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Original Contribution

Estimating the Strength of Associations Between Prenatal Diet Quality and Child Developmental Outcomes: Results From a Large Prospective Pregnancy Cohort Study

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Our aim in this study was to estimate the strength of associations between prenatal diet quality and child behavioral, language, and motor functions in the Norwegian Mother and Child Cohort Study (1999–2008). We created a prenatal diet quality index (PDQI) based on adherence to Norwegian dietary guidelines. Child outcomes were defined as sum scores on the Child Behavior Checklist, the Ages and Stages Questionnaire, and the Child Development Index at ages 18, 36, and 60 months. Using a longitudinal cohort study design and Bayesian hierarchical modeling, we estimated association strengths using inverse probability weighting to account for selection bias. In total, 27,529 mother-child pairs were eligible for inclusion. A 1–standard-deviation increase in PDQI score was associated with an absolute reduction in outcome sum scores of 0.02–0.21 and a 3%–7% relative decrease, with larger decreases seen for language and motor functions than for behavioral functions. PDQI scores were inversely associated with all child functions, but the estimated strength of each association was low. The results indicate that the observed variations in PDQI scores in an industrialized Western society may not profoundly influence the child functions studied.

Bayesian modeling; child behavior; child neurodevelopment; Norwegian Mother and Child Cohort Study (MoBa); nutritional epidemiology; prenatal diet quality

Abbreviations: ADHD, attention-deficit/hyperactivity disorder; AME, average marginal effect; ASQ, Ages and Stages Questionnaire; CBCL, Child Behavior Checklist; FFQ, food frequency questionnaire; HDI, high-density interval; MoBa, Norwegian Mother and Child Cohort Study; PDQI, prenatal diet quality index; SD, standard deviation.

Neurodevelopmental disorders are prevalent among children in Norway and worldwide (1, 2). Longitudinal studies show that symptoms and difficulties related to neurodevelopmental disorders, including behavioral, language, and motor impairments, have large negative implications for the subject, the immediate family, and others in a daily social context (3). Additionally, symptoms of nontypical or delayed neurodevelopment during childhood are, in many cases, a stable marker for difficulties in adolescence and adulthood—for instance, behavioral problems (4), language impairment (5, 6), and poorer social functioning (2). Advances have been made towards understanding the developmental origin of neurodevelopmental disorders and related difficulties, but the mechanisms behind the etiology remain largely unknown (7). There is consensus that the origins of these disorders are multifactorial and complex and that there is a substantial genetic contribution (8–10). Genetic vulnerability is not preventable, but there is potential to modify environmental factors. In fact, identification of environmental risk-related and protective components, like dietary factors, has been suggested as a key strategy for long-term prevention of neurodevelopmental disorders and related difficulties in children (11, 12).

Diet is a major contributor to both short- and long-term physical and mental health and well-being (13–15), and it plays a crucial role in brain development (16). This highlights the need for optimal nutrition, particularly during critical periods of development like the fetal period and the first years of life (8). Severe and prolonged prenatal macronutrient malnourishment

(17, 18) and micronutrient deficiency (19) can have detrimental neurodevelopmental effects on the child (20–22). In a recent meta-analysis, Borge et al. (23) summarized the still-scarce research on more subtle differences in prenatal diet quality and also reported an association with child neurodevelopmental outcomes. However, much of this research is based on small samples, heterogeneous exposure definitions, and outcome measurements and insufficient correction for selection bias (23). Hence, there is a need for further investigations of this relationship with large data sets and correction for selection bias.

In the present study, we estimated the strength of associations between prenatal diet quality and child development relating to language, motor, and behavioral difficulties at 18, 36, and 60 months of age in a large prospective pregnancy cohort study in Norway.

METHODS

We followed the Strengthening the Reporting of Observational Studies in Epidemiology (STROBE) statement (24) as a reporting guideline.

Study population and design

The Norwegian Mother and Child Cohort Study (MoBa) is an ongoing prospective population-based pregnancy cohort study being conducted by the Norwegian Institute of Public Health, aiming to investigate how genetic and environmental factors affect health outcomes (25). MoBa investigators recruited pregnant women across Norway during 1999–2008, and 41% of the invited women consented to participate. The cohort includes 114,500 children, 95,200 mothers, and 75,200 fathers. Participating mothers received questionnaires during pregnancy (at gestational weeks 15, 22, and 30) and after delivery (at child age 6 months, 18 months, and 3, 5, 7, and 8 years). The response rates for the 3 prenatal questionnaires were between 91% and 95%, followed by decreasing participation across time. At 36 months, the response rate was 59% (25). The current study is based on version 9 of the quality-assured MoBa data files released for research on November 16, 2016 (26). Figure 1 outlines the process of participant selection.

