Diet and physical activity in pregnancy and offspring’s cardiovascular health: a systematic review

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Abstract

There is increasing evidence linking maternal diet and physical activity before and during pregnancy with offspring’s cardiovascular health. Although many studies examined this association, the evidence has not been reviewed systematically. We therefore undertook a systematic review to synthesize evidence examining the association of maternal diet and physical activity before and during pregnancy with offspring’s blood pressure and vascular health. We systematically searched the databases MEDLINE and EMBASE from inception to June 30, 2017. Eligibility screening, data extraction and quality assessment were performed by two independent reviewers. A total of 19 articles were included comprising three randomized controlled trials and 16 observational studies. Of the studies that examined the association of interest, 60% (three out of five studies) showed that high maternal carbohydrate intake was associated with higher offspring’s blood pressure. Maternal protein intake during pregnancy was negatively associated with offspring carotid intima-media thickness in two out of two studies. No consistent findings for maternal fatty acid intake were found. There were too few studies to draw conclusions on energy intake, fibre intake, protein/carbohydrate ratio, specific foods, dietary patterns and maternal physical activity. Heterogeneity in exposure and outcome assessment hampered pooling. Also, owing to the observational nature of most studies, causality cannot be established. Harmonization of valid exposure and outcome measurements, and the development of core outcome sets are needed to enable more robust conclusions.

Introduction

Cardiovascular diseases are the number one cause of death globally.1 Although these diseases manifest in adulthood, there is a large body of evidence to suggest that these diseases originate in early life.2–4 It is thought that adaptations of the developing fetus to its environment may increase susceptibility to disease in later life.5–8 Maternal lifestyle preceding and during pregnancy is an important contributor to early-life programming of the offspring. Inadequate maternal nutrition during pregnancy increases the risks of cardiovascular diseases.9,10 Several studies have shown that the balance of macronutrients in the maternal diet during pregnancy is associated with offspring’s blood pressure decades later.9,11,12

Additionally, maternal exercise seems protective against the development of cardiovascular diseases in the offspring. Offspring of exercising pregnant women appear to have a lower resting heart rate, higher heart rate variability and improved vascular health.13 However, there is a lack of knowledge regarding the type and amount of exercise needed to favourably program cardiovascular health of the offspring.

Although many studies examined the association between maternal dietary intake and physical activity in pregnancy and cardiovascular health of the offspring, the evidence has not been reviewed systematically. Therefore, we systematically reviewed all currently available evidence on the association of dietary intake and physical activity of women before and during pregnancy with offspring’s blood pressure and vascular health. Secondary objectives were to study the potential...
modifying role of period of gestation, offspring’s sex and pre-pregnancy body mass index (BMI) of the mother.

**Methods**

This systematic review was reported according to the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) statement. The review protocol was registered in the prospective register of systematic reviews (PROSPERO; systematic review record CRD42015020244). The PICOS criteria, used to define the research question and to select the studies, are presented in Table 1. This paper is part of a broader systematic review project regarding the association between maternal lifestyle before and during pregnancy and offspring’s cardiometabolic health. In the current paper, we focussed on the cardiovascular outcomes as described in the outcome section of Table 1. A future paper will focus on the anthropometric and metabolic outcomes.

**Data sources and search strategy**

A clinical librarian (J.L.) performed a systematic search in OVID MEDLINE (including Epub ahead of print, in-process and other non-indexed citations) and OVID EMBASE from inception to June 30, 2017 to identify observational and experimental human studies on (pre)pregnancy maternal diet and physical activity and cardiometabolic health in the offspring. We searched for the concepts ‘maternal’, ‘dietary intake’ or ‘physical activity’, ‘(pre-)pregnancy’ and ‘offspring/child’, using a wide variety of controlled terms, including MESH and text words. We did not search for specific outcomes as this would increase the risk of missing studies, but combined the search with a broad search filter for observational and experimental human studies. In addition, we applied a systematic review filter to check the existence of systematic reviews. No date or language restrictions were applied. We cross-checked the reference lists and the citing articles of the identified relevant papers in Web of Science and adapted the search in case of additional relevant studies. The bibliographic records retrieved were imported and de-duplicated in ENDNOTE. The complete search strategies are presented in Supplementary Table S1.

