



Original article

Maternal dietary patterns during pregnancy and offspring cardiometabolic health at age 6 years: The generation R study



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SUMMARY

Background & aims: Maternal nutrition during pregnancy might be important in influencing offspring cardiometabolic health. However, research has focused mostly on specific nutrients or total energy, and possible effects of whole diet are unclear. We aimed to assess the associations between different dietary patterns during pregnancy and offspring cardiometabolic health among 2592 mother–child pairs from Generation R, a prospective population-based cohort study from fetal life onwards in Rotterdam, the Netherlands.

Methods: Maternal diet was assessed in early pregnancy with a food-frequency questionnaire. We identified three *a posteriori*-dietary patterns, namely a 'Vegetable, fish and oil', 'Nuts, soy and high-fiber cereals' and 'Margarine, snacks and sugar'-pattern. An *a priori*-pattern was created based on the 'Dutch Healthy Diet Index'. Cardiometabolic health (pulse wave velocity, blood pressure, insulin, HDL-cholesterol and triglycerides) was measured at the child's age of 6 years.

Results: In the crude models, the 'Vegetable, fish and oil', 'Nuts, soy and high-fiber cereals' and 'Dutch Healthy Diet Index' seemed beneficial, as higher adherence to these patterns was significantly associated with lower blood pressure and lower pulse wave velocity. After adjustment for other socio-demographic and lifestyle factors, most associations disappeared, except for lower pulse wave velocity with the 'Vegetable, fish and oil'-dietary pattern (−0.19 SD (95% CI −0.33; −0.06), highest quartile of adherence vs. lowest quartile). No associations were found between maternal dietary patterns and offspring blood lipids or insulin levels.

Conclusions: Our results suggest that there are no consistent independent associations of maternal dietary patterns with offspring cardiometabolic health at 6 years.

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1. Introduction

Cardiometabolic diseases in adults have been linked to exposures during early life [1]. One of the consequences of malnutrition

during pregnancy is low birth weight, and this may predispose higher risk of cardiometabolic diseases later in life [2,3]. However, the Hungerwinter study showed that maternal malnutrition was associated with offspring health without affecting size at birth [4]. In addition, micronutrient status during pregnancy has been related to cardiometabolic outcomes in the offspring, also independent of child's birth weight [5]. This suggests that total energy intake and fetal growth restriction are not the only pathways in predisposing these children to a higher risk of chronic disease, but that a direct effect of maternal diet might exist [6,7].

Severe energy restriction during pregnancy is suggested to influence offspring health [2]. However, what the optimal diet is during pregnancy for adequate child health is still an unresolved

Abbreviations: BF%, body fat percentage; DHD-index, Dutch healthy diet index; DBP, diastolic blood pressure; DXA, dual-energy X-ray absorptiometry; FFQ, food-frequency questionnaire; HDL-c, HDL cholesterol; ICC, intraclass correlation coefficients; PCA, principal component analysis; PWV, pulse wave velocity; SFA, saturated fat; SD, standard deviation; SDS, standard deviation score; SBP, systolic blood pressure; TFA, transfat.

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question [8]. In addition, human studies on intrauterine exposures and later cardiometabolic health mainly focused on birth weight, and studies on the role of maternal diet are scarce and inconsistent [8,9].

Last decades, research in nutritional epidemiology started focusing on overall diet instead of individual nutrients or foods, to take the interactions within diet into account [10,11]. Furthermore, studies based on dietary patterns are helpful in translating results from nutritional epidemiology to food-based dietary guidelines [12].

A priori-dietary patterns are usually defined based on dietary guidelines and expert advice, and thus generally reflect a diet that is related to health outcomes [10]. *A posteriori*-dietary patterns are data-driven and thus reflect actual dietary patterns within specific study populations. We examined the associations of different types of *a posteriori* and *a priori*-defined dietary patterns during pregnancy with cardiometabolic health in offspring at the age of 6 years.

2. Materials and methods

2.1. Design

The present study was embedded within the Generation R Study, a population-based cohort study from fetal life onwards that has been previously described in detail [13]. The study was conducted following the World Medical Association Declaration of Helsinki and was approved by the Medical Ethics Committee at Erasmus University Medical Center. Written consent was obtained from all participants.

2.2. Population

A flowchart of the selection process of the study population is shown in Fig. 1. Since cultural differences could influence dietary patterns and the food-frequency questionnaire (FFQ) was designed for a Dutch population, we included only mothers of Dutch national origin. Dietary patterns were determined in the 3479 mothers with dietary data available and a singleton live birth. At the child's age of 6 years, 2689 children visited the research center. Since not all children had all measurements done, population for analysis ranged from 1710 to 2548 (Fig. 1).

2.3. Dietary assessment

Diet in early pregnancy (median 13.4 weeks of gestation, 95%-range 9.9–22.8) was assessed with an adapted version of the semi-quantitative 170-item FFQ from Klipstein-Grobusch et al. [14]. In addition, for the purpose of this study, the FFQ was complemented with additional food items and the final FFQ consisted of 293 food items. This FFQ was validated with three 24 h-recalls in a group of Dutch pregnant women in Rotterdam ($n = 71$), who were visiting the community midwife practices. The intraclass correlation coefficients (ICCs) for energy-adjusted macronutrient intake were between 0.48 and 0.68 (unpublished data).

2.4. *A priori*-dietary patterns

An *a priori*-dietary pattern was defined based on the previously constructed 'Dutch Healthy Diet Index' (DHD-index) developed by van Lee et al. [15]. The DHD-index comprises of ten components: physical activity, vegetable, fruit, dietary fiber, fish, saturated fat (SFA), trans-fat (TFA), consumption occasions with acidic drinks and foods sodium and alcohol, which represent the 2006 Dutch dietary guidelines [16]. For the purpose of this study, we omitted the components 'physical activity', 'consumption of acidic drinks

and foods' and 'TFA' since this data was not collected during pregnancy.

