

Original article

Maternal dietary patterns during pregnancy and child internalising and externalising problems. The Generation R Study



Jolien Steenweg-de Graaff^{a,b}, Henning Tiemeier^{b,c,d}, Régine P.M. Steegers-Theunissen^{e,f}, Albert Hofman^c, Vincent W.V. Jaddoe^{a,c,g}, Frank C. Verhulst^b, Sabine J. Roza^{b,d,*}

^a The Generation R Study Group, Erasmus Medical Centre, Rotterdam, The Netherlands

^b Department of Child and Adolescent Psychiatry/Psychology, Erasmus Medical Centre, Rotterdam, The Netherlands

^c Department of Epidemiology, Erasmus Medical Centre, Rotterdam, The Netherlands

^d Department of Psychiatry, Erasmus Medical Centre, Rotterdam, The Netherlands

^e Department of Obstetrics and Gynaecology, Erasmus Medical Centre, Rotterdam, The Netherlands

^f Department of Clinical Genetics, Erasmus Medical Centre, Rotterdam, The Netherlands

^g Department of Paediatrics, Erasmus Medical Centre, Rotterdam, The Netherlands

ARTICLE INFO

Article history:

Received 30 July 2012

Accepted 4 March 2013

Keywords:

Prenatal

Dietary patterns

Child

Internalising problems

Externalising problems

SUMMARY

Background & aims: Maternal nutritional factors during pregnancy have been linked to foetal brain development and subsequent offspring behaviour. Less is known about associations between maternal dietary patterns and offspring behaviour.

Methods: Within a population-based cohort, we assessed maternal diet using a food frequency questionnaire. Three dietary patterns were derived by means of Principal Component Analysis. Child internalising (emotionally reactive, anxious/depressed or withdrawn, having somatic complaints) and externalising problems (inattention, aggression) were assessed with the Child Behaviour Checklist at 1.5, 3 and 6 years in 3104 children. We assessed the association of maternal Mediterranean, Traditionally Dutch and Confectionary dietary pattern during pregnancy with child internalising and externalising problems.

Results: After adjustment, the Mediterranean diet was negatively associated ($OR_{per\ SD}$ in Mediterranean score = 0.90, 95% CI: 0.83–0.97) and the Traditionally Dutch diet was positively associated with child externalising problems ($OR_{per\ SD}$ in Traditionally Dutch score = 1.11, 95% CI: 1.03–1.21). Neither diet was associated with internalising problems.

Conclusions: Both low adherence to the Mediterranean diet and high adherence to the Traditionally Dutch diet during pregnancy are associated with an increased risk of child externalising problems. Further research is needed to unravel the effects of nutrient interplay during and after pregnancy on child behavioural development.

© 2013 Elsevier Ltd and European Society for Clinical Nutrition and Metabolism. All rights reserved.

Non-standard abbreviations: CBCL, child behaviour checklist; FFQ, food frequency questionnaire; PCA, principal component analysis; GEE, generalised estimating equations.

* Corresponding author. Erasmus Medical Centre, Department of Psychiatry (Dp-1404), Postal Box 2040, 3000 CA Rotterdam, The Netherlands. Tel.: +31 10 704 0139; fax: +31 10 703 5867.

E-mail addresses: j.steenweg-degraaff@erasmusmc.nl (J. Steenweg-de Graaff), h.tiemeier@erasmusmc.nl (H. Tiemeier), r.steegers@erasmusmc.nl (R.P.M. Steegers-Theunissen), a.hofman@erasmusmc.nl (A. Hofman), v.jaddoe@erasmusmc.nl (V.W.V. Jaddoe), f.verhulst@erasmusmc.nl (F.C. Verhulst), s.roza@erasmusmc.nl (S.J. Roza).

1. Introduction

Over the past decades, both animal and human studies have provided evidence for the concept of foetal 'programming', which signifies the developmental adaptations due to an adverse foetal environment. These adaptations permanently program the foetus' structure, physiology, and metabolism.¹ One of the environmental factors that have been found to contribute to foetal and later human development is maternal nutrition during pregnancy.² A large part of the research comprises the impact of maternal prenatal nutrition on birth outcomes, physical development and chronic diseases.^{3,4} Nutritional factors also affect (foetal) brain development and subsequent offspring behavioural development.⁵ For example, prenatal

exposure to famine has been found to predict psychopathology in adulthood⁶ and maternal status of several nutrients, such as folate and vitamin D,^{7,8} has been associated with child behavioural development.

Until now, the majority of studies on associations between maternal nutrition and child behaviour have focused on individual foods or nutrients. However, most positive results of supplementation interventions come from interventions that involve multiple micronutrients.⁹ This finding is in line with the fact that people do not eat isolated nutrients. Instead, they eat meals, consisting of strongly correlated and interacting nutrients. As a result, the call for analyses of the diet as a whole has increased and dietary pattern analysis has emerged as an approach for studying diet-related research questions.^{3,10} Although some studies investigated the association between child dietary patterns and their mental health,^{11–13} to our knowledge dietary patterns during pregnancy and their relation with offspring behavioural development have not been studied before.

Our objective was to evaluate the effects of maternal dietary patterns in early pregnancy on child behavioural development. As a first step in this field, we chose to focus on the two global domains of child problem behaviour: internalising problems and externalising problems.¹⁴ Internalising problems comprise emotionally reactive and anxious/depressed symptoms, as well as somatic complaints and symptoms of being withdrawn. Externalising problems comprise attention problems and aggressive behaviour. We hypothesised that a healthy prenatal diet would be associated with a reduced risk whereas an unhealthy diet would be associated with an increased risk of internalising and externalising problems during childhood.

