Archival Report

Dietary Quality and Dietary Inflammatory Potential During Pregnancy and Offspring Emotional and Behavioral Symptoms in Childhood: An Individual Participant Data Meta-analysis of Four European Cohorts

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ABSTRACT

BACKGROUND: The impact of maternal diet during pregnancy on child neurodevelopment is of public health and clinical relevance. We evaluated the associations of dietary quality based on the Dietary Approaches to Stop Hypertension (DASH) score and dietary inflammatory potential based on the energy-adjusted Dietary Inflammatory Index (E-DII) score during pregnancy with emotional and behavioral symptoms of offspring at 7 to 10 years of age.

METHODS: Individual participant data for 11,870 mother–child pairs from four European cohorts participating in the ALPHABET project were analyzed. Maternal antenatal DASH and E-DII scores were generated from self-completed food frequency questionnaires. Symptoms of depression and anxiety, aggressive behavior, and attention-deficit/hyperactivity disorder in children were assessed using mother-reported tests and classified within the normal or borderline/clinical ranges using validated cutoffs. Adjusted odds ratios were determined by multivariable logistic regression models and aggregated by the two-level individual participant data meta-analysis method.

RESULTS: Higher maternal DASH scores (indicating better dietary quality) were associated with lower risk of depressive and anxiety symptoms, aggressive behavior symptoms, and attention-deficit/hyperactivity disorder symptoms within the borderline/clinical ranges: odds ratio [OR] 0.97, 95% confidence interval [CI], 0.95–0.99; OR 0.97, 95% CI, 0.94–0.99; OR 0.97, 95% CI, 0.95–0.98, per one-unit DASH score increase, respectively. For depression and anxiety, aggressive behavior, and attention-deficit/hyperactivity disorder symptoms, a one-unit increase in E-DII scores (a more proinflammatory diet) was associated with a 7% increased risk of all three analyzed emotional and behavioral symptoms: OR 1.07, 95% CI, 1.03–1.11; OR 1.07, 95% CI, 1.02–1.13; OR 1.07, 95% CI, 1.01–1.13, respectively.

CONCLUSIONS: Our findings suggest that a maternal low-quality and proinflammatory diet may increase the risk of emotional and behavioral symptoms in children.

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According to the developmental origins of health and disease theory, environmental factors during critical periods of development can contribute to long-term consequences in an offspring's health [1]. Neurodevelopment starts in fetal life with numerous processes continuing until adolescence [2]. An unbalanced diet within these periods can compromise brain development and cause neurobehavioral delays [3]. The worldwide prevalence of anxiety disorders, depressive disorders, and attention-deficit/hyperactivity disorder (ADHD) in

children and adolescents has been estimated to be 6.5%, 2.6%, and 3.4%, respectively [4]. These conditions can impact children's well-being, scholastic achievement, and social functioning later in life. Thus, identification of associations linking maternal antenatal diet with child neurodevelopment is of high potential public health and clinical relevance.

Studies have underlined the importance of assessing the health impact of dietary patterns or indices rather than focusing on single nutrients [5,6]. The meta-analysis performed

by Borge *et al.* (7) found that better maternal diet quality was weakly, but consistently, associated with several neurodevelopmental dimensions. Besides dietary quality indicators, another approach of interest has been to examine the potential inflammatory role of diet because some neurodevelopmental abnormalities can be linked to early-life immune activation and inflammation (8–12). A meta-analysis of observational studies focusing on the adult population indicated that avoiding a proinflammatory diet appears to confer some protection against depression (13). Moreover, a meta-analysis of randomized controlled trials revealed that dietary interventions in adults can significantly reduce symptoms of depression and anxiety (14). However, no previous studies have examined the inflammatory potential of maternal diet during pregnancy on an offspring's emotional and behavioral symptoms.

Thus, there is a need to strengthen the evidence on the role of prenatal nutrition in later child emotional and behavioral development. Our current study addresses this gap. Using a harmonized data and analysis approach we conducted an individual participant data meta-analysis of mother–child pairs from four European cohorts to evaluate the associations of maternal dietary quality (based on the Dietary Approaches to Stop Hypertension [DASH] score) and dietary inflammatory potential (based on the energy-adjusted Dietary Inflammatory Index [E-DII] score) during pregnancy with offspring emotional and behavioral symptoms.