We also excluded the alcohol component, because women who consume one unit of alcohol per day would still receive the maximum score for the DHD-index, while during pregnancy any alcohol consumption is discouraged because of the known adverse effects on the fetus [17].

The scores for the remaining six DHD-index components ranged between 0 and 10 points, resulting in a total summed score ranging between 0 and 60 points. Higher scores correspond to a higher level of adherence to the Dutch dietary guidelines and therefore a healthier diet.

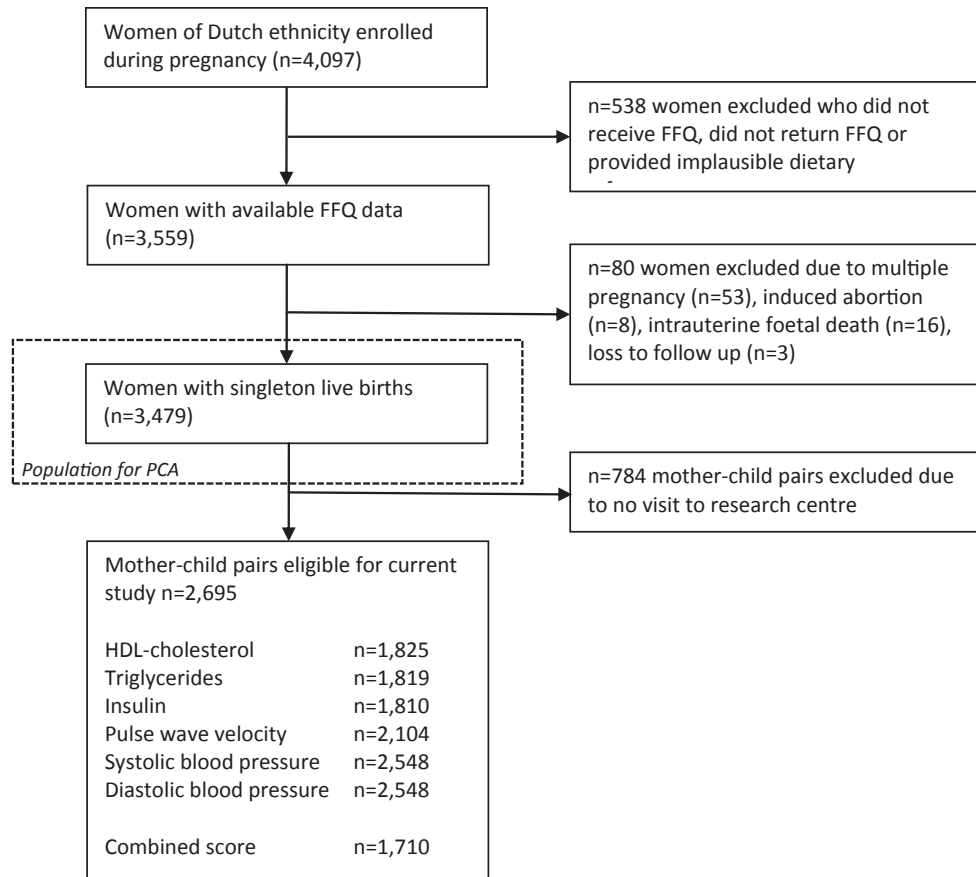
2.5. *A posteriori*-dietary patterns

Principal Component Analysis (PCA) [11] was used in order to determine *a posteriori*-dietary patterns. First, the 293 individual food items were reduced to 23 food groups (Table 1). This division was based on the Dutch National Food Consumption Survey classification [18], but some adjustments towards this division have been made in order to better capture specific nutrients (e.g. dividing cereals into low and high-fiber cereals). All factors (i.e. dietary patterns) with an eigenvalue of ≥ 1.5 were extracted. To improve interpretation of the dietary patterns, the Varimax rotation was used [19]. Subsequently, a factor loading was calculated for each single food group, which illustrates the extent to which each food group is correlated with the specific dietary pattern. The three highest factor loadings per dietary pattern were used to label the dietary pattern (Table 1). For each mother, regression-based scores were extracted and used as adherence scores for these dietary patterns. Subsequently, the adherence scores of the population for analysis ($n = 2695$) were categorized into quartiles.

2.6. Cardiometabolic risk factors

At age 6 years, all children were invited to our dedicated research facility at the Sophia's Children Hospital. While the children were lying, systolic and diastolic blood pressure (SBP and DBP) were measured at the right brachial artery for four times with one-minute intervals, using the validated automatic phycnomonometer Datascope Accutor Plus TM (Paramus, NJ, USA). Mean SBP and DBP were calculated, with exclusion of the first measurement. Carotid-femoral pulse wave velocity (PWV) was assessed using the automatic Complior SP device (Complior; Artech Medical, Pantin, France) with participants in supine position. Non-fasting blood samples were drawn by antecubital venipuncture. Insulin, HDL cholesterol (HDL-c), and triglyceride concentrations were measured with enzymatic methods (using a Cobas 8000 analyzer, Roche, Almere, The Netherlands). Quality control samples demonstrated intra-assay and inter-assay coefficients of variation ranging from 0.69 to 1.57%. Body fat was measured by Dual-energy X-ray absorptiometry (DXA) scans (iDXA; General Electric, 2008, Madison, WI, USA). Percentage body fat (BF%) was calculated as $100\% \times [\text{total body fat mass (g)}] / [\text{total body mass (fat mass + lean mass + bone mass)} (g)]$. Body fat percentage was analyzed as part of a separate study focused on body composition, and is therefore not presented. Age- and sex-specific SD scores were created for all outcomes based on the total Generation R population with available measurements. Insulin was not normally distributed and was therefore transformed with square root transformation before standardizing.