**Study selection**

The studies were independently screened by two reviewers (T.v.E. and M.K.) using the online screening and data extraction tool

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**Table 1. Description of the PICOS criteria used for the selection of studies**

| Criteria                         | Description                                                                 |
|----------------------------------|-----------------------------------------------------------------------------|
| Participants                     | **Inclusion:** Pregnant women or women planning to conceive, irrespective of BMI category or having pregnancy complications |
|                                  | **Exclusion:** Studies solely among participants with a pre-existing chronic condition or studies solely among participants treated with medication for overweight-related health problems. |
| Intervention/exposure            | **Inclusion:** Maternal diet and/or physical activity is self-reported or objectively measured before or during pregnancy, once or multiple times.  
Maternal dietary intake is assessed as: 
Macronutrient intake in grams: carbohydrates, protein, fatty acids;  
Compliance to country-specific recommended daily intakes as communicated to the national population by health organisations; 
Diet scores/indices of diet quality;  
Consumption of food products (e.g., fruit intake, vegetable intake) mentioned in grams or standard portions.  
Maternal physical activity is assessed as total physical activity or as physical activity in at least one of the four physical activity domains (work, transport, domestic tasks and leisure time): Hours/minutes spent on activities combined with the type of activity or intensity [low, moderate, vigorous or metabolic equivalent (MET)];  
Meeting or not meeting the country-specific physical activity guidelines |
|                                  | **Exclusion:** Studies solely focussed on determinants of healthy lifestyle or determinants associated with a successful implementation of a healthy lifestyle. Studies examining the effects of maternal undernutrition or the effects of maternal macronutrient and/or micronutrient supplementation on offspring’s health |
| Comparison                       | **Inclusion:** Not applicable in observational studies. For intervention studies, lower or higher levels of maternal dietary intake before/during pregnancy (e.g., lower fruit intake, higher fat intake), or lower physical activity exposure before/during pregnancy |
|                                  | **Exclusion:** Not applicable in observational studies. Intervention studies solely comparing an intervention group with a control group, without reporting quantitatively measured exposures as described earlier |
| Outcome                          | **Inclusion:** The following health outcomes are assessed in the offspring up to the age of 25 years:  
Cardiovascular outcomes: all outcomes related to micro- and macro circulation (e.g., blood pressure, heart rate, arterial stiffness, atherosclerosis) and cardiorespiratory fitness (e.g., endurance fitness test, VO2 max);  
Outcomes reported in a future systematic review:  
Anthropometric outcomes: weight, height, BMI, waist circumference, hip circumference, waist/hip ratio, outcomes related to body composition (e.g., body fat percentage, lean body mass, fat free mass);  
Metabolic outcomes: insulin sensitivity, lipid profiles (cholesterol and subfractions, triglyceride), adipokines, endothelial biomarkers, metabolic syndrome |
|                                  | **Exclusion:** Studies solely focussing on fetal or birth outcomes and studies solely including children with birth complications (e.g., low birth weight, premature birth) |
| Study design                     | **Inclusion:** Prospective observational or experimental studies |
|                                  | **Exclusion:** Letters, editorials, commentaries and animal studies |
Covidence (www.covidence.org). Studies were eligible for full-text screening if they met the inclusion criteria as described in Table 1. Full-text articles were independently read by the same reviewers (T.v.E. and M.K.) and inter-reviewer discrepancies were resolved by discussion with a third person (M.v.P., A.G. or R.G.).

Data extraction and quality assessment

The categories used for data extraction can be found in Supplementary Table S2. Data were initially extracted by the first reviewer (T.v.E.), subsequently the second reviewer (M.K.) independently extracted data for 20% of the included articles (n = 10 out of 48 articles; inter-reviewer discrepancy rate = 3.98%).

The quality of the included randomized controlled trials (RCTs) was assessed using the Cochrane collaboration’s tool for assessing risk of bias.14 For observational studies the quality assessment tool for observational cohort and cross-sectional studies of the National Institutes of Health (NIH) was used.15,16 Because of the lack of a scoring system, we did not include the quality rating of this tool in our quality assessment. The quality check was conducted by the first reviewer (Tv.E.), subsequently the second reviewer (M.K.) independently checked 20% of all included studies (n = 10 out of 48 articles: 8 out of 42 longitudinal studies and 2 out of 6 RCTs; inter-reviewer discrepancy rate = 5.69%). Because of the low inter-reviewer discrepancy and the expectation that the errors were not systematic and without influence on either the data extraction or the quality assessment, a duplicate percentage of 20% was considered sufficient.

Data analysis

Results were presented per cardiovascular outcome [blood pressure combined with heart rate, and vascular health which comprised intima-media thickness (IMT) and pulse wave velocity (PWV)] and were grouped per child development stage. Observed associations were subdivided into positive associations: the higher the maternal diet/physical activity exposure, the higher the offspring health outcome ▲; negative associations: the higher the maternal diet/physical activity exposure, the lower the offspring health outcome ▼; no association □ or other associations (as specified). When maternal exposure was reported continuously as well as categorically, we included the results from the continuous exposure assessment. We did not include results of substitution models when used additionally to study associations of maternal diet with offspring health. When multiple adjusted models were shown, we included results of the fully adjusted model. The full data extraction table is included as a supplement.

Results

Selection of articles and study characteristics

Of the 5145 articles retrieved and screened, 19 articles were judged to be eligible for inclusion in this systematic review. Reference checking of the cited and citing articles of the included articles yielded no additional relevant articles (Fig. 1).