2. Materials and methods

2.1. Study population

The present study was conducted within the Generation R Study, a population-based cohort from early foetal life onwards in Rotterdam, The Netherlands. The study design has been described in detail previously.¹⁵ The study was conducted in accordance with the guidelines proposed in the World Medical Association Declaration of Helsinki and was approved by the Medical Ethics Committee at Erasmus Medical Center, University Medical Center Rotterdam, The Netherlands. Written consent was obtained from all participants.

Only mothers of Dutch national origin were eligible for the current study, since nutrition generally differs between ethnic groups. Overall, 3486 children and their mothers were eligible at study baseline. Due to loss to follow-up, data for 3104 children (89%) and their mothers were included in one or more analyses (Fig. 1). Some mothers participated with two ($n = 255$), or three ($n = 3$) children. Since results did not differ after random exclusion of one or two of these siblings, they were included in the analyses.

2.2. Dietary assessment

Nutritional intake in the past three months was assessed in early pregnancy (median 13.5 weeks, 95% range 10.1–21.8) by using a modified version of a validated semi-quantitative food frequency questionnaire (FFQ).¹⁶ The FFQ consists of 293 food items and is structured according to meal patterns. Questions in the FFQ assess consumption frequency, portion size, preparation method and additions to the dish. Portion sizes were estimated using Dutch household measures and photographs. Average daily nutritional values were calculated using the Dutch food composition table 2006.¹⁷

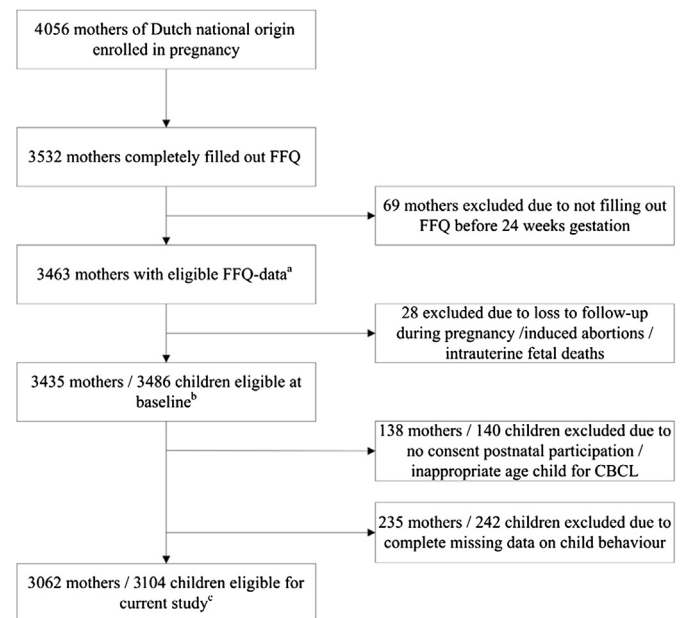


Fig. 1. Flow chart of study population: the Generation R Study Cohort, Rotterdam, The Netherlands.

^aEligible sample for Dietary Pattern analysis.

^b51 mothers participate with twin.

^cAnalytic sample, missings imputed by multiple imputation.

FFQ = food frequency questionnaire CBCL = Child Behaviour Checklist.

The 293 food items were reduced to 24 predefined food groups, according to The European Prospective Investigation into Cancer and Nutrition (EPIC)-soft classification, based on origin, culinary usage and nutrient profiles.¹⁸

To derive dietary patterns from food consumption data of women of Dutch origin within the Generation R Study Cohort ($n = 3463$), we used Principal Component Analysis (PCA) as previously described by Hu¹⁰ and applied in a number of recent studies of dietary patterns and child development.^{12,13} In short, with PCA the variance in dietary data is explained by determining which food groups correlate high and thus together can be interpreted as a dietary pattern. For each individual food group a factor loading was calculated, representing the extent to which the food group relates to a particular factor. Foods with factor loadings of an absolute value ≥ 0.2 on a factor were considered to have a “strong” association with that factor and were used to describe and label each pattern. Based on the scree plot and interpretability of the patterns, three major dietary patterns with an eigenvalue above 1.5 were identified, explaining in total 21% of the variation in the dietary data (Table 1). This percentage is comparable to those reported in other studies on dietary patterns.¹⁹ The first pattern has been labelled ‘Mediterranean’, because of its high loadings on vegetables, fish & shellfish, vegetable oil, fruit, and eggs, and relatively high negative loading on processed meat. The second component was characterized by high intakes of fresh and processed meat and potatoes, a relatively high intake of margarines and a very low intake of soy and diet products. This resembles the traditional Dutch eating pattern, which we labelled as ‘Traditionally Dutch’. The third component yielded a dietary pattern high in the consumption of cakes, sugar & confectionary products, tea, cereals, fruit and dairy products. We labelled this pattern ‘Confectionary’. Each woman received an individual score for each of the dietary patterns, calculated as the product of the food group value and its factor loadings summed across foods. For convenience we termed this score ‘adherence to dietary pattern’: a high score represents a

Table 1
Factor loadings of food groups in dietary patterns in mothers of Dutch national origin ($n = 3463$): the Generation R Study Cohort, Rotterdam, The Netherlands.