METHODS AND MATERIALS

Study Design and Population

Our present assessment includes the population-based birth cohorts participating in the ALPHABET project, which was aimed at investigating early-life nutritional programming of childhood health. We selected cohorts with available data allowing for generation of maternal dietary indices and offspring emotional and behavioral symptoms measures (see Harmonization Concept in the Supplement and Figure S1). Individual participant data from the following European birth cohorts were included in the study: Avon Longitudinal Study of Parents and Children (ALSPAC) in the United Kingdom (15,16), the study on the prenatal and early postnatal determinants of child health and development (EDEN) in France (17), the Generation R Study (Generation R) in the Netherlands (18), and the Polish Mother and Child Cohort (REPRO_PL) (19). The respective ethical review committees granted ethical approvals for the studies (see Ethical Approvals in the Supplement). The data were harmonized across the cohorts, and a total of 11,870 mother–child pairs were included in the analyses (see Harmonization Concept in the Supplement).

Dietary Assessment During Pregnancy

Dietary intakes during pregnancy were assessed using food frequency questionnaires (FFQ) (20–23). Participants completed the FFQs during the second trimester in the Generation R and REPRO_PL studies, the third trimester in the ALSPAC study, and at childbirth in the EDEN study. Data available from FFQ and food items selected for the calculation of dietary indices are presented in Table S1. Women reported their consumption for a list of foods on a frequency scale ranging from 5 to 9 response categories, standardized as frequency of consumption per day for comparability across cohorts. Participants with implausible energy intakes (<500 or >3500 kcal/day) were excluded from the analysis to avoid extreme misreporting (24,25).

A detailed description of the DASH score generation within the ALPHABET consortium has been published elsewhere (26). Briefly, the DASH score consisted of 8 food components (7 food groups and 1 nutrient) with a scoring system based on the quintile rankings (27). For the intake of total grains, vegetables (excluding potatoes and condiments), fruit, non-full-fat dairy products, and nuts/seeds/legumes, the women received a score from 1 (the lowest quintile) to 5 (the highest quintile). In contrast, for the intake of red and processed meat, sugar-sweetened beverages/sweets/added sugars, and sodium, the women received a score from 5 (the lowest quintile) to 1 (the highest quintile). Finally, the component scores were summed up and an overall DASH score for each participant was calculated based on frequencies (ALSPAC, EDEN, REPRO_PL) or amounts (Generation R). The DASH score (created using from 48% to 79% of the total FFQ food items as described in Table S1) ranged from 8 to 40 points, where a higher score indicates a better dietary quality.

Maternal dietary inflammatory potential was determined using the E-DII. A detailed description of the score is available elsewhere (28). Briefly, to calculate the E-DII, a total of 1943 articles were peer reviewed and scored. Scoring for each food parameter was based on its inflammatory potential on 6 inflammatory biomarkers including C-reactive protein, interleukin (IL)-1β, IL-4, IL-6, IL-10, and tumor necrosis factor-α. The dietary information on each participant was first converted to per-1000-kcal values and then linked to the mean and standard deviation of energy-adjusted food consumption datasets from 11 countries around the world. Standardized z scores were calculated by subtracting the global standard average from the amount reported and dividing by its standard deviation. These z scores were converted to centered proportions to minimize the effect of right-skewing. Each obtained value was multiplied by the corresponding food parameter effect score. All the food parameter–specific E-DII scores were summed to obtain the overall E-DII score. The E-DII scores in ALPHABET were generated from 20 to 28 (out of 44 possible) dietary parameters in all cohorts (Table S1). The E-DII scores ranged from −5.4 to 4.9, where a higher score indicates a more proinflammatory diet.

Emotional and Behavioral Symptoms Assessment

Child emotional and behavioral symptoms were assessed using the Strength and Difficulties Questionnaire (SDQ) (ALSPAC, EDEN, REPRO_PL) and the Child Behavior Checklist for ages 6 to 18 (CBCL/6–18) (Generation R) (19,20,22,23).

The SDQ, a widely used tool for the evaluation of child behavior, was completed by the mothers when the children were between 7 and 10 years old, depending on the cohort (29). The SDQ is a 25-item questionnaire that consists of 5 scales. The current analysis was restricted to the emotional problems scale as an indicator of a child's depressive and anxiety symptoms, the conduct problems scale as a measure of a child's aggressive behavior symptoms, and the

hyperactivity/inattention problems scale to evaluate ADHD symptoms. For each of the 5 items within each scale, 3 response categories were possible: "not true," "somewhat true," and "certainly true" (with the scoring of 0, 1, and 2, respectively), resulting in the final scoring for the scale falling in a range from 0 to 10. Summary scores were calculated only if at least 3 of the 5 items have been completed. Higher emotional, conduct, and hyperactivity/inattention scores indicate increased emotional and behavioral symptoms. Validated, scale-specific cutoffs were used to classify children with emotional and behavioral symptoms within the borderline or clinical range (from now on referred to as borderline/clinical range) and within the clinical range only (see Harmonization Concept in the Supplement).