The studies included in this review comprised three articles about intervention studies,17–19 of which two articles used data from the same RCT and 16 articles about observational studies,20–35 covering 12 mother–child cohorts (Table 2). During the offspring follow-up, one of the intervention studies did not examine their data as intervention v. control group but combined both groups.17 There were 16 articles reporting on the association of maternal diet during pregnancy with offspring’s cardiovascular health17,23,25–30,33,35 and three articles reporting on the association of maternal physical activity during pregnancy with offspring’s cardiovascular health.24,31,32 No studies included both maternal diet and physical activity in one paper, although the association

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Fig. 1. PRISMA flowchart of the literature search.

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| Study                  | Design     | Study name     | n   | Exposure                                                                 | Outcome                                                                 | Timinga                        |
|-----------------------|------------|----------------|-----|---------------------------------------------------------------------------|---------------------------------------------------------------------------|--------------------------------|
| Aaltonen, 200817      | RCT        | NAMI           | 256 | Energy and macronutrient intake; 3-day food diary                         | Blood pressure at age 6 months: Automated oscillometric recorder; DINAMP    | 1st trimester = baseline; 2nd and 3rd trimester = intake during pregnancy |
|                       |            |                |     |                                                                           | Measured three times from the right upper arm at heart level; sitting position and at rest on a parent's lap. Average of the three measurements was used in the analysis |
| Kizirian, 201624      | RCT        | GI Baby 3/GI Baby 4 study | 59  | Energy, fibre and macronutrient intake; special interest in GI values which were assigned to carbohydrate food items; 3-day food record | Aortic intima-media thickness at 12 months of age: Measured in a straight, non-branched longitudinal segment of the proximal abdominal aorta by high-resolution ultrasound; Aortic IMT was quantified by using semiautomated and validated offline software in a 0.5–1 cm long segment of the dorsal aortic wall, from 2 loops of 40 frames each | 2nd trimester = baseline; 3rd trimester = during pregnancy |
| Normia, 201325        | RCT        | NAMI           | 109 | Energy and macronutrient intake; 3-day food diary                         | Blood pressure at age 4 years: Automated oscillometric recorder; DINAMP     | Dietary intake during pregnancy = mean of 1st, 2nd and 3rd trimester |
|                       |            |                |     |                                                                           | Measured in triplicate after a 10-min seated rest. Average of the three measurements was used in the analysis |
| Adair, 200126         | Observational | CLHNS       | 2026| Energy and macronutrient intake; single 24-h dietary recall               | Blood pressure at age 15/16 years: Mercury sphygmomanometer Measured in triplicate after a 10-min seated rest. Average of the three measurements was used in the analysis | 3rd trimester                  |
| Blumfield, 201521     | Observational | WATCH study  | 129 | Energy, fibre and macronutrient intake; FFQ                              | Multiple blood pressure measurement moments up until 48 months of age: Automated oscillometric recorder; DINAMP Measured under standard conditions. Each measurement is included as repeated outcome measure (mixed models) | Dietary intake during pregnancy = mean of 6–24 weeks gestation (early pregnancy) and 24–40 weeks gestation (late pregnancy). Analysed as mean dietary intake |
| Bryant, 201522        | Observational | SWS          | 234 | Oily fish consumption; FFQ                                              | Blood pressure at 9.4 years of age: Right brachial blood pressure was recorded using a paediatric cuff immediately following the flow sequence acquisitions with an MRI-compatible patient monitor Aortic pulse wave velocity at 9.4 years of age: Aortic stiffness was assessed in the descending aorta on a 1.5T MRI scanner using a phased array spine coil in combination with a torso array coil. Velocity flow curves were generated using open source imaging software and PWV calculated in m/s using Matlab software | 1st trimester and 3rd trimester |
| Study               | Design   | Cohort/Study          | Participants | Outcome Measures                                                                 | Procedure                                                                                     |
|---------------------|----------|-----------------------|--------------|-----------------------------------------------------------------------------------|------------------------------------------------------------------------------------------------|
| Chatzi, 2017        | Observational | Project Viva/Rhea cohort 997/567 | Mediterranean Diet score; FFQ | Blood pressure at 7.7 (Project VIVA) and 4.2 (Rhea cohort) years of age: Automated oscillometric recorder; DINAMAP Measured at child’s right arm after 5 min rest in the seated position; five measurements taken 1 minute apart Average of the five measurements was used in the analysis |