Food group	Mediterranean pattern	Traditionally Dutch pattern	Confectionary pattern
Vegetables	0.68	0.00	−0.06
Fish and shellfish	0.67	−0.12	−0.01
Vegetable oil	0.65	0.13	−0.10
Fruit	0.47	−0.18	0.24
Fresh meat	0.06	0.76	−0.10
Miscellaneous (soy & diet)	−0.04	− 0.62	−0.10
Processed meat	− 0.25	0.56	0.14
Potatoes	−0.14	0.45	−0.16
Cakes	0.01	−0.03	0.70
Sugar and confectionary	−0.17	0.03	0.65
Tea	0.26	−0.02	0.43
Legumes	0.07	−0.09	−0.09
Cereals and cereal products	0.23	0.06	0.32
Butter	0.03	0.04	0.17
Margarines	−0.17	0.20	0.17
Coffee	0.02	0.02	0.03
Alcoholic drinks	0.12	0.03	0.04
Sauces	0.07	0.03	0.08
Soft drinks	−0.11	0.17	0.02
Eggs	0.23	−0.08	0.09
Fruit/vegetable juices	−0.14	0.01	−0.07
Dairy products	0.12	−0.01	0.22
Soups and bouillon	0.13	0.04	0.02
Milk	−0.02	0.12	−0.04
Variance explained (%)	8.1	6.9	6.1

Food groups with bold numbers are considered to have a strong association (absolute value of factor loading ≥ 0.2) with a factor.

high adherence to the particular dietary pattern, whereas a low score represents a low adherence to the pattern. When using PCA to define dietary patterns, participants receive a score on each of the dietary patterns. Although the dietary patterns are statistically uncorrelated, some individuals score high on more than one pattern. This is why we chose to adjust all analyses for the other dietary pattern scores.

2.3. Child internalising and externalising problems

Mothers were asked to fill out the Child Behaviour Checklist for toddlers (CBCL 1½–5) when their child was 1.5, 3 and 6 years old. The CBCL is a self-administered parents-report questionnaire to measure the degree of children's problem behaviour. It contains 99 problem items rated on a 3-point scale (0 = not true, 1 = somewhat or sometimes true, and 2 = very true or often true), based on the preceding two months. Together, these 99 items result in a Total problems score, which can be subdivided in Internalising problems and Externalising problems. Good reliability and validity have been reported for the CBCL.¹⁴

2.4. Covariates

Several parental characteristics were considered as possible confounding variables, based on previous studies of (maternal) diet and child (internalising and externalising) development.^{7,13} These were: maternal pre-pregnancy BMI, maternal age at enrolment, maternal prenatal smoking and folic acid and multivitamin use, paternal national origin, parental educational level, psychopathology, parity and marital status, and family income. Maternal folate, homocysteine and vitamin B₁₂ concentrations in early pregnancy were considered as possible mediators. Assessment of these covariates has been described in detail previously.^{20,21} To adjust for the effect of energy intake during pregnancy on the association between maternal diet and child problem behaviour, we also

considered prenatal average daily caloric intake, calculated by means of the FFQ-data and the Dutch food composition table 2006.¹⁷

Child characteristics that were considered comprised gestational age and weight at birth, gender, breastfeeding status at 6 months, and age of the child at the time of assessment, which have been described in detail previously.⁷ We also considered child consumption of snacks and sugar containing beverages at age 4/6, which was obtained from parental questionnaires at the age of 4 and 6 years.

All analyses of maternal dietary patterns and child problems were controlled for gender of the child and the age of the child at the time of the measurement (CBCL). Other covariates were included in the models if they changed the effect estimates meaningfully (defined as more than 5%). Following this criterion maternal age, pre-pregnancy BMI and parity, prenatal smoking, vitamin use and caloric intake, paternal national origin, parental educational level, psychopathology, family income, and marital status as well as child consumption of snacks and sugar containing beverages at the age of 4/6 years were included in the present analyses.

2.5. Statistical analyses

We used the CBCL internalising and externalising problem scores as outcome variables. To facilitate a clinical interpretation of problem behaviour, and because the scores could not be normalised, we analysed the internalising and externalising scores as dichotomous variables. In line with previous publications, we defined a non-optimal score as the highest 20% of internalising and externalising item scores.⁷

Multivariable logistic regression analyses using generalised estimating equations (GEE) were used to test for associations between maternal dietary patterns and repeatedly measured child internalising and externalising problems. GEE analysis assesses the association between two variables, correcting for the within-subject dependence of repeated ratings of child internalising and externalising problems. Such an overall estimate reduces the errors derived from multiple comparisons. A possible time trend is not easily interpretable in such a combined model. Because the number of repeated measures in the current study was small ($n = 3$ measures of child behaviour) and the data were balanced as well as complete (due to imputation of missing data), an unstructured working correlation structure was used in the GEE analyses as adjustment for the dependency between the repeated measurements.

First, we used the dietary pattern scores as continuous variables in the equation (1 unit increase on a diet score equals an increase of 1 SD). We also added quadratic terms of the dietary pattern variables to test for non-linear associations. All models were adjusted for gender and age of the child. To test the independent effect of each dietary pattern, all models were also mutually adjusted for the other dietary patterns. Subsequent models were additionally adjusted for the covariates mentioned earlier. To verify results, we re-analysed the data using the Mediterranean Diet Score as proposed by Trichopoulou et al.,²² though excluding alcohol use from the score.

Next, those dietary patterns that were statistically significant associated with child behavioural outcome in the primary analyses were divided by quintiles for ease of interpretation in secondary analyses.

Missing values on covariates and child outcome data for those children with at least one of three outcome measures available (approximately 0.1–24%) were imputed using the Markov Chain Monte Carlo multiple imputation technique with Predictive Mean

Matching for continuous variables. We generated 5 datasets and undertook 10 iteration procedures. Subsequently, GEE analyses were performed separately on each completed dataset and thereafter combined to one pooled estimate. Measures of association are presented with 95% confidence intervals (95% CI). Statistical analyses were carried out using PASW Statistics, version 17.0 for Windows (SPSS Inc., Chicago, Illinois) and Stata for Windows, Release 12 (StataCorp LP., College Station, Texas).