In addition to the individual cardiometabolic outcomes, we calculated a continuous cardiometabolic risk factor score. Following examples of previously defined metabolic syndrome scores for children [20], we included BF%, blood pressure (including DBP and



FFQ: food-frequency questionnaire

PCA: principal component analysis

Fig. 1. Population for analysis.

SBP), and serum levels of HDL-c, triglycerides, and insulin. We summed the age- and gender-specific SD-scores of these five variables, as proposed previously for pediatric populations [20]. Hence, the cardiometabolic risk factor score was calculated as: $\text{SDS BF\%} + 0.5 \cdot \text{SDS SBP} + 0.5 \cdot \text{SDS DBP} + \text{SDS triglycerides} + (-1 \cdot \text{SDS HDL-c}) + \text{SDS insulin}$.

2.7. Covariates

Information regarding paternal age, maternal age, pre-pregnancy BMI (self-reported pre-pregnancy weight divided by height measured at intake (squared)), education (low vs. high), family income (<2200 vs. >2200 euro per month), parity (nulliparous vs. multiparous), maternal smoking and alcohol during pregnancy (never, until pregnancy was known, or continued throughout pregnancy), folic acid supplementation (never, started during first 10 weeks, or started periconceptional) and stress during pregnancy (Global Severity Index) was obtained from prenatal questionnaires sent in different trimesters. Information regarding breastfeeding of the child (never, partially breastfed in the first 4 months, or exclusively breastfed for 4 months) was collected by a combination of delivery reports and postnatal questionnaires. Other postnatal questionnaires included information on watching television (hours/day) at 2 years and participation in sports (yes/

no) at 6 years. Diet at 1 year was assessed with an FFQ and a diet quality score was created [21].

2.8. Statistical analyses

The dietary patterns were analyzed categorically (in quartiles) as well as linearly (per SD score). All associations were first assessed in a crude model. Additionally, potential confounders were entered individually into a linear regression model of dietary patterns and the cardiometabolic risk factor score, and were included in all models when they induced a change in effect estimate of at least 5% for any dietary pattern. Hence, the same multivariable models were used for all exposures and outcomes.

To prevent bias due to missing data, we used multiple imputation [22] to replace missing values on covariates. Analyses were performed in each of the 10 imputed data sets separately, and final results were pooled.

We performed several sensitivity analyses. We repeated the analysis excluding mothers with pre-pregnancy comorbidities (hyperlipidemia, type 2 diabetes or hypertension) ($n = 48$), and mothers who vomited daily or a few days per week ($n = 321$), as this might alter the effect of maternal diet. Furthermore, additional adjustment was performed for maternal pregnancy complications (gestational diabetes, pregnancy-induced-

Table 1

Factor loadings of food groups in dietary patterns of the women during pregnancy (n = 3479).

Food group	Vegetables, fish & oil	Nuts, soy & high-fiber cereals	Margarine, snacks & sugar
Potatoes and other tubers	0.05	−0.53	0.21
Vegetables	0.78*	0.17	−0.03
Fruits	0.13	0.37	0.02
High-fat dairy	0.26	−0.26	0.29
Low-fat dairy	−0.15	0.29	0.16
High-fiber cereals	0.24	0.43*	0.36
Low-fiber cereals	0.23	−0.16	0.25
Meat	0.09	−0.54	0.33
Fish and shellfish	0.45*	0.24	−0.11
Eggs	0.27	0.05	0.19
Vegetable oils	0.74*	0.08	−0.12
Margarine and butter	−0.06	−0.03	0.62*
Sugar and confections	−0.11	0.13	0.56*
Snacks	0.05	0.08	0.40*
Coffee and tea	0.28	0.35	0.10
Sugar-containing beverages	−0.14	−0.28	0.29
Light drinks and water	0.13	0.28	−0.02
Alcoholic beverages	0.35	−0.00	−0.04
Condiments and sauces	0.05	−0.09	0.39
Soups and bouillon	0.20	−0.02	0.15
Nuts, seeds and olives	0.03	0.64*	0.30
Soy products	0.00	0.39*	−0.10
Legumes	0.44	−0.02	0.07
Explained % of variance	10.9%	8.0%	6.9%

Food groups with bold numbers are considered to have a strong association (factor loading ≥ 0.2 or ≤ -0.2) with a dietary pattern. The three highest positive factor loadings per dietary pattern are shown with an asterisk (*) and are used to label the pattern. The three dietary patterns together explained 25.8% of the total variance in maternal dietary intake.

hypertension, pre-eclampsia), maternal total energy intake and child weight at age 6 years, as they could be possible intermediates in the relationship between maternal diet and offspring cardiometabolic health. Also, we additionally adjusted for child diet quality at age 1 year in the subgroup in which child diet was assessed (n = 1591). Additional analyses were also performed with the *a priori*-Dutch Healthy Diet Index'-dietary pattern including the component of alcohol intake.

We tested for possible interactions between dietary patterns and maternal pre-pregnancy BMI, child birth weight-for-gestational-age and child gender by adding an interaction term to the multivariable model, because we considered these variables as potential effect modifiers. To avoid chance findings (type I errors) due to multiple testing, we corrected all p-values for the number of independent tests (i.e. number of dietary patterns). Thus, we used a p-value of $0.05/4 = 0.0125$ as significance level. All statistical analyses were performed using SPSS Statistics 21.0.