Exposure definition

The MoBa food frequency questionnaire (FFQ) was introduced in 2002 and provides detailed information about prenatal dietary habits and intake of foods, beverages, and dietary supplements during the first half of pregnancy (27). The MoBa FFQ has been carefully validated using biomarkers in urine and blood samples, in addition to a 4-day weighed food diary (28–31). We calculated intake in grams per day for 255 foods and beverages, assuming standard portion sizes, and calculated energy and nutrient intakes using FoodCalc (32) and the Norwegian food composition database (33).

We created a prenatal diet quality index (PDQI) based on the well-known Healthy Eating Index developed by the US Department of Agriculture's Center for Nutrition Policy and Promotion (34). Because such indices are founded on empirical consensus (35) and thus are similar in all Western industrialized countries (36–39), they are useful for assessing the impact of diet on health outcomes (40–42).

Diet score calculation

We calculated the PDQI score using the method put forward by von Ruesten et al. (40) and modified it to correspond to the updated Norwegian food-based dietary guidelines (43). The PDQI consists of 13 components, with a maximum score of 10 per component (with the exception of total fish and fatty fish), for a maximum PDQI score of 120. See Table 1 for a summary of the components and corresponding scores.

We used different formulae to calculate scores depending on the intake recommendation for each included food group/nutrient:

1. For food groups with a minimum intake recommendation (fruit/berries, vegetables, whole-grain foods, dairy foods): $\text{PDQI score} = \left(\frac{\text{Reported intake}}{\text{Recommended intake}}\right) \times 10$. For intakes above the recommended minimum intake, we allocated a maximum score of 10.
2. For food groups and nutrients with a maximum intake recommendation (red meat, saturated fat, *trans*- fat, added sugar, salt): $\text{PDQI score} = \left(\frac{\text{Recommended intake}}{\text{Reported intake}}\right) \times 10$. For intakes below the recommended maximum intake, we allocated a maximum score of 10.

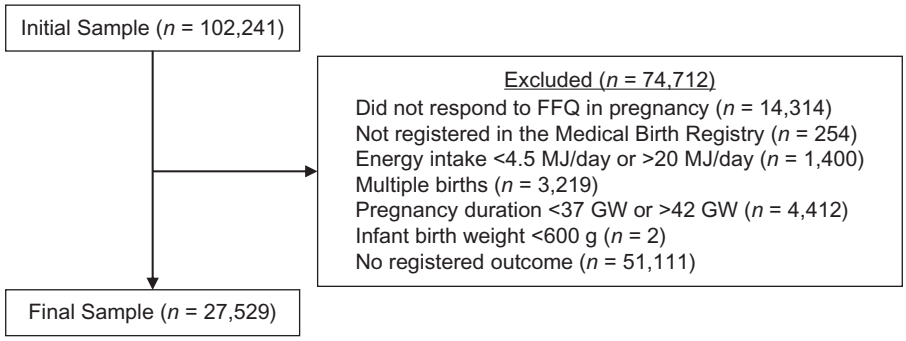

Figure 1. Inclusion and exclusion criteria for selection of mother-child dyads in an analysis of associations between prenatal diet quality and child development, Norwegian Mother and Child Cohort Study, 1999–2008. FFQ, food frequency questionnaire; GW, gestational weeks.

Table 1. Components of a Prenatal Diet Quality Index[a], Corresponding Recommended Intakes, and Maximum Component Scores in an Analysis of Associations Between Prenatal Diet Quality and Child Development, Norwegian Mother and Child Cohort Study, 1999–2008

PDQI Component	Recommended Intake	Maximum Component Score
Fresh fruits and berries	Minimum of 250 g/day	10
Vegetables	Minimum of 250 g/day	10
Whole grains	Approximately 70 g/day for women	10
Total fish	300–450 g/week	5
Fatty fish	Minimum of 200 g/week (to a maximum of 450 g/week)	5
Red meat	Maximum of 500 g/week	10
Dairy foods	3 servings (1 serving = 20 g of cheese or 2 dL of milk or 1 serving (125 g) of yogurt)	10
Saturated fat	Maximum of 10% of total energy	10
Trans- fats	Maximum of 1% of total energy	10
Salt	Maximum of 6 g/day (2.4 g of sodium per day)	10
Added sugar	Maximum of 10% of total energy intake	10
Dietary diversity score	Diversity of foods within 4 major food groups eaten daily (grains, vegetables, fruits, and dairy foods)	10
Meal pattern	Approximately 3 main meals and 2 snacks or 4 main meals and 1 snack	10

Abbreviation: PDQI, prenatal diet quality index.
[a] Maximum total score = 120.