| Danielsen, 2013     | Observational | Danish fetal origin cohort 389 | Daily amount of walking and bike riding; self-administered questionnaire. | Blood pressure at 20 years of age: Device is not reported; Measured after 7 min of rest, three times in the horizontal position The average value of the last two measurements was included in the analysis |
| Gale, 2006          | Observational | N.S. 216 | Energy and macronutrient intake; FFQ. | Intima-media thickness at 9 years of age: Children sat in a temperature-controlled room (20±2°C) for at least 10 min; The ultrasonographer measured IMT in the distal portion of the right common carotid artery using an Acuson XP128 scanner and a 7-MHz linear-array transducer, while the child was recumbent; Three measurements were done and the average of the three measurements were used in the analysis |
| Hrolfsdottir, 2017  | Observational | Aarhus birth cohort 434 | Protein intake (total, animal and plant protein); FFQ | Blood pressure at 20 years of age: Automatic measurement device; Omron Three readings during clinical examination after 7 min rest Average of the three measurements was used in the analysis |
| Huh, 2005           | Observational | Project VWA 947/910 | Protein intake; FFQ | Systolic blood pressure at 6 months of age: Automated oscillometric recorder; DINAMAP Five times at 1-min intervals. Each measurement is included as repeated outcome measure (mixed models) |
| Leary, 2005         | Observational | ALSPAC 6944 | Energy and macronutrient intake, intake of milk, meat, fish, fruit and vegetables; FFQ | Blood pressure at 7.5 years of age: Automated oscillometric recorder; DINAMAP Measured two times at the child’s right arm while seated Average of the two measurements was used in the analysis |
| Leary, 2013         | Observational | ALSPAC 4723 | Energy and macronutrient intake; FFQ | Blood pressure at 15 years of age: Automated oscillometric recorder; DINAMAP Measured two times at the child’s right arm while seated Average of the two measurements was used in the analysis |
| Study                                      | Design       | Study name | n\(^a\) | Exposure                                                                                                                      | Outcome                                                                                       | Timing\(^b\)                         |
|-------------------------------------------|--------------|------------|---------|-------------------------------------------------------------------------------------------------------------------------------|------------------------------------------------------------------------------------------------|-------------------------------------|
| Leermakers, 2017\(^{35}\)                | Observational| Generation R | 2035    | Dutch healthy diet index and a posteriori dietary patterns; FFQ                                                              | Blood pressure at 6 years of age: Automatic phymomanometer; Datascope Accutor Plus Lying position at the right brachial artery for four times with 1-min intervals Average was used for analysis with exclusion of the first measurement Carotid-femoral pulse wave velocity at 6 years of age: Automatic Compilior SP device with participants in supine position | 1st trimester                      |
| May, 2014\(^{36}\)                       | Observational| N.S.       | 43      | Physical activity; modifiable physical activity questionnaire (MPAQ)                                                          | Heart rate and heart rate variability at 1 month of age: A continuous, 18-min MCG recording was obtained using an investigational 83-channel fetal biomagnetometer housed in a magnetically shielded room Recordings were made when the infants were in a quiet, but alert state Data were sampled at 300 Hz. Digital filtering between 1 and 40 Hz was applied offline | During pregnancy                    |
| Millard, 2013\(^{32}\)                    | Observational| ALSPAC     | 4665    | Leisure time physical activity; self-administered questionnaire                                                             | Blood pressure at 15.5 years of age: Automated oscillometric recorder; DINAMAP Two readings of DBP and SBP were recorded with the child at rest and arm supported Average of the two measurements was used in the analysis | 2nd trimester                      |
| Rerkasem, 2012\(^{33}\)                  | Observational| N.S.       | 564     | Energy and macronutrient intake; 24-h recall and FFQ                                                                        | Blood pressure at 20 years of age: Device is not reported; Measured after sitting at least 20 min quietly, left arm at heart level, twice at an interval of 5–10 min; Average of the two measurements was used in the analysis Carotid intimal medial thickness at 20 years of age: Measured in the distal portion of the right common carotid artery using a Philip machine iE33 and a L10-4 MHz linear array transducer; The mean of six measurements was used in the analysis | 1st, 2nd and 3rd trimesters were analysed separately |
with both maternal exposures was studied in the Avon Longitudinal Study of Parents and Children (ALSPAC) cohort at the same child age. In addition, there were no studies examining maternal lifestyle before conception. Three mother–child studies examined offspring health twice over time and published the results in separate articles. However, studying similar maternal exposures and offspring health outcomes at both points in time was only done in the Nutrition, Allergy, Mucosal Immunology and Intestinal Microbiota (NAMI) RCT. In all included articles, maternal diet and physical activity were measured using self-reported questionnaires or interviews. Offspring health outcomes were all measured during clinical examination, according to standardized study protocols.