3. Results

Table 2 shows the characteristics of the study population. Mothers were on average 31.7 years old (SD 4.2) at enrollment, and most mothers were nulliparous (61.9%). Most mothers used folic acid supplements (57.8% periconceptional, 33.1% started in first weeks) and 75.9% never smoked during pregnancy, but 51.8% of the mothers continued alcohol drinking during pregnancy. Mothers who were not included in the analysis were on average lower educated, had a lower income, more often smoked during pregnancy, but less often consumed alcohol during pregnancy (Online Supplementary Material).

A posteriori-dietary patterns were a 'Vegetable, fish and oil'-dietary pattern, a 'Nuts, soy and high-fiber cereals'-dietary pattern and a 'Margarine, snacks and sugar'-dietary pattern (Table 1). Mean score on the *a priori*-Dutch Healthy Diet Index'-dietary pattern was 31.8 (SD 7.7), on a theoretical scale from 0 to 60. None of the mothers received the maximum score.

Table 2Characteristics of the participants (n = 2695).^a

Maternal characteristics	
Age (years)	31.7 ± 4.2
Pre-pregnancy BMI (kg/m ²)	23.3 ± 3.9
Gestational age at enrollment (weeks)	13.4 (9.9; 22.8)
Education level	
Primary or secondary	1019 (37.8%)
Higher	1640 (61.7%)
Missing	36 (1.3%)
Household income	
<2200 €/month	591 (23.8%)
>2200 €/month	1893 (76.2%)
Missing	211 (7.8%)
Parity	
0	1665 (61.9%)
≥1	1026 (38.1%)
Missing	4 (0.1%)
Smoking	
Never during pregnancy	1886 (75.9%)
Until pregnancy was known	236 (9.5%)
Continued during pregnancy	363 (14.6%)
Missing	210 (7.8%)
Alcohol	
Never during pregnancy	776 (28.8%)
Until pregnancy was known	413 (15.3%)
Continued during pregnancy	1278 (51.8%)
Missing	228 (8.5%)
Folic acid supplement use	
No	203 (9.2%)
Started first 10 weeks	734 (33.1%)
Started periconceptional	1281 (57.8%)
Missing	477 (17.7%)
Total energy intake (kcal/day)	2153 ± 503
Stress during pregnancy	0.12 (0.00; 0.77)
Child characteristics	
Gender (% boys)	1351 (50.1%)
Birth weight (grams)	3503 ± 541
Gestational age at births (weeks)	40.0 ± 1.7

Missing values for continuous variables were 373 (13.8%) for pre-pregnancy BMI, 284 (10.5%) for stress during pregnancy and 3 (0.001%) for birth weight. Abbreviations: BMI, body mass index; FFQ, food-frequency questionnaire; kcal, kilocalories.

^a Values are means ± SD, absolute numbers (valid percentages) or medians (95% range).

Table 3Association of maternal dietary patterns with metabolic outcomes at age 6 years.^a

	HDL-cholesterol n = 1825		Triglycerides n = 1819		Insulin n = 1810	
	Crude	Adjusted	Crude	Adjusted	Crude	Adjusted
'Vegetable, fish and oil'-dietary pattern						
Q1 Low	Reference	Reference	Reference	Reference	Reference	Reference
Q2	0.09 (−0.04; 0.22)	0.05 (−0.08; 0.19)	−0.01 (−0.15; 0.12)	0.02 (−0.12; 0.15)	0.00 (−0.13; 0.13)	−0.02 (−0.15; 0.12)
Q3	0.07 (−0.06; 0.20)	0.02 (−0.12; 0.15)	−0.10 (−0.23; 0.04)	−0.05 (−0.19; 0.09)	0.01 (−0.12; 0.14)	0.02 (−0.11; 0.16)
Q4 High	−0.00 (−0.13; 0.12)	−0.07 (−0.20; 0.07)	−0.07 (−0.20; 0.06)	−0.01 (−0.15; 0.14)	0.04 (−0.09; 0.17)	0.05 (−0.09; 0.19)
Per SD	−0.02 (−0.06; 0.03)	−0.04 (−0.09; 0.01)	−0.02 (−0.06; 0.03)	0.01 (−0.04; 0.06)	0.01 (−0.04; 0.05)	0.01 (−0.04; 0.06)
	p = 0.48	p = 0.09	p = 0.46	p = 0.76	p = 0.76	p = 0.66
'Nuts, soy and high-fiber cereals'-dietary pattern						
Q1 Low	Reference	Reference	Reference	Reference	Reference	Reference
Q2	−0.12 (−0.25; 0.00)	−0.15 (−0.28; −0.02)	0.13 (−0.01; 0.26)	0.15 (0.01; 0.29)	0.17 (0.04; 0.30)	0.15 (0.01; 0.28)
Q3	−0.01 (−0.14; 0.11)	−0.04 (−0.18; 0.09)	0.08 (−0.05; 0.21)	0.10 (−0.04; 0.24)	0.10 (−0.03; 0.23)	0.08 (−0.05; 0.22)
Q4 High	−0.00 (−0.13; 0.12)	−0.02 (−0.16; 0.12)	0.08 (−0.05; 0.21)	0.12 (−0.03; 0.27)	0.08 (−0.05; 0.21)	0.07 (−0.08; 0.21)
Per SD	0.02 (−0.02; 0.07)	0.02 (−0.03; 0.07)	0.03 (−0.02; 0.07)	0.04 (−0.01; 0.10)	0.02 (−0.03; 0.06)	0.01 (−0.04; 0.07)
	p = 0.31	p = 0.37	p = 0.27	p = 0.12	p = 0.48	p = 0.63
'Margarine, snacks and sugar'-dietary pattern						
Q1 Low	Reference	Reference	Reference	Reference	Reference	Reference
Q2	0.07 (−0.06; 0.19)	0.07 (−0.07; 0.21)	−0.12 (−0.25; 0.01)	−0.10 (−0.24; 0.05)	−0.02 (−0.15; 0.11)	−0.01 (−0.15; 0.13)
Q3	0.03 (−0.10; 0.15)	0.04 (−0.13; 0.21)	−0.10 (−0.24; 0.03)	−0.07 (−0.24; 0.11)	−0.05 (−0.18; 0.07)	−0.04 (−0.21; 0.13)
Q4 High	−0.11 (−0.23; 0.02)	−0.09 (−0.31; 0.13)	−0.12 (−0.25; 0.02)	−0.06 (−0.29; 0.17)	0.05 (−0.08; 0.17)	0.07 (−0.15; 0.29)
Per SD	−0.03 (−0.08; 0.01)	0.01 (−0.09; 0.10)	−0.04 (−0.08; 0.01)	−0.01 (−0.11; 0.09)	0.01 (−0.03; 0.06)	0.03 (−0.07; 0.12)
	p = 0.14	p = 0.92	p = 0.13	p = 0.82	p = 0.56	p = 0.60
'Dutch Healthy Diet index'-dietary pattern						
Q1 Low	Reference	Reference	Reference	Reference	Reference	Reference
Q2	0.05 (−0.08; 0.17)	0.04 (−0.09; 0.17)	0.07 (−0.06; 0.20)	0.08 (−0.05; 0.21)	0.04 (−0.09; 0.17)	0.03 (−0.10; 0.16)
Q3	−0.01 (−0.14; 0.11)	−0.02 (−0.15; 0.11)	0.10 (−0.03; 0.23)	0.11 (−0.03; 0.24)	0.09 (−0.04; 0.22)	0.09 (−0.04; 0.23)
Q4 High	−0.01 (−0.14; 0.11)	−0.02 (−0.15; 0.11)	0.05 (−0.08; 0.18)	0.06 (−0.08; 0.19)	0.07 (−0.05; 0.20)	0.08 (−0.06; 0.21)
Per SD	0.01 (−0.04; 0.05)	0.01 (−0.04; 0.05)	0.01 (−0.03; 0.06)	0.01 (−0.04; 0.06)	0.03 (−0.01; 0.08)	0.03 (−0.02; 0.08)
	p = 0.70	p = 0.85	p = 0.62	p = 0.68	p = 0.18	p = 0.19