3. For food groups with both a minimum and a maximum recommendation (total fish and fatty fish), we used the formulae in points 1 and 2 for intakes below the lower recommended intake level and above the upper recommended intake level, respectively. So as not to overemphasize fish intake in the total PDQI score (since fatty fish is part of the total fish component), we divided the scores for total fish and fatty fish by 2, with a possible maximum score of 5 for each component. For intakes within the recommended intake range, we allocated the maximum score.

Diet diversity and meal pattern

To reflect each participant's diet variation on both a food level and a meal level, we included 2 additional components in the PDQI: diet diversity and meal pattern. There are recommendations regarding both diet variation and meal frequency in the Norwegian food-based dietary guidelines which justify inclusion of these components.

The diet diversity component was based on the diet diversity component from the Revised Diet Quality Index (44), and we followed the score calculation put forward by the authors of the Revised Diet Quality Index. This component reflects the intake variation of 25 food categories (depicted in Table 2), with a higher score equaling greater diversity. To get a positive score for each food category, the participant had to have eaten at least 1/4 of a serving of that respective food, with an overall maximum diet diversity score of 10.

Meal pattern is an integral part of a person's diet (45). The PDQI meal pattern component was based on the meal pattern component from the Diet Quality Index for Pregnancy (46) and aimed to reflect the average daily meal pattern of each participant, with 3 main meals and 2 snacks or 4 main meals and 1 snack defined as being good options (43). We based the PDQI meal pattern score on the daily consumption frequency of main meals, supper, and snacks as reported in the MoBa FFQ, for a maximum score of 10. For additional details on the diet diversity and meal pattern calculations, see the Web Appendix (available at https://academic.oup.com/aje).

We calculated the total PDQI score for each participant by summing the scores for all components.

Outcome definitions

The Child Behavior Checklist (CBCL) (47), a widely used parent-report instrument designed to identify aspects of problem behavior in children, assesses externalizing and internalizing symptoms at ages 18, 36, and 60 months. In the MoBa CBCL, 25 questions comprising 4 categories constitute a broader dimension of internalizing symptoms (emotionally reactive, anxious/depressed, somatic complaints, withdrawn), and 2 categories constitute an externalizing dimension (attention problems and aggressive behavior). Mothers report the extent to which they agree with each questionnaire item, with the following response options: "not true," "somewhat or sometimes true," and "very true or often true." All subscales of the CBCL have shown good test-retest reliability and adequate sensitivity (71%) and specificity (92%) (47).

MoBa investigators assessed language and motor functions with the parent-completed Ages and Stages Questionnaire (ASQ) at child ages 18, 36, and 60 months and the Child Development Inventory (48) at age 60 months. The ASQ is a

Table 2. Components of Diet Diversity in the Norwegian Mother and Child Cohort Study, 1999–2008

Food Group	Representative Foods	Size of 1/4 Portion, g
Grains		
Non–whole-grain breads	Low-fiber bread, crispbread[a], and biscuits	10
Non–whole-grain cereals	Low-fiber cereals	13
Non–whole-grain crackers	Low-fiber crispbread and biscuits	2
Pasta	All pasta dishes	50
Whole-grain breads	High-fiber bread and crispbread	11
Whole-grain crispbread	High-fiber crispbread	2.5
Whole-grain cereals	High-fiber muesli and porridge	33
Rice	Rice and couscous	43
Vegetables		
White potatoes	Mashed and fried potatoes, French fries	30
Nuts	Almonds, peanuts, other nuts	13
Legumes (pulses)	Lentils, kidney beans, soy products	56
Root vegetables	Rutabagas (swedes), carrots	25
Cruciferous vegetables	Cauliflower, broccoli, cabbage, brussels sprouts	25
Dark green and leafy vegetables	Spinach, lettuce	25
Other vegetables	Alliums, mushrooms, peppers, cucumbers, celery, squash, corn, tomatoes, peas, avocados	25
Fruits		
Citrus fruit, melons, berries	Oranges, grapefruit, all berries	25
All other fruits and juices	Apples, bananas, grapes, raisins, pears, mangoes, papayas, plums	25
Animal products		
Red meat	Beef, pork, lamb, offal	34–71
Milk	Plain milk, chocolate milk	50
Game	Reindeer, moose, wild boar	38
Poultry	Chicken, turkey	38
Cheese	White cheese, brown cheese, blue cheese	5
Eggs	Eggs, seagull eggs	14
Fish	Seafood, lean fish, fatty fish, fish roe, fish sticks	11
Yogurt	Yogurt, probiotic milk	31