**Blood pressure and heart rate**

In total, 16 articles described the association of maternal lifestyle with offspring blood pressure and three articles described the association of maternal lifestyle with offspring heart rate (Table 3; Supplementary Table S2). Maternal carbohydrate intake during pregnancy was studied in five articles. Its association with infant blood pressure was U-shaped, while it was positively linearly associated to systolic blood pressure in pre-school and school-aged offspring. These linear associations were not observed for diastolic blood pressure. No associations of maternal carbohydrate intake with blood pressure were observed in older offspring.

Maternal fatty acid intake was studied in eight articles and was examined as total fat intake and/or as intake of different specific fatty acids during pregnancy. Maternal mono-unsaturated fat intake during pregnancy had an U-shaped association to infant diastolic blood pressure. Maternal omega-6 and total poly-unsaturated fat intake were positively linearly associated to systolic blood pressure in pre-school-aged children. In addition, systolic blood pressure was lowest in offspring of mothers with a fat intake closest to the recommended intake (second tertile intake). These associations were not observed for diastolic blood pressure. Five articles reported no association of maternal fat intake during pregnancy with blood pressure in older offspring (total fat intake during pregnancy and offspring blood pressure). However, Adair et al. observed a negative linear association of total fat intake with both systolic and diastolic blood pressure in adolescent girls.

Eight articles reported no association of maternal protein intake with offspring blood pressure. Hrolfsdottir et al. reported a positive linear association of maternal protein intake and offspring diastolic blood pressure in young adults. In contrast, Rerkasem et al. observed a negative linear association of maternal protein intake with offspring diastolic blood pressure. These associations were not observed for systolic blood pressure.

Associations of maternal energy intake and protein/carbohydrate ratio (P:C ratio) and fibre intake during pregnancy with offspring blood pressure were only reported in two or three articles with contrasting results. Maternal intake of specific foods and dietary patterns during pregnancy, as well as maternal physical activity during pregnancy, in association with offspring blood pressure, were rarely studied. Furthermore, associations with offspring heart rate were rarely studied.

**Vascular health**

In total, five articles described the association of maternal lifestyle with offspring vascular health (Table 4; Supplementary...
Table S2). PWV as well as IMT were studied in the carotid or in the aortic artery (descending thoracic aorta or proximal abdominal aorta). Two articles reported that maternal protein intake during pregnancy was negatively linearly associated to carotid IMT in school-aged offspring and in young adults. The association of maternal carbohydrate intake with offspring IMT was assessed inconsistently: maternal exposure was defined as glycaemic index or total carbohydrate intake, and vascular health measurements were done in the aortic or carotid artery. The association of maternal energy intake during pregnancy with offspring carotid IMT was only reported once. Maternal fat intake and its association with offspring carotid IMT was reported in two articles with contrasting results. Maternal intake of specific foods and dietary patterns were rarely studied in

| Maternal dietary intake – energy and macronutrients | Infancy 0–2 years | Pre-school 3–5 years | School 6–12 years | Adolescence 13–18 years | Young adult 19–25 years |
|-----------------------------------------------------|-------------------|----------------------|------------------|------------------------|------------------------|
| Energy intake                                       | Trend U-shaped SBP\(^\uparrow\) |
| Carbohydrates                                       | U-shaped SBP&DBP\(^\uparrow\) |
| Protein                                             | SBP\(^\downarrow\) & DBP\(^\downarrow\) |
| P:C ratio                                           | SBP\(^\uparrow\) & DBP\(^\downarrow\) |
| Fat                                                 | MUFA: U-shaped DBP\(^\uparrow\) n – 6 and PUFA: SBP\(^\downarrow\) |
| Fibre                                               | Trend U-shaped DBP\(^\uparrow\) |

| Maternal dietary intake – food products              | Infancy 0–2 years | Pre-school 3–5 years | School 6–12 years | Adolescence 13–18 years | Young adult 19–25 years |
|-----------------------------------------------------|-------------------|----------------------|------------------|------------------------|------------------------|
| Fruit intake                                        | Trend reversed U-shaped SBP\(^\uparrow\) |
| Vegetable intake                                    | SBP&DBP\(^\downarrow\) |
| Milk intake                                         | SBP&DBP\(^\downarrow\) |
| Meat intake                                         | SBP&DBP\(^\downarrow\) |
| Fish intake                                         | SBP&DBP\(^\downarrow\) |

| Maternal dietary intake – dietary patterns           | Infancy 0–2 years | Pre-school 3–5 years | School 6–12 years | Adolescence 13–18 years | Young adult 19–25 years |
|-----------------------------------------------------|-------------------|----------------------|------------------|------------------------|------------------------|
| Mediterranean diet score                             | SBP&DBP\(^\downarrow\) |
| Dutch healthy diet index                             | SBP&DBP\(^\downarrow\) |
| A posteriori dietary patterns                        | SBP&DBP\(^\downarrow\) |

| Maternal physical activity                           | Infancy 0–2 years | Pre-school 3–5 years | School 6–12 years | Adolescence 13–18 years | Young adult 19–25 years |
|-----------------------------------------------------|-------------------|----------------------|------------------|------------------------|------------------------|
| MV aerobic exercise for \(\geq 30\) min, 3 x /week  | RMSSD, LF, HF\(^\downarrow\) |
| Daily amount of walking and bike riding             | SBP \(^\downarrow\) & DBP \(^\downarrow\) |
| Leisure time physical activity                       | SBP \(^\downarrow\) |

\(^\uparrow\), The higher the maternal diet/physical activity exposure, the higher the offspring health outcome; \(^\downarrow\), the higher the maternal diet/physical activity exposure, the lower the offspring health outcome; –, there is no effect observed of maternal diet/physical activity exposure with infant health outcome. SBP, systolic blood pressure; DBP, diastolic blood pressure; MUFA, mono-unsaturated fatty acids; \(n – 6\), omega-6 fatty acids; PUFA, polyunsaturated fatty acids; HR, heart rate; SSDN, standard deviation of normal-to-normal inter-beat intervals; RMSSD, root mean square successive difference; LF, low frequency; HF, high frequency; \(^\sigma\), results were stratified for male (♂) and female (♀) offspring.
association to offspring vascular health. There were no articles describing the association of maternal physical activity with offspring vascular health.