3. Results

3.1. Response analysis

Analyses of missing data showed that, compared with children with behavioural data ($n = 3104$), children without behavioural data ($n = 382$, 9.1%) had a shorter gestation [median of 39.9 wk (95% range: 32.2–42.0 wk) compared with 40.1 wk (95% range: 35.4–42.4 wk); $P < 0.001$] and, on average, a 193 gram (95% CI: 121; 265, $t = 5.3$) lower birth weight. The mothers of children not included on average had a 0.3 points (95% CI: 0.2; 0.4, $t = 5.0$) lower score on the Mediterranean diet, a 0.1 points (95% CI: -0.2; -0.02, $t = -2.3$) higher score on the Traditionally Dutch diet and a 0.3 points (95% CI: 0.2; 0.4, $t = 5.1$) lower score on the Confectionary diet in their first trimester of pregnancy. They were, on average, 2.5 (95% CI: 1.9; 3.1, $t = 8.5$) years younger and less educated [31.6% compared with 62.7%, $\chi^2 = 132$ (1); $P < 0.001$]. They also more often continued smoking during their pregnancy [34.5% compared with 13.5%, $\chi^2 = 111$ (2); $P < 0.001$] and less often adequately used vitamins during early pregnancy [58% compared with 81%, $\chi^2 = 88$ (2); $P < 0.001$]. The income of families not included in the analyses was lower than that of families included in the study [60.2% compared with 83.7%, $\chi^2 = 83$ (1); $P < 0.001$]. Descriptive characteristics of the participating parents and their children are presented in Table 2.

Table 2
Subject characteristics: The Generation R Study Cohort, Rotterdam, The Netherlands.

<i>Child characteristics</i>	$n = 3104$
Female (%)	49.5
Gestational age at birth (wk)	40.1 (35.4–42.4) ^a
Birth weight (g)	3478 ± 570 ^b
Breastfeeding until 6 mo (%)	31.8
Age child at assessment (mo)	
at 1.5 yr	18.1 (17.6–21.5)
at 3 yr	36.2 (35.4–40.1)
at 6 yr	71.2 (66.9–82.1)
Snacks at age 4/6 yr, ≥2/day (%)	13.8
Sugar containing beverages at age 4/6 yr, > 2/day (%)	21.1
<i>Parental characteristics</i>	$n = 3062$
Maternal age at enrolment (yr)	31.7 ± 4.1
Maternal education, higher (%)	62.6
Paternal education, higher (%)	58.1
Family income (> 2000 €/mo)	82.7
Maternal psychopathology in mid-pregnancy (GSI-score)	0.12 (0.00–0.78)
Paternal psychopathology in mid-pregnancy (GSI-score)	0.06 (0.00–0.59)
Maternal smoking during pregnancy (%)	
Never	78.2
Until pregnancy was known	8.3
Continued throughout pregnancy	13.5
Maternal vitamin use during early pregnancy (%)	
Folic acid only supplement use	52.6
Multivitamin use	29.6
No vitamin use	17.8
Maternal prenatal caloric intake (kcal/day)	2150 ± 503
Maternal pre-pregnancy BMI (kg/m ²)	23.3 ± 3.9
Parity, primiparae (%)	61.1
Marital status, cohabitation (%)	94.6
Paternal national origin, Dutch (%)	80.2

^a Median; 95% range in parentheses (all such values).

^b Mean ± SD (all such values).

3.2. Maternal dietary patterns and child internalising and externalising problems

The associations between maternal dietary patterns and child internalising and externalising problems are presented in Table 3. In the basic models, both the Mediterranean and the Traditionally Dutch pattern were associated with child externalising problems (OR_{per SD of Mediterranean score} = 0.88, 95% CI: 0.82; 0.94, $P < 0.001$; OR_{per SD of Traditionally Dutch score} = 1.15, 95% CI: 1.06; 1.26, $P = 0.001$). Including quadratic terms of the dietary pattern variables in the model did not add to the results (data not shown).

Next, the associations were adjusted for confounders. Since pregnant women are advised to use vitamin supplements, the use of supplements was examined in more detail for each dietary pattern. Only the Mediterranean pattern was associated with supplement use (dietary pattern divided by tertiles; $\chi^2(4) = 12.5$, $P = 0.014$). After adjustment for confounders, the associations remained statistically significant (OR_{per SD of Mediterranean score} = 0.90, 95% CI: 0.83; 0.97, $P = 0.006$; OR_{per SD of Traditionally Dutch score} = 1.11, 95% CI: 1.03; 1.21, $P = 0.011$). When re-analysing the association using the Mediterranean Diet Score, we found very similar results (OR = 0.94, 95% CI: 0.90; 0.98, $P = 0.004$). There were no associations between these dietary patterns and child internalising problems (OR_{per SD of Mediterranean score} = 0.95, 95% CI: 0.88; 1.02, $P = 0.132$; OR_{per SD of Traditionally Dutch score} = 1.05, 95% CI: 0.97; 1.13, $P = 0.244$). However, as can be seen by the overlap in the confidence intervals, the associations between the dietary patterns and internalising problems and externalising problems did not differ statistically.

Additional adjustment for the maternal nutritional biomarkers folate, homocysteine and vitamin B₁₂ by adding these variables to the model did not meaningfully change the results. We did not find any association between the Confectionary pattern and child internalising or externalising problems (see Table 3).