*p < 0.0125.

Multivariable model: adjusted for maternal age at intake, gestational age at dietary assessment, folic acid use, smoking and alcohol during pregnancy, maternal educational level, family income, parity, maternal pre-pregnancy BMI, maternal stress during pregnancy, child gender, breast feeding, watching television at age 2 years, participation in sports at age 6 years and height at age 6 years.

^a Values are regression coefficients (95% confidence interval) and reflect differences in age-and-gender-specific SD-scores of the outcomes for quartiles 2 to 4, as compared to quartile 1 (lowest adherence to the dietary pattern). The P values represents P values for linear trend tests (per SD increase of maternal adherence to the dietary pattern).

Table 3 shows the associations between maternal dietary patterns and offspring metabolic outcomes. There were no significant associations between any of the *a posteriori*-dietary patterns or the *a priori*-dietary pattern during pregnancy and child HDL-cholesterol, triglyceride levels or insulin levels at age 6 years.

Table 4 shows the associations of maternal dietary patterns with offspring cardiovascular outcomes at age 6. There were no significant associations between any of the *a posteriori*-dietary patterns or the *a priori*-dietary pattern during pregnancy and systolic or diastolic blood pressure of the child at age 6 after adjustment for confounders. Also, the 'Nuts, soy and high-fiber cereals'-dietary pattern and 'Margarine, snacks and sugar'-dietary pattern were not significantly associated with pulse wave velocity of the child. However, a higher adherence score on the *a posteriori*-'Vegetable, fish and oil'-dietary pattern was associated with a lower pulse wave velocity of the child at age 6 (SD −0.19 (95%CI −0.33; −0.06), highest vs. lowest quartile). Also, a higher score for the modified version of the *a priori*-'Dutch Healthy Diet index' was associated with a lower pulse wave velocity of the child, but this was significant only in the third quartile.

Table 5 shows the associations between the different maternal dietary patterns with the combined cardiometabolic risk factor score at age 6. In the crude model, only the third quartile of the *a posteriori*-'Vegetable, fish and oil'-dietary pattern was significantly associated with a lower cardiometabolic risk factor. In the multivariable model, there were no significant associations between any of the *a posteriori*-dietary patterns or the *a priori*-dietary pattern during pregnancy with the cardiometabolic risk factor score in offspring at 6 years of age.

3.1. Additional analyses (data not shown)

Additional analyses for the *a priori*-'Dutch Healthy Diet Index'-dietary pattern including the alcohol component did not change the results. Also, the results did not change after the exclusion of mothers with pre-pregnancy comorbidities or mothers who vomited daily or a few days per week. Furthermore, additional adjustment for maternal pregnancy complications, total energy intake, child diet quality at age 1 year or child weight at age 6 years had no effect on the results.

We observed no significant interactions between any of the dietary patterns and maternal pre-pregnancy BMI, child birth weight for gestational age, or child gender (p-interaction all non-significant).

4. Discussion

In a population-based prospective cohort from fetal life onwards, we observed no consistent associations of dietary patterns (*a posteriori* and *a priori*) with cardiometabolic risk factors individually or combined as a score after adjusting for potential confounders including socio-demographic and lifestyle factors. The highest quartile of adherence on the *a posteriori*-'Vegetable, fish and oil'-dietary pattern, and the third quartile of adherence to the *a priori*-'Dutch Healthy Diet index', were significantly associated with a lower pulse wave velocity of the child at the age of 6 years. We observed no associations between the 'Nuts, soy and high-fiber cereals'- or the 'Margarine, snacks and sugar'-dietary patterns with offspring pulse wave velocity.