[a] A dry, flat cracker.

screening and diagnostic tool for assessment of nontypical development (49–51) that has been validated in a Norwegian setting (49). For specified activities, mothers answer "yes," "sometimes," or "not yet" according to whether or not the child can perform the activity. The Child Development Inventory aims to identify children with specific deviations from age-typical development (52). In MoBa, only items on fine motor development (5 items) and gross motor development (6 items) were included in the questionnaire at age 60 months. Parents answer "yes" if a child holds a skill and "no" if s/he does not.

We defined outcome dimensions according to the respective instrument manuals. Because most of our outcome data were highly skewed to the right and had varying degrees of zero inflation, we calculated sum scores rather than standardized scores as the basis for analysis, with a higher score indicating a greater level of difficulty. If a participant had less than 50% missing items for a scale (approximately 3%), we imputed these items with the participant's mean score over the other items. For each participant, we excluded scales with more than 50% of items missing (per time point).

Histograms of PDQI and outcome distributions and a visualization of the relationship between the PDQI and outcomes are shown in Web Figures 1–3, respectively.

Statistical analyses

To assess the validity of the PDQI, we investigated both its construct validity and its reliability. To estimate the strength of associations between the PDQI score and sum scores from the CBCL, ASQ, and Child Development Inventory at ages 18, 36, and 60 months, we fitted a Bayesian hierarchical beta-binomial model for all outcome variables simultaneously. This hierarchical

modeling approach improves estimation of group-specific associations for different outcomes through partial pooling (53). For the analysis, we utilized R statistical software, version 3.4.4 (R Foundation for Statistical Computing, Vienna, Austria) (54) and the "brms" package, version 2.1.0 (55). Continued participation in MoBa is characterized by self-selection, which is particularly dependent on maternal education, age, and parity (number of births). Hence, we used inverse probability weighting (56) based on these variables to control for bias due to self-selection into the study and attrition. We calculated weights from simple participation probabilities—that is, the number of mothers in a population subgroup in the study sample divided by the number of mothers in the same subgroup in the source population. We obtained population data as microtables from Statistics Norway, which provided information on maternal age, parity, and education for the Norwegian pregnant population for the MoBa recruitment period (57). Using inverse probability weighting justified our choice to perform the analysis on complete cases rather than use multiple imputation, which could cause more bias in the analysis than only performing complete-case analysis without inverse probability weighting (58).

We assessed a number of covariates for inclusion in the analysis. The set of final covariates was selected on the basis of a directed acyclic graph (Web Figure 4), following the suggestions by Shrier and Platt (59) to reduce the degree of bias. The final covariates were: maternal prepregnancy body mass index, total energy intake, maternal education, alcohol consumption and smoking during pregnancy, maternal symptoms of depression and attention-deficit/hyperactivity disorder (ADHD), maternal age, child sex, duration of breastfeeding, and child diet quality (frequency of raw vegetable consumption). We adjusted for child diet quality because this removed bias from a common unobserved cause of maternal and child diet.

For each outcome, we report the results as average marginal effect (AME)—that is, the average change in the outcome for a 1-unit change in the exposure. We report both absolute AME (change in mean score) and relative AME (change in percentage) with corresponding high-density intervals. For ease of interpretation, we report AMEs relative to a 1–standard-deviation (SD) increase in the PDQI score. We fitted 2 separate models—one crude, with only the PDQI score, and one adjusted, including all covariates. Additionally, we stratified our sample by child sex and maternal ADHD symptoms to investigate possible differences in associations.