Next, for ease of interpretation and to illustrate the associations, we examined the quintiles of the maternal Mediterranean and Traditionally Dutch pattern in relation to child externalising problems. We used the highest quintile (high adherence) of the Mediterranean pattern and the lowest quintile (low adherence) of the

Table 3
Associations of maternal prenatal dietary patterns with child internalising and externalising problems up to 6 years ($n = 3104$): the Generation R Study Cohort, Rotterdam, The Netherlands.^{a,b,c}

Maternal dietary pattern (per SD)	Basic ^d		Adjusted for environmental covariates ^e	
	OR (95% CI)	P	OR (95% CI)	P
<i>Internalising problems</i>				
Mediterranean	0.94 (0.88; 1.01)	0.089	0.95 (0.88; 1.02)	0.132
Traditionally Dutch	1.04 (0.97; 1.12)	0.292	1.05 (0.97; 1.13)	0.244
Confectionary	1.03 (0.96; 1.10)	0.392	1.00 (0.91; 1.09)	0.956
<i>Externalising problems</i>				
Mediterranean	0.88 (0.82; 0.94)	<0.001	0.90 (0.83; 0.97)	0.006
Traditionally Dutch	1.15 (1.06; 1.26)	0.001	1.11 (1.03; 1.21)	0.011
Confectionary	1.04 (0.97; 1.13)	0.251	0.99 (0.90; 1.10)	0.912

^a Values are odds ratios from logistic generalised estimating equations (GEE) analyses.

^b Child measures at 1.5, 3 and 6 years.

^c Child outcome data imputed for those children with at least one of three outcome measures available.

^d Model 1: adjusted for the other dietary patterns, gender and age child at time of measurement.

^e Model 2: model 1, additionally adjusted for parental educational level, income and psychopathology, maternal smoking, vitamin use and average daily caloric intake during pregnancy, age, parity, marital status, and pre-pregnancy BMI, paternal national origin and child consumption of snacks and sugar containing beverages at age 4/6.

Traditionally Dutch pattern as the reference categories. With regard to the previous analyses, we found a similar pattern of results (Fig. 2). Those children of mothers in the lowest quintile of adherence to the Mediterranean pattern had a 35% increased odds (OR = 1.35, 95% CI: 1.07; 1.70, $P = 0.011$) of scoring in the high levels of the CBCL-scale of externalising problems, compared with children of mothers in the highest quintile of adherence to the Mediterranean pattern (P for trend = 0.017). For children of mothers in the highest and second highest quintile of adherence to the Traditionally Dutch pattern, these odds were increased by respectively 44% (OR = 1.44, 95% CI: 1.13; 1.84, $P = 0.004$) and 31% (OR = 1.31, 95% CI: 1.03; 1.65, $P = 0.026$), compared with children of mothers in the lowest quintile of adherence to the Traditionally Dutch pattern (P for trend = 0.003).

4. Discussion

In this population-based study, both a low adherence to the Mediterranean diet and a high adherence to the Traditionally Dutch diet during pregnancy were associated with increased risk of externalising problems in the offspring.

Although there is no single “Mediterranean” diet, common characteristics of a Mediterranean-type or “healthy” diet include moderate to high intakes of fruit, vegetables, vegetable oil, and fish, and lower intake of meat. In contrast, the more “Traditional” patterns in Western countries often exist of higher consumption of meat and potatoes, and lower intake of fruit and vegetables.¹⁹ Similar to our current findings, associations of prenatal Mediterranean and Traditional diets with foetal and child characteristics have been reported. For example, higher adherence to a Mediterranean-type diet during pregnancy has been found to reduce the risk of neural tube defects and orofacial clefts whereas adherence to a Traditional-like diet was found to increase this risk.²³ Likewise, the Mediterranean diet has been found to be beneficial for foetal growth, in contrast to the Traditional-type diet.²¹ Several potential mechanisms may underlie the observed effect of the maternal diet on child externalising problems in the current study.

A first explanation for this observation is the hypothesised neurodevelopmental origin of psychiatric disorders. Neuroimaging studies have shown altered brain structure and function in children with mental disorders such as attention-deficit/hyperactivity disorder, major depressive disorder and conduct disorder.²⁴ Although the human brain continues to develop throughout childhood, many alterations in the brains of children with mental disorders, such as aggressive behaviour and attention problems, might arise prenatally. An example may be found

in maternal status of unsaturated fatty acids during pregnancy. The ω -3 and ω -6 long-chain polyunsaturated fatty acids (LC-PUFAs) have been found to influence development and maturation of neuronal structures and to be involved in numerous neuronal processes, ranging from effects on membrane fluidity to gene expression regulation.²⁵ In particular the imbalance between maternal ω -3 and ω -6 fatty acids has been associated with subtle negative effects on child mental development.²⁶ During pregnancy, LC-PUFAs are transferred to the foetus across the placenta. The concentration of fatty acids in the foetus is dependent on maternal fatty acid status and the mother's dietary intake. ω -6 LC-PUFAs are mainly found in common vegetable oils (sunflower and corn oil), meat, eggs and lean fish. Fatty fish and vegetable oils such as linseed and soybean oil are the major suppliers of ω -3 LC-PUFAs.²⁶ As a consequence, mothers with a high adherence to the Mediterranean pattern may have a better ω -3: ω -6 ratio than mothers who highly adhere to the Traditionally Dutch pattern, which mainly provides them with ω -6 fatty acids.