In the Generation R cohort, the mothers completed the CBCL/6–18 when the children were 10 years old (30). The CBCL/6–18 is a widely used rating scale that assesses a broad range of emotional and behavioral syndromes in children. It includes 8 syndrome scales and a set of DSM-IV–oriented scales (31). The anxious/depressed syndrome scale (13 items) and the withdrawn/depressed syndrome scale (8 items) were used as indicators of a child's depressive and anxiety symptoms. The rule-breaking behavior scale (17 items) and the aggressive behavior scale (18 items) were selected to measure child aggressive behavior symptoms and the DSM-IV–oriented attention-deficit/hyperactivity problems scale (7 items) to measure ADHD symptoms. Each item describing specific child behaviors was rated on 3-point scale (0 = "not true"; 1 = "somewhat or sometimes true"; 2 = "very true or often true"). Up to 25% of items with missing values were allowed; in such cases, the weighted score was calculated. Higher scores indicate more symptoms. The 93rd and 98th percentiles, which have been validated and standardized, were used as cutoff scores to classify the children with symptoms within the borderline/clinical range and within the clinical range only, respectively (see Harmonization Concept in the Supplement) (30).

Covariates

Covariates were defined a priori based on the literature and considering the availability of data across the cohorts (see Harmonization Concept in the Supplement). The following variables were included: parental birthplace/ethnic background (European, non-European), parental age (in years), educational level and household income (low, medium, or high based on the cohort-specific classifications), household status during pregnancy (single, parents living together), tobacco smoking and alcohol consumption during pregnancy (yes, no), maternal passive smoking status (yes, no based on paternal smoking during pregnancy), parity (nulliparous, multiparous), maternal height (cm), and prepregnancy body mass index (kg/m^2). Information about gestational diabetes, hypertension, and preeclampsia (yes, no) were abstracted from medical records. Data regarding maternal depression or psychological distress during pregnancy (yes, no) were available for ALSPAC (based on the question "Have you had severe depression?" [yes, no]), EDEN (based on the Center for Epidemiologic Studies Depression scale, with a score ≥23 considered as yes), and Generation R (based on the Brief Symptom Inventory, with a score >0.71 on the overall distress scale considered as yes)

(15,16,23,32). Models focused on the DASH score were additionally adjusted for energy intake during pregnancy (in kcal/day). Child characteristics included sex and age (in months). In addition, based on dietary data collected from the children, E-DII was calculated (ALSPAC, Generation R, REPRO_PL) (33).

Statistical Analysis

Multiple imputation of missing data using chained equations was performed per cohort, where 20 completed datasets were generated by fully conditional specification with the predictive mean matching method and were analyzed using standard combination rules for multiple imputation (Tables S2 and S3) (34,35).

Generalized additive models with spline smoothers were used to assess the linearity of the potential relationships between maternal dietary scores and child emotional and behavioral symptoms scores. Linear and smooth functions provided similar fit quality, and linear relationships were assumed for the subsequent analyses.

For the main analyses a 2-level approach was implemented: as the first level, the associations based on individual participant data were analyzed separately within each cohort; then, as the second level, the cohort-specific estimates were combined, weighting by the inverse variance of each effect size using a random-effects meta-analysis. The heterogeneity in the estimates was assessed using the Cochran Q test and I^2 statistic (36,37). To estimate the associations between DASH and E-DII scores and emotional and behavioral symptoms, logistic regression models were used. In the main analyses emotional and behavioral symptom scores were dichotomized in normal versus borderline/clinical ranges. Initially, the effect estimates were obtained from the models minimally adjusted for child sex, child age, and maternal energy intake. In the next step, fully adjusted regression models were fitted with additional inclusion of the covariates. The generalized variance inflation factors were computed for each model to exclude the possibility of excessive multicollinearity among explanatory variables.