MoBa assesses maternal ADHD symptoms with the Adult ADHD Self-Report Scale, which consists of 6 questions relating to symptoms of adult ADHD based on the diagnostic criteria of the *Diagnostic and Statistical Manual of Mental Disorders, Fourth Edition* (60). Stratifying on maternal ADHD symptoms is an attempt to, in part, adjust for genetic vulnerability to ADHD, considering that ADHD is hereditary and that children with ADHD generally present with more difficulties relating to the outcomes studied.

Furthermore, we calculate the predicted number of children below the threshold for normal development on the ASQ language dimension at age 60 months with incremental changes in the PDQI score between −3 SDs and +3 SDs. We chose this outcome because indications of language difficulties at age 60 months are more stable predictors of future language difficulties than difficulties assessed at age 18 or 36 months (61). We recalculated the sum score according to the manual, where 70 is the maximum score and scoring below a threshold score of 31.7 indicates possible deviation from normal development (48).

On the basis of prior predictive simulations (62), we set the prior for population-level ("fixed") effects to a normal distribution with a mean of 0 and an SD of 2 and the prior for the SD of random effects to a normal distribution with a mean of 0 and an SD of 2. Note that, given the large sample size in MoBa, priors will not have a substantial influence on the final parameter estimates (63, 64).

RESULTS

In total, 27,529 mother-child pairs were eligible for inclusion. The mean PDQI score was 93 (range, 45–116). At the time of delivery, mothers were on average 30.7 years of age, and they had generally high educational attainment (71% had at least a bachelor's degree). Furthermore, 60% of the mothers reported fully breastfeeding the infant for at least 4 months, and few (<5%) reported smoking in pregnancy. The sample consisted of 51% boys, and overall the children presented with low levels of difficulties across all outcomes. Table 3 gives descriptive statistics for the PDQI score, outcomes, and covariates.

Reliability and validity of the PDQI

Reliability analysis revealed a Cronbach's α of 0.66 for the PDQI, which is similar to that of the original Healthy Eating Index (65). To investigate construct validity, we explored whether the PDQI was able to differentiate between groups known to have different diet quality: smokers versus nonsmokers, lower (<12 years of education) versus higher (master's degree) educational attainment, younger (≤21 years) versus older (≥30 years) maternal age, and people with and without depressive symptoms. We calculated the standardized mean difference between groups, reported as Hedges' g, with a large effect size seen for education ($g = 0.86$) and age ($g = 0.80$), a medium effect size for smoking ($g = 0.59$), and a small-to-medium effect size for depressive symptoms ($g = 0.33$). Furthermore, we observed a low correlation between total energy intake and PDQI score ($r = 0.15$), indicating that the PDQI assesses diet quality independently of diet quantity. Lastly, PDQI scores were correlated with energy-adjusted intakes of key nutrients in the FFQ in the expected direction and at a satisfactory level (fiber: $r = 0.50$; sugar: $r = -0.32$; saturated fat: $r = -0.33$), as well as with key nutrients such as protein, iron, zinc, and B vitamins (r's = 0.36–0.54).

On the basis of the adjusted models, the results showed that a 1-SD increase in PDQI score was associated with a relative AME (%) decrease in difficulties both globally (4%, high-density interval (HDI): 2, 7) (Figure 2A) and across all time points (for language skills (7%, HDI: 3, 10), motor function (4%, HDI: 1, 7), externalizing (4%, HDI: 2, 5), and internalizing (3%, HDI: 1, 5)) (Figure 2B). This corresponds to a reduction in sum scores (absolute AMEs) of 0.02–0.21 points (Figures 2C–2F and Web Table 1). Web Figures 5 and 6 present results from the analyses stratified by child sex and maternal ADHD symptoms, respectively. These results suggest that the associations did not differ substantially by sex or by maternal ADHD symptom level.

Table 3. Characteristics of Mother-Child Dyads Included in an Analysis of Associations Between Prenatal Diet Quality and Child Development, Norwegian Mother and Child Cohort Study, 1999–2008