Table 4Association of maternal dietary patterns with cardiovascular outcomes at age 6 years.^a

	Pulse wave velocity n = 2104		Systolic BP n = 2548		Diastolic BP n = 2548	
	Crude	Adjusted	Crude	Adjusted	Crude	Adjusted
<i>'Vegetable, fish and oil'-dietary pattern</i>						
Q1 Low	Reference	Reference	Reference	Reference	Reference	Reference
Q2	−0.09 (−0.21; 0.04)	−0.09 (−0.22; 0.04)	−0.04 (−0.15; 0.07)	−0.02 (−0.13; 0.09)	−0.06 (−0.17; 0.05)	−0.02 (−0.14; 0.09)
Q3	−0.10 (−0.23; 0.02)	−0.11 (−0.24; 0.02)	−0.18 (−0.28; −0.07)*	−0.11 (−0.22; 0.01)	−0.15 (−0.26; −0.04)*	−0.09 (−0.20; 0.03)
Q4 High	−0.19 (−0.31; −0.07)*	−0.19 (−0.33; −0.06)*	−0.11 (−0.21; 0.00)	−0.03 (−0.14; 0.09)	−0.13 (−0.24; −0.03)	−0.05 (−0.17; 0.06)
Per SD	−0.05 (−0.10; −0.01)	−0.05 (−0.10; −0.01)	−0.03 (−0.07; 0.01)	0.00 (−0.04; 0.04)	−0.03 (−0.07; 0.01)	0.00 (−0.04; 0.04)
	p = 0.02	p = 0.03	p = 0.13	p = 0.96	p = 0.10	p = 0.98
<i>'Nuts, soy and high-fiber cereals'-dietary pattern</i>						
Q1 Low	Reference	Reference	Reference	Reference	Reference	Reference
Q2	−0.03 (−0.16; 0.10)	−0.01 (−0.15; 0.12)	−0.02 (−0.13; 0.09)	0.01 (−0.10; 0.12)	0.06 (−0.05; 0.17)	0.09 (−0.02; 0.21)
Q3	−0.08 (−0.20; 0.05)	−0.06 (−0.19; 0.08)	−0.04 (−0.15; 0.07)	0.01 (−0.11; 0.12)	0.01 (−0.10; 0.12)	0.06 (−0.06; 0.17)
Q4 High	−0.02 (−0.15; 0.11)	−0.01 (−0.15; 0.13)	−0.13 (−0.24; −0.02)	−0.08 (−0.20; 0.04)	−0.04 (−0.15; 0.07)	0.01 (−0.11; 0.13)
Per SD	−0.02 (−0.07; 0.02)	−0.02 (−0.07; 0.03)	−0.05 (−0.09; −0.01)	−0.03 (−0.07; 0.01)	−0.02 (−0.05; 0.02)	0.00 (−0.04; 0.05)
	p = 0.34	p = 0.37	p = 0.01	p = 0.14	p = 0.43	p = 0.96
<i>'Margarine, snacks and sugar'-dietary pattern</i>						
Q1 Low	Reference	Reference	Reference	Reference	Reference	Reference
Q2	−0.08 (−0.21; 0.04)	−0.10 (−0.24; 0.04)	−0.05 (−0.15; 0.06)	−0.03 (−0.15; 0.09)	−0.01 (−0.12; 0.09)	−0.01 (−0.13; 0.11)
Q3	0.07 (−0.05; 0.19)	0.03 (−0.14; 0.19)	0.03 (−0.08; 0.13)	0.03 (−0.12; 0.17)	0.02 (−0.09; 0.13)	0.01 (−0.14; 0.15)
Q4 High	−0.01 (−0.13; 0.12)	−0.08 (−0.30; 0.14)	−0.01 (−0.12; 0.10)	0.01 (−0.18; 0.19)	−0.02 (−0.13; 0.09)	−0.04 (−0.23; 0.15)
Per SD	0.02 (−0.02; 0.07)	0.02 (−0.08; 0.11)	0.01 (−0.03; 0.04)	0.01 (−0.07; 0.09)	−0.00 (−0.04; 0.04)	−0.01 (−0.10; 0.07)
	p = 0.31	p = 0.71	p = 0.78	p = 0.75	p = 0.86	p = 0.73
<i>'Dutch Healthy Diet index'-dietary pattern</i>						
Q1 Low	Reference	Reference	Reference	Reference	Reference	Reference
Q2	−0.01 (−0.13; 0.12)	−0.01 (−0.14; 0.11)	−0.10 (−0.21; −0.01)	−0.08 (−0.19; 0.03)	−0.05 (−0.15; 0.06)	−0.03 (−0.14; 0.08)
Q3	−0.17 (−0.29; −0.05)*	−0.18 (−0.30; −0.05)*	−0.11 (−0.20; 0.01)	−0.06 (−0.16; 0.05)	−0.03 (−0.14; 0.08)	0.01 (−0.10; 0.12)
Q4 High	−0.09 (−0.21; 0.04)	−0.09 (−0.22; 0.04)	−0.04 (−0.15; 0.06)	−0.01 (−0.12; 0.10)	0.03 (−0.08; 0.14)	0.06 (−0.05; 0.17)
Per SD	−0.05 (−0.10; −0.01)	0.05 (−0.10; −0.01)	−0.02 (−0.05; 0.02)	0.00 (−0.04; 0.04)	0.01 (−0.03; 0.05)	0.02 (−0.02; 0.06)
	p = 0.02	p = 0.03	p = 0.45	p = 0.99	p = 0.60	p = 0.23

p < 0.0125.