The following sensitivity analyses were run (based on the fully adjusted model): 1) leaving out one cohort at a time to determine the influence of any particular population; 2) restricting child emotional and behavioral symptoms scores to the clinical range to reduce the possibility of outcome misclassification; 3) limiting the population to mothers with a European birthplace/ethnic background because the FFQ had been mainly developed for a European population; 4) adjusting for pregnancy complications to eliminate these conditions as a source of association; 5) adjusting for maternal depression/psychological distress during pregnancy as a potential confounder; 6) stratifying the analyses according to early- and late-pregnancy dietary assessments to explore the potential effect of the timing of exposure; 7) performing mutual adjustment of the DASH and E-DII scores to obtain the net effect of each dietary measure; and 8) adjusting for child E-DII to assess whether any association could be explained by the child's dietary inflammation. To investigate whether a child's sex was a potential modifier for the associations of DASH and E-DII with emotional and behavioral symptoms, an interaction term was

included in the models. Sex-stratified analyses were considered if *p*-interaction ≤ .10.

Additionally, 2-level logistic regression models were run on pooled data (with the cohort treated as a random effect). The exposures were considered as 1) continuous variables and 2) variables categorized as DASH score <10th percentile versus DASH ≥10th, and E-DII score >90th percentile versus E-DII ≤90th percentile. Finally, if consistent associations were observed, the population attributable risk fraction was calculated, based on the adjusted odds ratio and the prevalence of a low DASH score and high E-DII score in the population. The facilities of base *R* system for statistical computing were used for regression modeling, and the *mice* package was applied for the multiple imputation analysis (34,38).

RESULTS

Characteristics of the Population

The basic information for each cohort is presented in Table 1. Of these, ALSPAC was the largest cohort with the earliest period of recruitment, and REPRO_PL was the smallest study, conducted slightly later than the other three studies. Overall, 13% of the children were classified within borderline/clinical range for depressive and anxiety symptoms and ADHD symptoms and 15% for aggressive behavior symptoms (Table 1 and Table S4). About 6% of the children were classified as within the clinical range for each of the analyzed behavioral symptom scores. The DASH score distributions were similar between the cohorts (Table 1). The mean E-DII score ranged from −1.2 ± 1.5 for REPRO_PL to 0.7 ± 1.6 for

EDEN. There were notable differences in the participants' characteristics across the cohorts (Table S2).

Maternal Diet Quality and Child Emotional and Behavioral Symptoms

The mean DASH scores during pregnancy were lower among the children classified within borderline/clinical ranges as compared to normal ranges of all emotional and behavioral symptoms scores (*p* < .001) (Table 2).

In the minimally adjusted models, higher maternal dietary quality was associated with lower risk of offspring emotional and behavioral symptoms (Figure S2). The fully adjusted logistic regression analyses were consistent with the minimally adjusted models. Higher maternal DASH scores were associated with lower risk of offspring depressive and anxiety symptoms, aggressive behavior symptoms, and ADHD symptoms within the borderline/clinical ranges: OR 0.97, 95% CI, 0.95–0.99; OR 0.97, 95% CI, 0.94–0.99; and OR 0.97, 95% CI, 0.95–0.98 per one-unit DASH score increase, respectively (Figure 1). There were, at most, moderate degrees of statistical heterogeneity between the cohorts except for the association between DASH score and aggressive behavior symptoms (I^2 = 61%; *p* = .05).

Inflammatory Potential of the Maternal Diet and Child Emotional and Behavioral Symptoms

The mean E-DII scores during pregnancy were higher among the children classified within the borderline/clinical range as compared with the normal range for all emotional and behavioral symptoms scores (*p* < .001) (Table 2). In the model

Table 1. Description of the Cohorts, Exposures, and Outcome Variables in the ALPHABET Consortium

Cohort	ALSPAC	EDEN	Generation R	REPRO_PL
Country (Cities)	England (Bristol)	France (Nancy and Poitiers)	The Netherlands (Rotterdam)	Poland (Multicenter)
Period of Recruitment	1990–1992	2003–2006	2002–2006	2007–2011
Number of Mother–Child Pairs With Information on Exposure and Outcome	7177	806	3571	316
FFQ Window Period	LP	LP	EP	EP
DASH Score, Mean ± SD	24.3 ± 4.0	24.3 ± 4.1	24.6 ± 4.4	24.0 ± 4.3
E-DII Score, Mean ± SD	0.4 ± 1.8	0.7 ± 1.6	−0.5 ± 1.1	−1.2 ± 1.5
Test Used for Emotional and Behavioral Problems Assessment	SDQ	SDQ	CBCL/6–18	SDQ
Age at Emotional and Behavioral Problems Assessment,Years, Mean ± SD	9.6 ± 0.1	8.0 ± 0.1	9.7 ± 0.3	7.5 ± 0.6
Depressive and Anxiety Symptoms, *n* (%)				
Borderline/clinical range	939 (13.2)	217 (26.9)	251 (7.0)	71 (22.5)
Clinical range	503 (7.1)	132 (16.4)	87 (2.4)	37 (11.7)
Aggressive Behavior Symptoms, *n* (%)				
Borderline/clinical range	1226 (17.2)	209 (25.9)	272 (7.6)	88 (27.8)
Clinical range	519 (7.3)	103 (12.8)	82 (2.3)	29 (9.2)
ADHD Symptoms, *n* (%)				
Borderline/clinical range	926 (13.0)	140 (17.4)	359 (10.1)	78 (24.7)
Clinical range	557 (7.8)	93 (11.5)	102 (2.9)	52 (16.5)