Variable	No. of Mother-Child Pairs	No. of Pairs With Missing Data	Mean (SD)	Median (IQR)	Range
Exposure variable: PDQI score	27,529	0	93.0 (9.2)	94 (88–100)	45–116
Outcome variables					
Motor function					
Age 18 months	27,529	0	1.2 (1.8)	0 (0–2)	0–20
Age 36 months	27,529	0	1.2 (1.3)	1 (0–2)	0–8
Age 60 months	27,529	0	0.9 (1.4)	0 (0–1)	0–10
Language skills					
Age 18 months	27,529	0	1.2 (1.5)	1 (0–2)	0–6
Age 36 months	27,529	0	0.6 (1.1)	0 (0–1)	0–12
Age 60 months	27,529	0	0.8 (1.3)	0 (0–1)	0–14
Externalizing					
Age 18 months	27,529	0	3.8 (2.2)	4 (2–5)	0–14
Age 36 months	27,529	0	5.4 (3.1)	5 (3–7)	0–20
Age 60 months	27,529	0	1.3 (1.6)	1 (0–2)	0–18
Internalizing					
Age 18 months	27,529	0	1.3 (1.2)	1 (0–2)	0–10
Age 36 months	27,529	0	2.2 (1.9)	2 (1–3)	0–14
Age 60 months	27,529	0	3.7 (3.0)	3 (1–5)	0–21
Covariates[a]					
Maternal age, years	27,529	0	30.7 (4.3)	31 (28–34)	14–47
Prepregnancy body mass index[b]	27,051	478	24.0 (4.0)	23 (21–26)	13–56
Maternal ADHD score	27,303	226	1.1 (0.7)	1 (1–1)	0–3
Maternal Hopkins score[c]	27,170	359	1.1 (1.8)	0 (0–2)	0–15
Maternal education	27,529	0			
Prenatal alcohol use		3,180			
Yes	2,755				
No	21,594				
Prenatal smoking		126			
Yes	1,223				
No	26,180				
Prenatal energy intake, MJ/day	27,529	0	9.6 (2.4)	9.3 (7.9–10.9)	4.5–19.9
Parity	27,529	0	0.7 (0.9)	1 (0–1)	0–4
Child sex		0			
Female	13,557				
Male	13,972				
Breastfeeding for <6 months	25,457	2,072	5.6 (1.3)	6 (6–6)	0–6
Child diet quality[d]	27,006	523	1.8 (0.9)	2 (1–2)	1–4

Abbreviations: ADHD, attention-deficit/hyperactivity disorder; IQR, interquartile range; PDQI, prenatal diet quality index; SD, standard deviation.

[a] For categorical and dichotomous variables, only the number of mother-child pairs is given.

[b] Weight (kg)/height $(m)^2$.

[c] Based on 5 questions from the Hopkins Symptom Checklist, measuring symptoms of depression (0 = no symptoms and 3 = high symptom level, with a possible maximum total score of 15) (84).

[d] Frequency of raw vegetable intake (1 = never/seldom, 2 = 1–3 times/week, 3 = 4–6 times/week, and 4 = daily or more often).