Multivariable model: adjusted for maternal age at intake, gestational age at dietary assessment, folic acid use, smoking and alcohol during pregnancy, maternal educational level, family income, parity, maternal pre-pregnancy BMI, maternal stress during pregnancy, child gender, breast feeding, watching television at age 2 years, participation in sports at age 6 years and height at age 6 years. Abbreviation: BP, blood pressure.

^a Values are regression coefficients (95% confidence interval) and reflect differences in age-and-gender-specific SD-scores of the outcomes for quartiles 2 to 4, as compared to quartile 1 (lowest adherence to the dietary pattern). The P values represents P values for linear trend tests (per SD increase of maternal adherence to the dietary pattern).

Based on the developmental origins of health and disease hypothesis [23], it could be expected that diet during pregnancy can have a long-term effect on the offspring's cardiometabolic profile, such as blood pressure, lipid profile and insulin sensitivity. Our results do not demonstrate this potential effect at an early age (6 years). Perhaps the effect could occur at a later age, however the age of our population does not permit us to evaluate these effects in subsequent age periods.

Previous research on the effects of maternal nutrition on offspring cardiometabolic health focused mostly on total energy, macronutrients, or micronutrients, and literature on overall diet is lacking. Studies on maternal diet often use birth weight as a marker of infant health [3]. However, observations from the Dutch famine have shown that malnutrition during pregnancy could affect offspring cardiometabolic health at middle-age, without influencing birth weight [24]. Furthermore, many studies used indirect measures of nutritional status, such as anthropometric measurements [25]. However, nutritional status is much more complex and much remains unknown about optimal diet during pregnancy for child health [9]. Thus, studies on the effects of overall maternal diet on cardiometabolic health in offspring are necessary.

The only significant relationship that we observed was on pulse wave velocity. Higher adherence to the *a posteriori*-'Vegetable, fish and oil'-dietary pattern during pregnancy was associated with a lower pulse wave velocity in the offspring. The third quartile of *a priori*-'Dutch Healthy Diet index' was also significantly associated with a lower pulse wave velocity, while the highest quartile was not. This may be a chance finding, but it may also suggest that there is not a linear dose-response relationship. However, the association of the 'Vegetable, fish and oil'-dietary pattern with lower pulse

wave velocity was significant in the highest quartile of adherence, and results from this pattern may indicate that a dose-response relationship does exist. Although statistically significant, it is not known whether this effect will also be clinically significant. Pulse wave velocity is a measure arterial stiffness, and a large meta-analysis in adults has shown that participants with a high pulse wave velocity had a higher risk for cardiovascular events [26]. As there are indications that the atherosclerotic process begins much earlier in life, lower pulse wave velocity in children is thus suggested to be beneficial for long-term cardiometabolic health, but this has not yet been demonstrated in this age-group.

Nevertheless, we did not observe consistent associations with other cardiometabolic outcomes, or the combined cardiometabolic risk factor score. The lack of consistent associations between maternal dietary patterns and cardiometabolic health in our study can be explained in several ways.

First, the original hypothesis on the effects of maternal nutrition on child health is based on studies that observed extreme malnourishment [2,24], and many of the studies that found associations between maternal diet and infant outcomes were done in nutritionally at-risk populations [8]. Studying extremes might make it easier to detect associations, but it could also be that the associations only exist in extreme undernutrition or overnutrition. Our population has a selection towards a healthy population of pregnant women and perhaps the effect of maternal dietary patterns on offspring cardiometabolic health is just not relevant in our population. Also, the suggested relation between maternal diet and offspring health came to the attention because increased incidence of cardiometabolic diseases. Cardiometabolic diseases occur late in life, and it might be that the variation in outcome in children is too

Table 5

Association of maternal dietary patterns with cardiometabolic risk factor score at age 6 years.^a

Cardiometabolic risk factor score n = 1710		
	Crude	Adjusted
<i>'Vegetable, fish and oil'- dietary pattern</i>		
Q1 Low	Reference	Reference
Q2	−0.13 (−0.26; 0.00)	−0.06 (−0.19; 0.08)
Q3	−0.21 (−0.34; −0.08)*	−0.08 (−0.22; 0.05)
Q4 High	−0.16 (−0.29; −0.03)	−0.01 (−0.15; 0.13)
Per SD	−0.04 (−0.08; 0.01) <i>p</i> = 0.11	0.19 (−0.03; 0.07) <i>p</i> = 0.45
<i>'Nuts, soy and high-fiber cereals'- dietary pattern</i>		
Q1 Low	Reference	Reference
Q2	0.11 (−0.03; 0.24)	0.17 (0.03; 0.30)
Q3	0.03 (−0.11; 0.16)	0.11 (−0.03; 0.25)
Q4 High	−0.04 (0.17; 0.09)	0.08 (−0.07; 0.22)
Per SD	−0.03 (−0.08; 0.02) <i>p</i> = 0.22	0.11 (−0.04; 0.06) <i>p</i> = 0.68
<i>'Margarine, snacks and sugar'- dietary pattern</i>		
Q1 Low	Reference	Reference
Q2	−0.09 (−0.22; 0.04)	−0.03 (−0.17; 0.11)
Q3	−0.08 (−0.21; 0.05)	0.00 (−0.17; 0.17)
Q4 High	−0.00 (−0.13; 0.13)	0.12 (−0.10; 0.35)
Per SD	0.00 (−0.05; 0.05) <i>p</i> = 0.98	0.05 (−0.04; 0.15) <i>p</i> = 0.27
<i>'Dutch Healthy Diet index'- dietary pattern</i>		
Q1 Low	Reference	Reference
Q2	0.01 (−0.12; 0.15)	0.05 (−0.08; 0.18)
Q3	−0.01 (−0.13; 0.13)	0.06 (−0.07; 0.19)
Q4 High	0.02 (−0.11; 0.15)	0.08 (−0.05; 0.21)
Per SD	−0.01 (−0.06; 0.04) <i>p</i> = 0.70	0.13 (−0.03; 0.06) <i>p</i> = 0.58

**p* < 0.0125.

Multivariable model: adjusted for maternal age at intake, gestational age at dietary assessment, folic acid use, smoking and alcohol during pregnancy, maternal educational level, family income, parity, maternal pre-pregnancy BMI, maternal stress during pregnancy, child gender, breast feeding, watching television at age 2 years, participation in sports at age 6 years and height at age 6 years.