Another example of the neurodevelopmental perspective of psychiatric disorders is a pathway through increased prenatal oxidative stress which may provide a possible explanation for the association of maternal dietary patterns and child externalising problems. Oxidative stress represents an imbalance in the body, characterized by an excessive production of free radicals and inadequate antioxidant defence mechanisms. A diet high in saturated fat, such as the Traditionally Dutch diet, increases the level of oxidative stress. Antioxidants, mainly found in vegetables and fruits as in the Mediterranean diet, decrease the level of oxidative stress.²⁷ Increased levels of oxidative stress have been found to reduce the level of Brain Derived Neurotrophic Factor (BDNF) in the rat brain.²⁷ BDNF is necessary for neuronal growth and differentiation in the nervous system during foetal development. The Confectionary pattern is high in sugar and fat intake. However, fruit intake is also considerably high in this pattern, which may compensate the negative effects of high sugar and fat intake on the level of oxidative stress. Although we were able to additionally adjust for nutritional biomarkers, known to be related to oxidative stress, the number of biomarkers was limited, which may clarify why the association was not further explained.

Second, growth of the foetal body may mediate the observed association. Foetal growth has been found to be inversely related to child behavioural problems.²⁸ Although birth weight did not change the association between maternal diet and child behaviour in our study, other characteristics of foetal growth may explain the association.

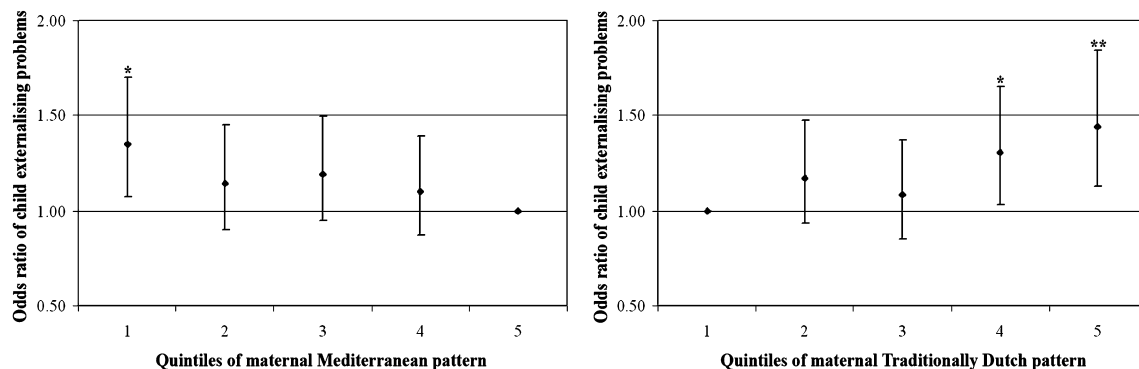


Fig. 2. Quintiles of maternal Mediterranean and Traditionally Dutch pattern and odds ratio of child externalising problems.

* $P < 0.05$

** $P < 0.01$.

Finally, in observational studies, this type of associations is highly sensitive to effects of confounding factors. A decline in the effect of maternal dietary patterns on the offspring's externalising problems was noticeable after adjustment for several parental and child characteristics, which stresses the substantial role of confounding factors. For example, Waylen et al., in their study of early intake of dietary ω -3 and childhood externalising behaviour, found any association to be completely confounded with socio-demographic factors.²⁹ Diet is a proxy for lifestyle, which in itself is difficult to disentangle. Although we accounted for many socio-demographic factors, further (residual) confounding cannot be excluded. For example, we were not able to completely adjust for the diet of the child itself. Also, other behavioural or lifestyle factors which are associated with both better maternal dietary habits and child behaviour may have gone unnoticed. Possibly, not only high socioeconomic status, but also better home environment or parenting style, account for the association of maternal diet with child externalising problems.

We found an effect of maternal diet almost exclusively on externalising problems. Possibly, specific brain structures, involved in the aetiology of externalising problems such as inattention and aggression, are specifically affected through biological mechanisms as described before. However, this contrast must be interpreted cautiously as the effect of maternal diet on child internalising and externalising problems was not different. Also, it is known that there is comorbidity of internalising and externalising problems in individuals.¹⁴

4.1. Strengths and limitations

The strengths of our study were its large sample size, the repeated measures of child problem behaviour throughout early childhood, and the ability to adjust for considerable numbers of covariates. An advantage of using PCA to define dietary patterns is that participants get a score on each of the dietary patterns. This allows for more realistic scenarios in which individuals eat according to a mixture of patterns.

The study also has its limitations. Selective attrition may have influenced our results. Mothers of children not included generally had less favourable dietary habits and socioeconomic circumstances. This selective attrition can only lead to bias if “exposed” children not included in the study had different levels of behavioural problems than exposed children who were included in the study. Next to this, maternal report of child internalising and externalising problems may have introduced information bias. However, for young children, mothers are still primarily the main caregivers and may thus also be the best reporters of their child's behaviour.

A point of critique in using PCA is that the obtained patterns are population-specific. Newby and Tucker have, however, shown in their review that a “Healthy”, “Traditional” and “Sweets” pattern are fairly reproducible across populations.³⁰ Furthermore, when using PCA to determine dietary patterns one has to make choices. For example, researchers have to decide on the number of food groups to include in the analysis and the number of factors to extract. However, no single method of dietary pattern analysis is considered the best and PCA is now widely used in nutritional epidemiology. To reduce possible subjectivity, we applied an existing food group classification (EPIC) and used common criteria to select the factors. The amount of variance (21%) explained by the dietary patterns is quite low, but nevertheless comparable to those reported in other studies on dietary patterns.¹⁹ Moreover, we verified our results by re-analysing the association using the Mediterranean Diet Score and found very similar results.