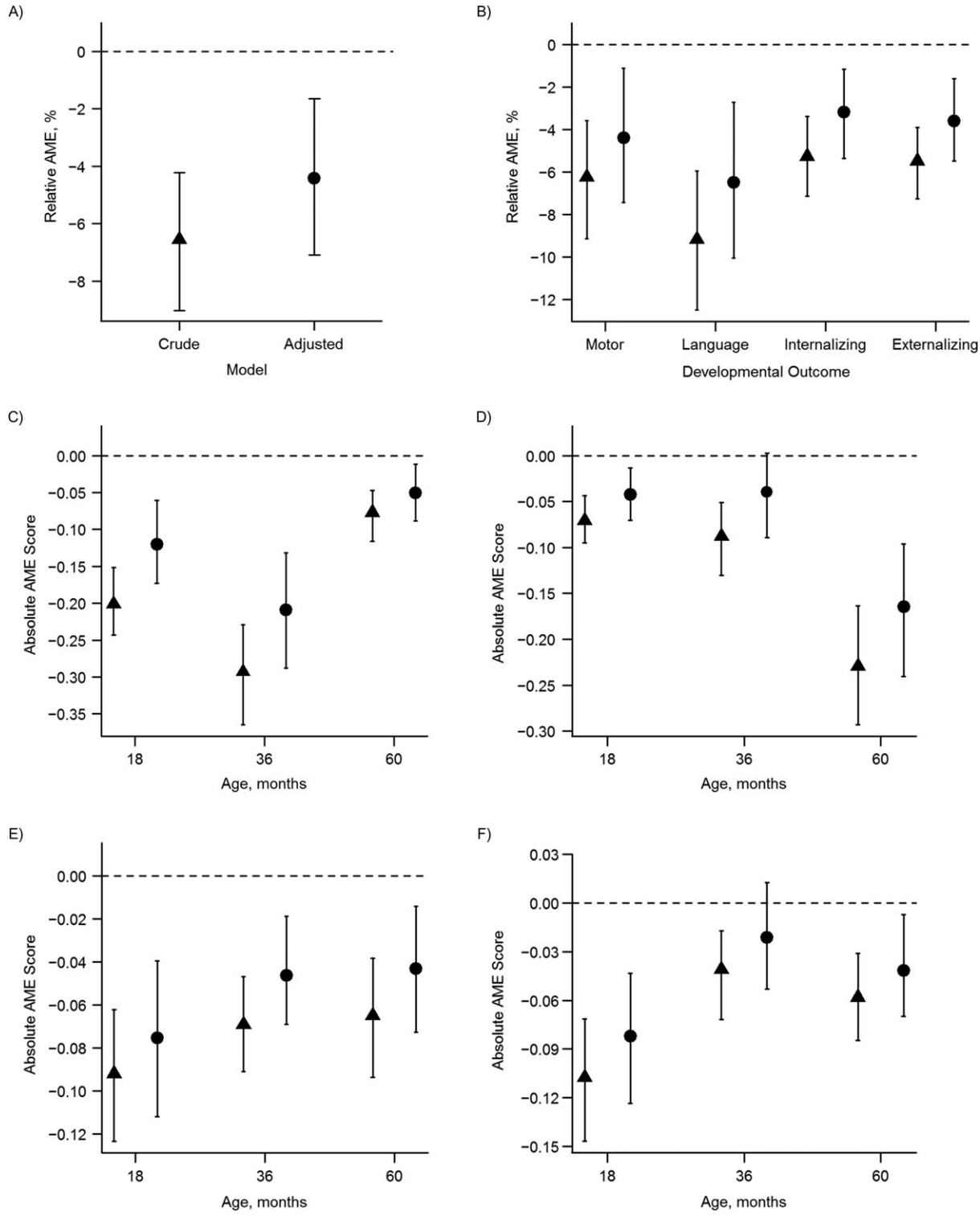

Figure 2. Relative average marginal effects (AMEs) globally (A) and longitudinally (B) across developmental outcomes and absolute AME scores (C–F) for individual developmental outcomes (externalizing (C), internalizing (D), language skills (E), and motor difficulties (F)) at each time point for a 1–standard-deviation increase in prenatal diet quality index score, Norwegian Mother and Child Cohort Study, 1999–2008. ▲, crude model; ●, adjusted model. The adjusted model included total energy intake (MJ/day), prepregnancy body mass index, maternal education, maternal age, smoking and alcohol use during pregnancy, maternal symptoms of depression during pregnancy, maternal symptoms of attention-deficit/hyperactivity disorder, child sex, duration of breastfeeding, and child diet quality. Bars, high-density intervals.

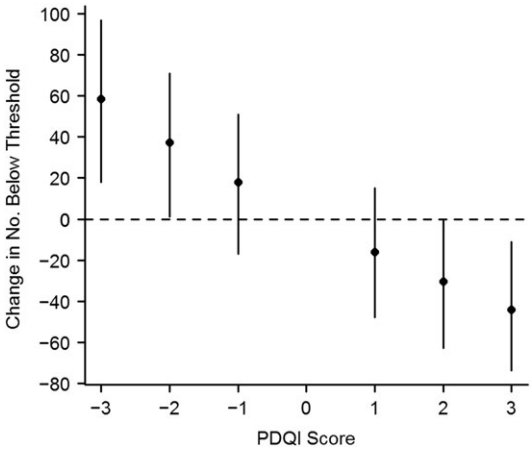

Figure 3. Predicted change in number of children below the threshold for the Ages and Stages Questionnaire language dimension at age 60 months for a 1–standard-deviation incremental change from the mean prenatal diet quality index (PDQI) score (represented by 0 on the *x*-axis), Norwegian Mother and Child Cohort Study, 1999–2008. Bars, high-density intervals.

Figure 3 displays the predicted change in the number of children below the threshold for the ASQ language dimension at age 60 months with a −3-SD to +3-SD change in PDQI score. A 1-SD increase was equal to a +9.2 change in the PDQI score, which is equivalent to (for example) an increase in daily vegetable or fruit/berry intake from 0 g to 230 g. At the mean PDQI score (0), the total number of children below the threshold was 107 (out of 27,529).