**Secondary research questions**

We additionally focussed on the period of gestation, offspring’s sex, and obese v. normal weight mothers. In total, eight articles examined maternal lifestyle multiple times during pregnancy17–19,21,22,25,27,33 (Table 2). Of those articles, four reported their results stratified for pregnancy period22,25,27,33 with mixed results: Two articles22,27 did not observe differences in associations stratified for pregnancy period for offspring blood pressure outcomes. However, two other articles only observed associations of maternal carbohydrate intake in late pregnancy25 and of maternal protein intake in the first trimester of pregnancy33 with offspring carotid IMT.

Two articles20,24 stratified their results by sex (Table 3). Adair et al.20 only observed a negative linear association of maternal total fat intake with blood pressure in females. Danielsen et al.24 only observed a positive linear association of maternal daily amount of walking and bike riding with systolic blood pressure in males. In total, three articles did not take offspring’s sex into account in their final analysis.17,19,31

Two articles23,30 added maternal pre-pregnancy BMI as an interaction term into their models, but in both studies it was a no-effect modifier. Seven articles did not take maternal (pre-pregnancy) BMI into account in their final model17,19,21,27,31,33 (Supplementary Table S2).

**Quality of the included studies**

The included RCTs scored generally low in the risk of bias assessment (Table 5). However, performance bias was present.

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**Table 4. Overview of the reported associations of diet and physical activity before or during pregnancy with offspring’s vascular health**

| Maternal dietary intake – energy and macronutrients | Infancy 0–2 years | Pre-school 3–5 years | School 6–12 years | Adolescence 13–18 years | Young adult 19–25 years |
|---------------------------------------------------|-------------------|---------------------|--------------------|------------------------|------------------------|
| Energy intake                                      | ▼ Carotid intima-media thickness25 |                     |                    |                        |                        |
| Carbohydrates                                      | GI index: ● Aortic intima-media thickness15 | ▼ Carotid intima-media thickness (late pregnancy)25 | ● Aortic intima-media thickness (early pregnancy)25 |                     |                        |
|                                                   |                   |                     |                    |                        |                        |
| Protein                                           | ▼ Carotid intima-media thickness25 |                     |                    |                        |                        |
| Fat                                                | ▼ Carotid intima-media thickness25 |                     |                    |                        |                        |

| Maternal dietary intake – food products            |                             |                     |                    |                        |                        |
| Fish intake                                        | ▼ Aortic pulse wave velocity (only late pregnancy)22 |                     |                    |                        |                        |
|                                                   | ● Aortic pulse wave velocity (only early pregnancy)22 |                     |                    |                        |                        |

| Maternal dietary intake – dietary patterns         |                             |                     |                    |                        |                        |
| Dutch Healthy Diet Index                           | ▼ Carotid-femoral pulse wave velocity70 |                     |                    |                        |                        |
| A posteriori dietary patterns                      | Vegetable, fish and oil pattern: ▼ Carotid-femoral pulse wave velocity70 | Nuts, soy and high fibre pattern and margarine, snacks and sugar pattern: ● Carotid-femoral pulse wave velocity70 |                     |                        |                        |

| Other                                              | Low GI v. HF diet: thinner aortic intima-media thickness18 |                     |                    |                        |                        |

▲, The higher the maternal diet/physical activity exposure, the higher the offspring health outcome; ▼, the higher the maternal diet/physical activity exposure, the lower the offspring health outcome; ●, there is no effect observed of maternal diet/physical activity exposure with infant health outcome.

GI, glycaemic index; HF, high fibre.
For the observational studies, all articles clearly reported the objective and recruited study participants from the same population applying clear inclusion and exclusion criteria (Table 6). Different levels of exposure were studied in association to the outcome, with exception of May et al.\(^{31}\) who used the level of exposure to define two groups for analysis. Most studies used self-reported questionnaires to determine maternal exposure, which were not always validated for the particular exposure of interest, nor a pregnant study population. All outcome assessments in the offspring were rated at low risk of bias, with exception of those in the article by Blumfield et al.\(^{21}\) who measured blood pressure only once per study visit.\(^{36}\) The follow-up rate of 80% was most often not reached, with exception of the follow-up rate in the article by May et al.\(^{31}\) who measured the offspring at 1 month of age. The majority of studies did not correct for key potential confounding variables such as breastfeeding, maternal smoking, maternal age, maternal pre-pregnancy BMI and birth weight, with exception of Chatzi et al.\(^{23}\) None of the studies gave a sample size justification. Because of the low number of RCTs and the heterogeneity in exposures, we were not able to conclude if RCTs showed different results compared with observational studies.