ADHD, attention-deficit/hyperactivity disorder; CBCL/6–18, Child Behavior Checklist for ages 6 to 18; DASH, Dietary Approaches to Stop Hypertension; E-DII, energy-adjusted Dietary Inflammatory Index; EP, early pregnancy; FFQ, food frequency questionnaire; LP, late pregnancy; SDQ, Strength and Difficulties Questionnaire.

Table 2. Comparison of the Mean Maternal DASH and E-DII Scores in Normal and Borderline/Clinical Ranges of Emotional and Behavioral Symptoms in the ALPHABET Consortium

Exposure/ Outcome	No. of Subjects	Depressive and Anxiety Symptoms			Aggressive Behavior Symptoms			ADHD Symptoms		
		Normal Range	Borderline/ Clinical Range	p^a	Normal Range	Borderline/ Clinical Range	p^a	Normal Range	Borderline/ Clinical Range	p^a
ALSPAC, n	7177	6190	939		5915	1226		6219	926	
DASH score		24.3 ± 4.0	23.9 ± 4.0	.004	24.4 ± 4.0	23.8 ± 4.0	<.001	24.4 ± 4.0	23.7 ± 3.9	<.001
E-DII score		0.4 ± 1.8	0.5 ± 1.8	.002	0.3 ± 1.8	0.6 ± 1.8	<.001	0.3 ± 1.8	0.6 ± 1.8	<.001
EDEN, n	806	589	217		597	209		666	140	
DASH score		24.5 ± 4.1	23.9 ± 3.8	.05	24.5 ± 3.9	23.8 ± 4.3	.04	24.5 ± 3.9	23.5 ± 4.4	.01
E-DII score		0.7 ± 1.6	1.0 ± 1.6	.02	0.7 ± 1.6	0.9 ± 1.7	.08	0.6 ± 1.6	1.1 ± 1.6	.001
Generation R, n	3571	3315	251		3294	272		3203	359	
DASH score		24.7 ± 4.4	23.8 ± 4.6	.003	24.7 ± 4.4	23.6 ± 4.5	<.001	24.7 ± 4.4	23.5 ± 4.5	<.001
E-DII score		−0.5 ± 1.1	−0.3 ± 1.2	.03	−0.5 ± 1.1	−0.3 ± 1.2	.005	−0.5 ± 1.1	−0.3 ± 1.1	.01
REPRO_PL, n	316	245	71		228	88		238	78	
DASH score		24.0 ± 4.2	24.2 ± 4.6	.72	24.3 ± 4.3	23.4 ± 4.5	.10	24.1 ± 4.2	23.8 ± 4.7	.65
E-DII score		−1.2 ± 1.5	−1.2 ± 1.4	.93	−1.2 ± 1.6	−1.0 ± 1.3	.20	−1.1 ± 1.5	−1.3 ± 1.5	.55
ALPHABET Overall, n	11,870	10,339	1478		10,034	1795		10,326	1503	
DASH score		24.4 ± 4.1	23.9 ± 4.1	<.001	24.5 ± 4.1	23.8 ± 4.1	<.001	24.5 ± 4.1	23.6 ± 4.2	<.001
E-DII score		0.1 ± 1.7	0.4 ± 1.7	<.001	0.1 ± 1.6	0.4 ± 1.7	<.001	0.1 ± 1.7	0.4 ± 1.7	<.001

Values are presented as mean ± SD unless otherwise indicated.

ADHD, attention-deficit/hyperactivity disorder; DASH, Dietary Approaches to Stop Hypertension; E-DII, energy-adjusted Dietary Inflammatory Index.