Further, the use of an FFQ to capture dietary intake can be questioned. First, the FFQ we used was originally designed for elderly and has not been validated for use in a pregnant population. However, the dietary patterns we found are comparable to those found in other studies that used an FFQ specifically designed or validated for use in pregnant women.^{31,32} Next, for this particular population, one could question whether nutrient intake comes from natural foods or is provided in large quantities by supplements. Indeed we found the Mediterranean dietary pattern to be associated with supplement use. Nevertheless, we found statistically significant effects of the maternal dietary patterns after adjusting for supplement use. Finally, the use of an FFQ to measure dietary intake limits the possibility of making clear recommendations about the optimal prenatal nutrient intake as a way to favourably contribute to foetal neurodevelopment and further child behavioural development. To that extent, FFQ-data should be combined with more accurate alternatives to measure nutrient intake, such as automated multiple 24-h recalls, food records, dietary biomarker measurements, and doubly labelled water measurements to estimate energy expenditure.³³ However, in large prospective cohort studies, these alternatives are not feasible because of inconvenience and costs. Yet for the purpose of gaining insight in the overall composition of the diet and ranking individuals according to their usual consumption, the FFQ seems to be well suited.³⁴ Signs of diet-disease associations may be detected in FFQ-based studies³³ and, moreover, combined effects may indeed be greater than the sum of individual nutrient effects.²³ This does not imply that studying single nutrients is not important. Rather, dietary pattern analysis is complementary to the analysis of individual nutrients or foods. After dietary patterns analysis, further research into foods actually consumed is needed to unravel nutrient interplay and its effect on foetal development.

4.2. Relevance

The current study presents novel associations between maternal prenatal dietary patterns and child externalising problems. In a multi-causal phenomenon such as development of the brain and behaviour, large effects of nutrition are not expected. Indeed the effect sizes presented here are very small. Nevertheless, each small effect contributes to development and should therefore be considered as an opportunity to improve prenatal conditions in such a way that the foetus can optimally develop. In contrast to, for example, genetic traits and socioeconomic status, nutrition is a factor that is relatively easy to modify for pregnant women. Therefore, the effects of prenatal food consumption and nutrient interplay on child behavioural development should be further explored.

Sources of funding

The general design of the Generation R Study was made possible by financial support from the Erasmus Medical Centre, Rotterdam, the Erasmus University Rotterdam, the Dutch Ministry of Health, Welfare and Sport, and the Netherlands Organization for Health Research and Development (ZonMw). The present study was additionally supported by a grant from ZonMw (grant no.10.000.1003) and a research grant from the European Community's 7th Framework Programme (FP7/2008–2013) under grant agreement 212652 (NUTRIMENTHE project, “The Effect of Diet on the Mental Performance of Children”). The work of HT is supported by a NWO-ZonMW VIDI grant (grant no. 017.106.370).

Statement of Authorship

The authors' responsibilities were as follows—JS-dG and SJR: designed the study and analysed the data; JS-dG, HT, and SJR: wrote the manuscript; RPMS-T, AH, VVWJ, and FCV: provided comments and consultation regarding analyses and the manuscript; and SJR: had primary responsibility for the final content.

Conflict of interest

All authors read and approved the final manuscript. FCV is a contributing author of the Achenbach System of Empirically Based Assessment, from which he receives remuneration. The other authors did not declare any conflicts of interest.

Acknowledgements

The Generation R Study is conducted by the Erasmus Medical Center in close collaboration with the School of Law and the Faculty of Social Sciences at the Erasmus University, Rotterdam, the Municipal Health Service, Rotterdam area, and the Stichting Trombosedienst & Artsenlaboratorium Rijnmond (Star-MDC), Rotterdam. We gratefully acknowledge the contribution of participating mothers, general practitioners, hospitals, midwives, and pharmacies in Rotterdam, The Netherlands.