^a Values are regression coefficients (95% confidence interval) and reflect differences in age-and-gender-specific SD-scores of the outcomes for quartiles 2 to 4, as compared to quartile 1 (lowest adherence to the dietary pattern). The *P* values represents *P* values for linear trend tests (per SD increase of maternal adherence to the dietary pattern).

small and all within a range of healthy. While currently we found no effect, it could be that effects become visible when children are older and outcomes are more deviated towards cardiometabolic risk. In addition, it may be argued that the outcome measures used in adults are not sensitive enough to assess cardiometabolic risk early in life.

Second, if epigenetic mechanisms may influence cardiometabolic health, it may be the case that dietary effects are mainly caused by for specific dietary components influencing gene expression or DNA methylation. For example, epigenetic effects have been described for methyl-donor nutrients, iron, zinc and flavonoids [7]. Although dietary patterns analyses can be useful for creating food-based dietary guidelines [12], the downside of studying dietary patterns may be that effects of specific nutrients influencing epigenetic mechanisms may be diluted [11]. If associations between maternal diet and child cardiometabolic health are fully driven by certain nutrients, analyses using dietary patterns might not detect these effects, which might explain why we did not find clear associations.

We studied both *a priori*- and *a posteriori*-dietary patterns during pregnancy. *A posteriori*-patterns are not hypothesis-driven but data-driven, but the hypothesis is important when defining food groups [11]. If food groups are too heterogeneous or contain food products with opposite effects on health, they may not be useful in predicting disease risk. Therefore, we created the food groups based on a possible relation with the outcome, for example we separated high fat dairy products from

low fat dairy products, and separated cereals based on their fiber content. However, we were restricted by the design of the FFQ and were therefore for example not able to separate vegetables based on their folate content, which would have been interesting in light of the previously mentioned epigenetic programming effects [7].

A priori-dietary patterns are hypothesis-oriented and the food groups should be correctly chosen for that purpose [27]. The Dutch Healthy Diet index was developed based on Dutch guidelines [15], which we slightly modified based on our available data and for the use during pregnancy. Although we removed the alcohol component from the score because of known adverse effects of alcohol on the fetus, the *a priori*-dietary pattern was mostly developed based on hypothesized effects for health of the mother herself, and not for fetal health. Nevertheless, to our knowledge, there are currently no dietary indexes for the use during pregnancy that are designed based on offspring health outcomes.

Dietary patterns can capture the totality of diet but also overall lifestyle, since dietary patterns cluster with other lifestyle behaviors as well [28]. Nevertheless, it is important to take socio-demographic and lifestyle factors into account that can confound the relation between maternal diet and child cardiometabolic health, including also vitamin supplementation [27]. We had detailed information about periconceptional folic acid supplement use and many other possible confounders, and we observed that adjustment for these factors had large effects on our results for diastolic and systolic blood pressure, but only a little effect on the association with pulse wave velocity. Nevertheless, a limitation may be that residual confounding might still be present due to lack of information on potential confounding factors, such as physical activity and sedentary behavior during pregnancy.

We used a self-administered FFQ to measure diet during pregnancy, which is considered an appropriate method to assess average dietary intake over an extended period of time in epidemiological studies [29]. However, as a consequence of self-reported dietary intake, measurement error might exist. Although the ICCs for nutrients were similar to other studies [30], previous studies on nutrient intake have suggested that this may lead to an underestimation of the true relation between diet and health outcomes [31]. Nonetheless, the latter may not be applicable to dietary pattern analysis since this does not include absolute intake of nutrients or foods but underlying patterns of food intake. Unfortunately, we were not able to validate our dietary patterns in this population but several studies have shown that dietary pattern analysis using PCA can be a valid and reproducible method [32–35].

In conclusion, low birth weight or severe maternal malnutrition has been related to cardiometabolic diseases in later life [3,24], but the effects of overall dietary patterns during pregnancy with offspring health outcomes are unknown. In our population-based prospective cohort study, we examined the associations of different *a priori*- and *a posteriori*-dietary patterns during pregnancy with offspring cardiometabolic health. We found no independent associations between different maternal dietary patterns during pregnancy with blood lipids, blood pressure or insulin in offspring, but higher adherence to an *a posteriori*-'Vegetable, fish and oils'-dietary pattern was associated with lower pulse wave velocity at offspring age 6. Further studies are needed to enable recommendations for maternal dietary patterns that are optimal for child cardiometabolic health.

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Conflict of interest

The authors declare that they have no conflicts of interest.

Statement of authorship

ETML, JCKdJ designed the research project. OHF and VVVJ provided consultation. ETML, MJT, MvdB performed the analyses. ETML wrote the manuscript. All authors contributed to interpretation of the results, and edited the manuscript. All significant contributors to this manuscript are included as co-author, the authors approved the final manuscript as submitted. The manuscript represents original work, has currently not been published, simultaneously submitted, or already accepted for publication elsewhere.

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Appendix A. Supplementary data

Supplementary data related to this article can be found at <http://dx.doi.org/10.1016/j.clnu.2015.12.017>.

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