Discussion

To our knowledge this is the first systematic review on the association of dietary intake and physical activity of pregnant women with offspring's cardiovascular health, including both observational and experimental human studies. In total, we included 19 studies with over 29,000 participants. High maternal carbohydrate intake in pregnancy was consistently associated with higher blood pressure of the offspring. Less consistent associations were observed for high maternal intake of unsaturated fatty acids and low total fat intake with higher offspring blood pressure. There was no evidence for a programming effect of maternal protein intake on offspring blood pressure. Maternal protein intake during pregnancy was negatively associated to carotid IMT in school-aged and young adult offspring. We were unable to assess the potential modifying role of period of gestation, offspring’s sex or BMI of the mother, because of the small number of studies reporting stratified results.

Underlying mechanism

We speculate, in line with the results of previous studies,\(^{11,12,37}\) that the observed associations between offspring blood pressure with maternal carbohydrate intake can be explained by the ratio between maternal protein to carbohydrate intake (P/C ratio). Maternal energy and protein needs increase during pregnancy, which enables the fetus and placenta to grow.\(^{38}\) A low intake of maternal protein and an increased intake of carbohydrates are associated with reduced placental weight.\(^{12,39}\) Reduced placental size might induce increased placental flow with lasting consequences for the pressure against which the fetal heart develops.\(^{40}\) Such increased levels of pressure may have lasting effects for the physiology of heart and blood vessels and might increase later blood pressure. Indeed, there is evidence that reduced placental size is linked to increased risks of hypertension in later life.\(^{41}\)

This also explain the observed association of a lower maternal protein intake with a higher offspring’s carotid IMT. But lower overall maternal energy intake altering endothelium-dependent responses in the offspring’s aorta\(^{42}\) could also explain this association, as there is evidence for a negative linear association of adequate maternal energy intake with carotid IMT in school-aged offspring.\(^{43}\)

We observed weak evidence for a programming effect of maternal fat intake with offspring blood pressure.\(^{17,19–21}\) This is in line with evidence from animal studies, showing that high fat diets before and during pregnancy induced high blood pressure through endothelial dysfunction, including reduced endothelium-dependent vasodilatation in both small and large vessels and increased aortic stiffness.\(^{43}\)

Interpretation of the results

Most of the included studies assumed a linear association of maternal lifestyle with offspring cardiovascular health, or did not report whether assumptions for linearity were justified. U-shaped or trends towards (reversed) U-shaped relationships were also observed.\(^{17}\) It could be that associations went undetected by using inappropriate statistical models.

Associations may also have gone undetected since most studies failed to report stratified analyses for sex. There is evidence for sex differences in the programming of cardiovascular diseases\(^{20,24}\) and although the underlying mechanism is unclear, it seems that male offspring are more sensitive to their prenatal environment.\(^{44–46}\) For example, intrauterine growth restriction caused by placental insufficiency resulted in a significant increase in blood pressure in young adulthood in male offspring, whereas female offspring were normotensive.\(^{44,47}\)
| Question | Adair, 2001<sup>20</sup> | Blumfield, 2015<sup>25</sup> | Bryant, 2015<sup>22</sup> | Chatzi, 2017<sup>3</sup> | Danielsen, 2013<sup>24</sup> | Gale, 2006<sup>21</sup> | Hrolfsdottir, 2017<sup>26</sup> | Huh, 2005<sup>27</sup> | Leary, 2005<sup>25</sup> | Leary, 2013<sup>25</sup> | Leemakers, 2017<sup>20</sup> | May, 2014<sup>21</sup> | Millard, 2013<sup>22</sup> | Rerkasem, 2012<sup>23</sup> | Rytter, 2013<sup>24</sup> | van den Hil, 2013<sup>25</sup> |
|----------|-------------------------|-----------------------------|--------------------------|-----------------------------|-----------------------------|-----------------------------|-----------------------------|-----------------------------|-----------------------------|-----------------------------|-----------------------------|-----------------------------|-----------------------------|-----------------------------|-----------------------------|-----------------------------|
| Question 1<sup>a</sup> | Y | Y | Y | Y | Y | Y | Y | Y | Y | Y | Y | Y | Y | Y | Y | Y |
| Question 2 | Y | Y | Y | Y | Y | Y | Y | Y | Y | Y | Y | Y | Y | Y | Y | Y |
| Question 3 | Y | Y | Y | Y | Y | Y | Y | Y | Y | Y | Y | CD | Y | Y | Y | CD |
| Question 4 | Y | Y | Y | Y | Y | Y | Y | Y | Y | Y | Y | Y | Y | Y | Y | Y |
| Question 5 | N | N | N | N | N | N | N | N | N | N | N | N | N | N | N | N |
| Question 6 | Y | Y | Y | Y | Y | Y | Y | Y | Y | Y | Y | Y | Y | Y | Y | Y |
| Question 7 | NA | NA | NA | NA | NA | NA | NA | NA | NA | NA | NA | NA | NA | NA | NA | NA |
| Question 8 | Y | Y | Y | Y | Y | Y | Y | Y | Y | Y | Y | Y | Y | Y | Y | Y |
| Question 9 | Y | Y | Y | Y | N | Y | N | N | N | N | N | N | N | N | N | N |
| Question 10 | N | Y | Y | N | N | Y | N | N | N | N | Y | N | N | N | N | N |
| Question 11 | Y | N<sup>b</sup> | Y | Y | Y | Y | Y | Y | Y | Y | Y | Y | Y | Y | Y | Y |
| Question 12 | CD | CD | CD | CD | CD | CD | CD | CD | CD | CD | CD | CD | CD | CD | CD | CD |
| Question 13 | N | N | N | N | N | N | N | N | N | N | Y | N | N | N | N | N |
| Question 14 | N | N | N | N | N | N | N | N | N | N | N | N | N | N | N | N |