References

- Barker DJ. Intrauterine programming of adult disease. *Mol Med Today* 1995 Dec; **1**(9):418–23.
- Waterland RA, Michels KB. Epigenetic epidemiology of the developmental origins hypothesis. *Annu Rev Nutr* 2007; **27**:363–88.
- Abu-Saad K, Fraser D. Maternal nutrition and birth outcomes. *Epidemiol Rev* 2010 Apr; **32**(1):5–25.
- Christian P, Stewart CP. Maternal micronutrient deficiency, fetal development, and the risk of chronic disease. *J Nutr* 2010 Mar; **140**(3):437–45.
- Georgieff MK. Nutrition and the developing brain: nutrient priorities and measurement. *Am J Clin Nutr* 2007 Feb; **85**(2):614S–20S.
- Susser E, Hoek HW, Brown A. Neurodevelopmental disorders after prenatal famine: the story of the Dutch Famine Study. *Am J Epidemiol* 1998 Feb 1; **147**(3):213–6.
- Steenweg-de Graaff J, Roza SJ, Steegers EA, Hofman A, Verhulst FC, Jaddoe VW, et al. Maternal folate status in early pregnancy and child emotional and behavioral problems: the Generation R Study. *Am J Clin Nutr* 2012; **95**(6):1413–21.
- McGrath J, Eyles D, Mowry B, Yolken R, Buka S. Low maternal vitamin D as a risk factor for schizophrenia: a pilot study using banked sera. *Schizophr Res* 2003 Sep 1; **63**(1–2):73–8.
- Leung BM, Wiens KP, Kaplan BJ. Does prenatal micronutrient supplementation improve children's mental development? A systematic review. *BMC Pregnancy Childbirth* 2011; **11**:12.
- Hu FB. Dietary pattern analysis: a new direction in nutritional epidemiology. *Curr Opin Lipidol* 2002 Feb; **13**(1):3–9.
- Wiles NJ, Northstone K, Emmett P, Lewis G. 'Junk food' diet and childhood behavioural problems: results from the ALSPAC cohort. *Eur J Clin Nutr* 2009 Apr; **63**(4):491–8.
- Oddy WH, Robinson M, Ambrosini GL, O'Sullivan TA, de Klerk NH, Beilin LJ, et al. The association between dietary patterns and mental health in early adolescence. *Prev Med* 2009 Aug; **49**(1):39–44.
- Northstone K, Joinson C, Emmett P, Ness A, Paus T. Are dietary patterns in childhood associated with IQ at 8 years of age? a population-based cohort study. *J Epidemiol Community Health* 2011 Feb 7.
- Achenbach TM, Rescorla LA. *Manual for the ASEBA preschool forms & profiles*. Burlington, VT: University of Vermont, Research Center for Children, Youth, & Families; 2000.
- Jaddoe VW, van Duijn CM, van der Heijden AJ, Mackenbach JP, Moll HA, Steegers EA, et al. The Generation R Study: design and cohort update 2010. *Eur J Epidemiol* 2010 Nov; **25**(11):823–41.
- Klipstein-Grobusch K, den Breeijen JH, Goldbohm RA, Geleijnse JM, Hofman A, Grobbee DE, et al. Dietary assessment in the elderly: validation of a semi-quantitative food frequency questionnaire. *Eur J Clin Nutr* 1998 Aug; **52**(8):588–96.
- Netherlands Nutrition Centre. *Nevo: Dutch food composition database 2006*. The Hague: Netherlands Nutrition Centre; 2006.
- Slimani N, Fahey M, Welch AA, Wirfalt E, Stripp C, Bergstrom E, et al. Diversity of dietary patterns observed in the European Prospective Investigation into Cancer and Nutrition (EPIC) project. *Public Health Nutr* 2002 Dec; **5**(6B):1311–28.
- Balder HF, Virtanen M, Brants HA, Krogh V, Dixon LB, Tan F, et al. Common and country-specific dietary patterns in four European cohort studies. *J Nutr* 2003 Dec; **133**(12):4246–51.
- Jansen PW, Raat H, Mackenbach JP, Jaddoe VW, Hofman A, van Oort FV, et al. National origin and behavioural problems of toddlers: the role of family risk factors and maternal immigration characteristics. *J Abnorm Child Psychol* 2010 Nov; **38**(8):1151–64.
- Timmermans S, Steegers-Theunissen RP, Vujkovic M, den Breeijen H, Russcher H, Lindemans J, et al. The Mediterranean diet and fetal size parameters: the Generation R Study. *Br J Nutr* 2012 Feb 21; **11**:1–11.
- Trichopoulos A, Orfanos P, Norat T, Bueno-de-Mesquita B, Ocke MC, Peeters PH, et al. Modified Mediterranean diet and survival: EPIC-elderly prospective cohort study. *BMJ* 2005 Apr 30; **330**(7498):991.
- Carmichael SL, Yang W, Feldkamp ML, Munger RG, Siega-Riz AM, Botto LD, et al. National Birth Defects Prevention S. Reduced risks of neural tube defects and orofacial clefts with higher diet quality. *Arch Pediatr Adolesc Med* 2012 Feb; **166**(2):121–6.
- Arnsten AF, Rubia K. Neurobiological circuits regulating attention, cognitive control, motivation, and emotion: disruptions in neurodevelopmental psychiatric disorders. *J Am Acad Child Adolesc Psychiatry* 2012 Apr; **51**(4):356–67.
- Schuchardt JP, Huss M, Stauss-Grabo M, Hahn A. Significance of long-chain polyunsaturated fatty acids (PUFAs) for the development and behaviour of children. *Eur J Pediatr* 2010 Feb; **169**(2):149–64.
- Hadders-Algra M. Prenatal long-chain polyunsaturated fatty acid status: the importance of a balanced intake of docosahexaenoic acid and arachidonic acid. *J Perinat Med* 2008; **36**(2):101–9.
- Wu A, Ying Z, Gomez-Pinilla F. The interplay between oxidative stress and brain-derived neurotrophic factor modulates the outcome of a saturated fat diet on synaptic plasticity and cognition. *Eur J Neurosci* 2004 Apr; **19**(7):1699–707.
- Schlott W, Jones A, Godfrey KM, Phillips DI. Effortful control mediates associations of fetal growth with hyperactivity and behavioural problems in 7- to 9-year-old children. *J Child Psychol Psychiatry* 2008 Nov; **49**(11):1228–36.
- Waylen A, Ford T, Goodman R, Samara M, Wolke D. Can early intake of dietary omega-3 predict childhood externalizing behaviour? *Acta Paediatr* 2009 Nov; **98**(11):1805–8.
- Newby PK, Tucker KL. Empirically derived eating patterns using factor or cluster analysis: a review. *Nutr Rev* 2004 May; **62**(5):177–203.
- Sanchez-Villegas A, Brito N, Doreste-Alonso J, Nissensohn M, Henriquez P, Hermoso M, et al. Methodological aspects of the study of dietary patterns during pregnancy and maternal and infant health outcomes. A systematic review. *Matern Child Nutr* 2010 Oct; **6**(Suppl. 2):100–11.
- Northstone K, Emmett PM, Rogers I. Dietary patterns in pregnancy and associations with nutrient intakes. *Br J Nutr* 2008 Feb; **99**(2):406–15.
- Freedman LS, Schatzkin A, Thiebaut AC, Potischman N, Subar AF, Thompson FE, et al. Abandon neither the food frequency questionnaire nor the dietary fat-breast cancer hypothesis. *Cancer Epidemiol Biomarkers Prev* 2007 Jun; **16**(6):1321–2.
- Thompson FE, Subar AF. Dietary assessment methodology. In: Coulston A, Boushey C, editors. *Nutrition in the prevention and treatment of disease*. 2nd ed. San Diego, CA: Academic Press; 2008.