DISCUSSION

In this longitudinal study, we estimated the strength of associations between an a priori-defined prenatal diet quality index and developmental outcomes in children. The results indicated a global reduction of sum scores across all outcomes of approximately 5% for a 1-SD increase in PDQI score, with somewhat stronger associations for language and motor outcomes than for behavioral outcomes. These results are consistent with the finding from a recent meta-analysis of studies on maternal diet quality and child development in Western industrialized countries published up to November 2016 (23). The results are also in agreement with more recent studies reporting associations between prenatal diet quality and less child hyperactivity (66, 67), fewer emotional problems (66), and higher verbal and full-scale intelligence quotient (68).

The literature on prenatal diet and child development proposes a number of mechanisms that could explain associations between improved diet quality and reduced child developmental difficulties. One possible mechanism is that better prenatal diet quality leads to a more favorable nutritional environment in utero. Some nutrients are particularly important for prenatal brain development, like protein, iron, zinc, copper, selenium, vitamin A, vitamin B6, and folate (69). Associations between symptoms of neurodevelopmental deviations and suboptimal levels of several of these nutrients have been documented (16, 70). In MoBa, the PDQI score correlates positively with estimated levels of all of these nutrients.

Prenatal inflammation or impaired immune function (71) constitutes a plausible alternative (indirect) biological mechanism. Prenatal malnutrition is associated with enhanced inflammation, which might negatively affect child neurodevelopment (72). Higher scores on both a priori-defined dietary indices and data-driven healthy dietary patterns have been associated with lower concentrations of inflammatory markers (73–75), which supports the notion that poorer prenatal diet quality can potentially influence fetal neurodevelopment via maternal inflammatory processes.

Regarding the differences in the magnitude of AMEs seen between neurodevelopmental and behavioral outcomes, it is possible that these stem from differences in measurement quality. The ASQ and the Child Development Inventory measure specific skills/abilities or lack thereof, which can be easier for parents to observe and objectively report on (76) compared with CBCL items that measure emotionally based behaviors, which often are more difficult to assess (77).

To view the findings in a more tangible perspective, using the results shown in Figure 3, we calculated that for a 1-SD increase in PDQI score, the number of children below the ASQ threshold for normal development would decrease from 46/10,000 children aged 60 months to 39/10,000. It is important to consider that we based our findings on a study sample from a wealthy industrialized country with low levels of developmental difficulties. Therefore, while prenatal diet quality did not have a large impact on child developmental difficulties in our sample, improving prenatal diet quality in populations with overall lower socioeconomic status and/or with higher levels of developmental difficulty might be of more importance as a preventive measure.

The strengths of this study include a large sample size, repeated measures, a robust method for estimating associations, and use of inverse probability weighting to account for selection bias. The large sample size also allowed us to investigate possible differences in associations by sex and by maternal ADHD symptoms.

One limitation of this study is that self-reported data pose many challenges, particularly for health-related questions (78–80). The FFQ method has been subject to much criticism (81). However, the FFQ utilized in this study was specifically developed for the target population and has been extensively validated (28). Furthermore, we used a composite measure of overall diet quality, which is less vulnerable to misreporting and is a recommended method for investigating diet-disease relationships, rather than the use of single macro- or micronutrients as exposures (82).

Another limitation is that MoBa is not fully representative of the total population of Norwegian mothers and children, due to selection bias related to both study inclusion and attrition. MoBa mothers are older and have a higher level of education than the general pregnant population (83), which are factors associated with better prenatal diet quality and lower levels of child difficulties. However, since we used inverse probability weighting for maternal age, education, and child parity in our analysis, one might generalize the results with less caution, mainly to populations in wealthy industrialized regions.

Furthermore, despite the advantages of using a priori-defined diet quality indices like the PDQI, its development still relies on decisions made by the investigators on how to create

the index—for example, regarding the number and weighting of components contributing to the PDQI score.

Lastly, it is important to recognize that a causal interpretation of association estimates always rests on assumptions, only some of which are testable in a particular study. One important assumption in the current study was the absence of important unobserved confounders that could drive the association between prenatal diet quality and child development.

In conclusion, we estimated the strength of associations between prenatal diet quality and developmental difficulties in children at 18, 36, and 60 months of age. Associations were inverse across all difficulties and were somewhat stronger for language and motor difficulties. However, the strength of the associations was low, with varying degrees of uncertainty, and we cannot conclude that the observed differences in prenatal diet quality had a profound influence on the child outcomes studied in this population.

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