splines link function with three nodes located at the quantiles of the SDQ conduct problems subscale score distribution for the conduct problems trajectories.

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