[a]The p values for statistical significance of the difference between normal and borderline/clinical outcomes are obtained from t test for two samples with unequal variances (single cohorts) or two-way analysis of variance (all cohorts).

adjusted for the child's sex and age at assessment, a more proinflammatory maternal diet was associated with a higher risk of all analyzed outcomes (Figure S2). In the fully adjusted model, for depression and anxiety, aggressive behavior, and ADHD symptoms a one-unit increase in E-DII scores during pregnancy was associated with a 7% increased risk of all three analyzed emotional and behavioral symptoms in the offspring: OR 1.07, 95% CI, 1.03–1.11; OR 1.07, 95% CI, 1.02–1.13; OR 1.07, 95% CI, 1.01–1.13, respectively (Figure 1). There were, at most, moderate degrees of statistical heterogeneity between the cohorts.

Sensitivity Analyses

The main results did not change meaningfully when the cohorts were excluded one by one, when the analyses were restricted to the outcomes within the clinical range, when the analysis was restricted to mothers with a European birthplace/ethnic background, or with additional adjustment for pregnancy complications and maternal depression/psychological distress (Table S5; Figures S3–S6). The analyses stratified by pregnancy period for dietary assessments indicated comparable results, although the associations of both dietary scores assessed in early pregnancy with depressive and anxiety symptoms and ADHD symptoms became not statistically significant (Table S6).

When the DASH and E-DII scores were mutually adjusted, the associations remained similar, except for the association between E-DII and ADHD symptoms, for which the effect estimates became attenuated (Figure S7). A subsequent analysis with additional adjustment for child E-DII indicated similar

directions of the associations to those observed in the main models. However, only the association with child depressive and anxiety symptoms remained statistically significant (Table S7). There was no interaction for child's sex between the DASH and E-DII scores and child emotional and behavioral symptoms (p-interaction > .1).

The fully adjusted logistic regression model based on pooled data indicated similar associations between DASH and E-DII scores (considered as continuous variables) and child emotional and behavioral symptoms to that obtained from the individual participant data meta-analysis (Table S8). When the exposures were dichotomized, we observed no consistent associations of high E-DII score with any of analyzed outcomes; however, a low DASH score (<10th percentile) was associated with a higher risk of depressive and anxiety symptoms (OR 1.26, 95% CI, 1.03–1.53) and aggressive behavior symptoms (OR 1.28, 95% CI, 1.07–1.53) compared with a ≥10th percentile DASH score. The estimated population-attributable risk fractions of those outcomes attributed to a low DASH score were 1.9% and 2.1%, respectively.