<sup>a</sup>CD, cannot determine; NA, not applicable; NR, not reported.
<sup>b</sup>Question 1. Was the research question or objective in this paper clearly stated?; Question 2. Was the study population clearly specified and defined?; Question 3. Was the participation rate of eligible persons at least 50%?; Question 4. Were all the subjects selected or recruited from the same or similar populations (including the same time period)? Were inclusion and exclusion criteria for being in the study pre-specified and applied uniformly to all participants?; Question 5. Was a sample size justification, power description or variance and effect estimates provided?; Question 6. For the analyses in this paper, were the exposure(s) of interest measured before the outcome(s) being measured?; Question 7. Was the timeframe sufficient so that one could reasonably expect to see an association between exposure and outcome if it existed? This question has been answered with ‘Not applicable’ for all studies, as we were interested in outcomes that may be considered proxies for cardiovascular disease risk instead of the so-called ‘hard outcomes’ as cardiovascular disease itself; Question 8. For exposures that can vary in amount or level, did the study examine different levels of the exposure as related to the outcome (e.g., categories of exposure, or exposure measured as continuous variable)?; Question 9. Were the exposure measures (independent variables) clearly defined, valid, reliable and implemented consistently across all study participants?; Question 10. Was the exposure(s) assessed more than once over time? Question 11. Were the outcome measures (dependent variables) clearly defined, valid, reliable and implemented consistently across all study participants?; Question 12. Were the outcome assessors blinded to the exposure status of participants?; Question 13. Was loss to follow-up after baseline 20% or less? Question 14. Were key potential confounding variables measured and adjusted statistically for their impact on the relationship between exposure(s) and outcome(s), which were considered breastfeeding, maternal smoking, maternal age, maternal pre-pregnancy BMI and birth weight.
<sup>c</sup>Assessed for both included cohorts independently.
<sup>d</sup>According to study protocol, blood pressure was only measured 1 time unless the outcome exceeded the reference values.
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98.
T.M. van Elten and M.D.A. Karsten are supported by Nature more research should focus on the associations between maternal diet and offspring cardiovascular health up to the age of 25 years. Nevertheless, there is evidence that the associations between maternal diet and offspring blood pressure persist into adulthood and may increase over time.  

Strengths and limitations
The strength of this review is the systematic approach in finding and summarizing the available evidence on the association of maternal diet and physical activity with offspring cardiovascular health including both observational and experimental human studies. We were therefore able to give a comprehensive overview of the available literature. Owing to the heterogeneity in the assessment of maternal dietary intake and physical activity, the vascular outcomes, and the differences in offspring age, a meta-analysis was not possible. Associations of maternal lifestyle with offspring cardiovascular health were rarely studied using an RCT design. Therefore, we were not able to infer causality. There are, however, indications for causality from the UPBEAT trial, showing that a lifestyle intervention targeting maternal diet and physical activity during pregnancy had the potential to reduce infant adiposity.  

Recommendations for further research
In order to optimally use the information from studies on maternal lifestyle and offspring health, harmonization of valid exposure and outcome measurements and the development of core outcome sets would reduce research waste and speed up scientific progress in this field.  

Conclusions
Currently there is a lack of consistent evidence to be able to draw robust conclusions on the association of women’s dietary intake and physical activity before and during pregnancy with offspring’s blood pressure and vascular health. We did find evidence for an association of high maternal carbohydrate intake with higher offspring blood pressure, and a negative linear association of maternal protein intake with offspring carotid IMT. We hypothesize that the macronutrient composition of the diet underlies these associations. However, no consistent findings for maternal fatty acid intake were found. There were too few studies to draw conclusions on energy intake, fibre intake, P:C ratio, specific foods, dietary patterns and maternal physical activity. Harmonization of valid exposure and outcome measurements, and the development of core outcome sets are needed to enable more robust conclusions.

Supplementary material. To view supplementary material for this article, please visit https://doi.org/10.1017/S204017441800082X

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Conflict of Interest. None

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