DISCUSSION

In this study, using harmonized individual participant data from 4 European countries, we observed that a higher maternal dietary quality during pregnancy was associated with a lower risk of offspring emotional and behavioral symptoms, whereas a more proinflammatory diet was associated with a higher risk of symptoms. These results were consistent across cohorts and robust to a range of sensitivity analyses.
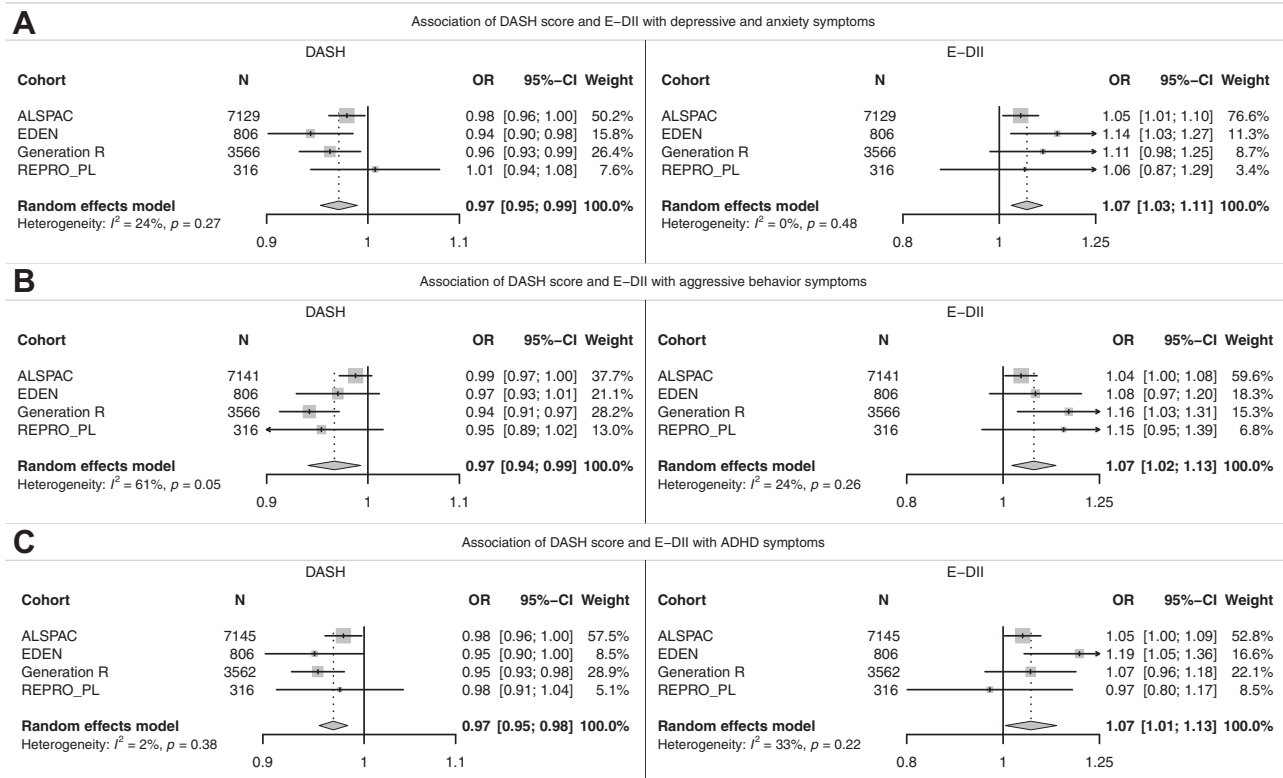
Figure 1. Fully adjusted associations between Dietary Approaches to Stop Hypertension (DASH) score and energy-adjusted Dietary Inflammatory Index (E-DII) score during pregnancy and **(A)** depressive and anxiety symptoms, **(B)** aggressive behavior symptoms, and **(C)** attention-deficit/hyperactivity disorder (ADHD) symptoms scores within the borderline/clinical range in the ALPHABET consortium. Cohort-specific odds ratio (OR) and 95% confidence interval (CI) were estimated by multivariable logistic regression models, and overall OR and 95% CI were estimated by random-effects meta-analysis by cohort. Estimates of OR calculated per 1-unit increments of DASH score and E-DII score, respectively. Gray squares around cohort-specific OR represent the relative weight that the estimate contributes to the overall estimates. Models were adjusted for parental birthplace/ethnic background, parental age, parental education, income, household status during pregnancy, parity, maternal prepregnancy body mass index, maternal height, prenatal active and passive smoking, alcohol consumption, child's sex, and child's age at assessment. Models for DASH were additionally adjusted for total energy intake (kcal/day). I^2, percentage of the total variability attributable to between-cohort heterogeneity; p, p value of heterogeneity using the Cochran's Q test.

Our results are in agreement with existing research (7,20,22,23,39). In previously published studies, including for 3 European cohorts involved in this investigation, an unhealthy maternal diet during pregnancy was related to an increased risk of child hyperactivity–inattention (23), externalizing problems (20), and emotional–behavioral dysregulation (22). Moreover, a meta-analysis presented an association between an unhealthy maternal diet and an increased risk of socioemotional and externalizing problems (7). Publication bias and significant heterogeneity between studies were identified by the investigators (7). In our own investigation the use of harmonized individual participant data and a more precise definition of maternal diet and outcome measures overcame most the aforementioned limitations. In addition, our current study, according to our knowledge, is the first to evaluate the association between maternal DASH and E-DII scores and child emotional and behavioral symptoms. When the DASH and E-DII scores were mutually adjusted, the results were comparable to those from the separate models except for the association between E-DII and ADHD symptoms, for which the effect estimates became attenuated. This might indicate that

the effect of a proinflammatory diet on ADHD symptoms may be partly explained by overall dietary quality. Moreover, in the majority of previous studies the child's diet was not considered (7). In our study, after including the child's diet in the models, the observed associations did not change meaningfully.

The effect sizes observed in our study were rather small, similar to that noted by Borge et al. (7). However, given 100% exposure of diet in the population, such small effects translate into an important impact at the population level. Supporting this are data from the Global Burden of Disease Study, which demonstrated that increased consumption of unhealthy foods globally over the past 2 decades and poor dietary quality were associated with an increased risk of noncommunicable diseases (40–42). Collectively, these data highlight the need to improve dietary quality through policy and the wider food environment to reduce the health burden of suboptimal diet.

Both macronutrient and micronutrient overintake or underintake during pregnancy can alter an offspring's neurodevelopment (43–46,8–12). The effect of specific nutrients on the following neurodevelopmental processes has been described: neuron proliferation, axon and dendrite growth,

synapse formation, pruning and function, myelination, and neuronal apoptosis (8–12). Thus, the putative mechanism includes a direct impact of nutrition on the developing brain, fetal programming, oxidative stress, and influences on the microbiota and immune system (23,44). Studies addressing the association of maternal inflammatory biomarkers with child neurodevelopment are still not fully conclusive (47). Most of them have shown that higher maternal immunoglobulin antibodies (IL-4, IL-5, IL-6, IL-8), C-reactive protein, proinflammatory and anti-inflammatory cytokines, and/or tumor necrosis factor-α during pregnancy are associated with an offspring's neurodevelopmental delay, internalizing and externalizing problems, and autism spectrum disorder (48–51). However, there are also studies showing no association or protective effects (52–54). Girchenko et al. (55) found that higher levels of maternal inflammation (measured as maternal plasma high-sensitivity C-reactive protein and glycoprotein acetyls), when persisting throughout pregnancy, increased the risk of neurodevelopmental delay in the offspring and mediated the effect of prenatal environmental adversity on child neurodevelopment. Taken collectively with our findings, they suggest that maternal antenatal inflammation may provide a target for dietary interventions. It would be worthwhile to examine dietary quality (especially dietary pro/anti-inflammatory potential) associations with offspring risk of neurodevelopmental adversity specifically in mothers with increased inflammation during pregnancy (obesity, gestational diabetes, preeclampsia, or other diseases inducing an increased proinflammatory state).

Maternal depression, psychopathology, or psychological distress are well-known risk factors for offspring internalizing and externalizing problems (56–59). Our analysis with adjustment for maternal depression/psychological distress confirmed that maternal low-quality and proinflammatory diets are independent risk factors for offspring emotional and behavioral symptoms. Similar conclusions have been drawn in other studies (20,22,23,60).

An important issue raised here is whether the observed associations were based on direct effects of maternal diet quality or whether they are markers for the child's diet (7). According to our assumption, maternal diet quality and child diet can have a common cause, so an unbiased estimate of the direct effects of maternal diet on child development requires controlling for the child's diet (7). Our sensitivity analysis with additional adjustment for child E-DII indicated that estimates vary little from the results of the previous models.

One of the main strengths of our study is the use of a large sample size with harmonized data from four cohorts in different countries to provide some geographical representation of different dietary profiles and sociodemographic characteristics across Europe. This study is the first multicenter collaborative effort to evaluate the influence of maternal dietary quality and inflammatory potential on child emotional and behavioral symptoms. Both maternal dietary indices were calculated based FFQ. Moreover, child emotional and behavioral symptoms were assessed at a comparable age based on two widely used standardized and validated questionnaires (29,61). The use of advanced statistical methods including multiple imputation is a further strength of the study. Finally, we were able to adjust for a comprehensive range of covariates.

The limitations of the study should be also considered. The obtained results can largely be generalized to the European population. Some limitations related to the exposure assessment are discussed elsewhere (26). Briefly, all attempts to harmonize data across studies can lead to a loss of information, which may be compensated for by a larger sample size. One can argue that clinical diagnostic data might give a more accurate classification of the symptoms, but such data are often not available. Moreover, quantitatively assessed data allow examination of the symptoms in the whole spectrum, which still might have an impact on an individual's health and can result in long-term consequences (62). Although the models were adjusted for numerous variables, the possibility of residual or unmeasured confounding cannot be excluded. Salient aspects of maternal psychopathology, the home environment, or other factors that may have an impact on both the maternal diet and the offspring's neurodevelopment may not have been captured. Moreover, exposure, outcomes, and covariates were based on maternal self-report, which can create recall and reporting bias. It also needs to be pointed out that there are some differences between the cohorts related to the sample size and time period for recruitment as well as slight differences in child age and different tools for assessing mental health. These limitations were overcome by repeating the analyses after eliminating individual cohorts. Finally, causality cannot be inferred from a single set of observational studies. Additional data are needed from other longitudinal cohorts and, despite obvious methodological and practical impediments, from randomized controlled trials.

In conclusion, the results of this individual participant data meta-analysis indicate that a higher dietary quality during pregnancy is associated with a lower risk of offspring emotional and behavioral symptoms, and a more proinflammatory diet is associated with a higher risk of symptoms. Although replication in other studies is needed, our results represent a significant contribution to the evidence base regarding the importance of maternal diet during pregnancy on offspring neurodevelopment.

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