Department of Clinical Chemistry and Laboratory Medicine
Faculty of Medicine
Saarland University, Homburg/Saar

The Impact of Plant-Based Diets on Maternal and Offspring Health
-
A Health Technology Assessment

Dissertation to acquire the doctoral degree (Dr. med.)
at the Faculty of Medicine
at SAARLAND UNIVERSITY
2021

presented by: Arved Pannenbäcker
born on 23 September 1995 in Krummsee

Tag der Promotion: 04.08.2022

Dekan: Univ.-Prof. Dr. med. Michael D. Menger

Berichterstatter: Prof. Dr. rer. med. Rima Obeid

Univ. Prof. Dr. med. Michael Zemlin

Contents

List of Figures

List of Tables

List of Abbreviations

AGA	appropriate for gestational age
ALA	alpha-linoleic acid
BMELV	Bundesministerium für Ernährung, Landwirtschaft und Verbraucherschutz
BMG	Bundesministerium für Gesundheit
BMI	body mass index
BP	blood pressure
CHD	congenital heart defect
CI	confidence interval
DHA	docosahexaenoic acid
FGR	fetal growth restriction
GDM	gestational diabetes
GW	gestational weeks
GWG	gestational weight gain
HAZ	height-for-age z-score
Hb	hemoglobin
HR	hazard ratio
HTA	Health Technology Assessment
IADPSG	International Association of the Diabetes and Pregnancy Study Groups
IOM	Institute of Medicine
IOTF	International Obesity Task Force
IUGR	intrauterine growth retardation
IVF	in vitro fertilization
LAZ	length-for-age z-score
LBW	low birth weight
LOV	lacto-ovo-vegetarian
LV	lacto-vegetarian
MBD	Macrobiotic diet
MD	Mediterranean diet
MDS	Mediterranean diet score
NDDG	National Diabetes Data Group
NHLBI	National Heart, Lung, and Blood Institute
NTD	neural tube defect
MBD	Macrobiotic diet
OR	odds ratio
OV	ovo-vegetarian
RCT	randomized controlled trial
RR	risk ratio
SD	standard deviation
SDS	standard deviation score
SE	standard error
SGA	small for gestational age
vs	versus
WAZ	weight-for-age z-score
WHO	World Health Organization
WHZ	weight-for-height z-score
WLZ	weight-for-length z-score

1 Abstract

The number of women choosing a plant-based diet or a diet with reduced amounts of foods of animal origin increases. Vegetarian diet forms showed beneficial effects on coronary heart disease, certain types of cancer, and type 2 diabetes in adults, but the recommendations regarding critical stages of life such as pregnancy, lactation, and childhood are inconsistent due to potential nutrient deficiencies. The objective was to conduct a Health Technology Assessment to evaluate the evidence in terms of harms and benefits of plant-based diets and provide guidelines for health care professionals.

A literature search in *PubMed* was carried out, including the keywords related to the forms of nutrition (vegetarian diet, vegan diet, macrobiotic diet, low meat diet, and Mediterranean diet) and the stages of life of mother and child which were relevant for the research question. Outcomes of interest in the mother were early abortion, preeclampsia, gestational diabetes, anemia, neurological and neuropsychiatric symptoms. Outcomes of interest in the child were preterm birth, low birth weight, small for gestational age/intrauterine growth restriction, congenital heart defects, neural tube defects, hypospadias, feeding difficulties, neurological symptoms, anemia, physical growth markers, fine and gross motor skills, asthma and wheezing, and cognitive functions. A systematic review of evidence was performed. Meta-analyses were conducted to generate a pooled effect size if study designs allowed it.

113 publications met the inclusion criteria. The results of the meta-analyses showed a significantly lower risk of gestational diabetes mellitus and preterm delivery in women with high Mediterranean diet adherence. Women who followed a Mediterranean diet were less likely to develop other pregnancy-related outcomes such as hypertensive disorders and small for gestational age fetuses/intrauterine growth retardation/fetal growth restriction/low birth weight, but these associations were not statistically significant. Moreover, the findings indicated that a high Mediterranean diet adherence correlated with lower risks of overweight and obesity. Additionally, a trend towards a lower body mass index, a lower risk of asthma and wheezing and higher scores in cognitive functions in children who followed a Mediterranean diet was observed.

Analyses investigating the associations between vegetarian, vegan and low meat diet and maternal and offspring health yielded no clear results. Only the association between vegetarian diet and a lower mean BMI in children and adolescents was statistically significant.

The results suggest that the Mediterranean diet could be an essential component of metabolically healthy pregnancies and the basis of early prevention of metabolic disorders in children and adolescents. The Mediterranean diet as a cost-effective, low-risk intervention should not be neglected in future dietary recommendations and guidelines. Considering the present evidence regarding vegetarian diet forms, it would be inappropriate to discourage pregnant women from following a vegetarian or vegan diet as long as macronutrient and micronutrient requirements are fulfilled. Further research is needed to confirm the findings.

Die Anzahl der Frauen, die sich für die Reduktion oder den Verzicht auf tierische Lebensmittel in der Ernährung entscheiden, wächst stetig. In Studien zeigten vegetarische Ernährungsformen protektive Effekte auf die Entstehung von koronarer Herzerkrankung, Krebserkrankungen und Typ 2 Diabetes bei Erwachsenen. Jedoch sind die Empfehlungen verschiedener Fachgesellschaften für kritische Lebensphasen wie Schwangerschaft, Stillzeit und Kindheit widersprüchlich aufgrund möglicher Nährstoffmängel. Das Ziel der Untersuchung war die Bewertung der aktuellen Evidenzlage in Form eines Health Technology Assessments, um Risiken und Nutzen pflanzlicher Ernährungsformen abzuwägen und Leitlinien für Fachleute im Gesundheitswesen zu erstellen.

Für die Literaturrecherche bei *PubMed* wurde ein Term generiert, der die Schlüsselbegriffe in Bezug auf Ernährungsform (vegetarische, vegane, makrobiotische und fleischarme Ernährung sowie Mediterrane Diät) und für unsere Fragestellung relevanten Lebensphasen von Mutter und Kind enthielt. Outcomes von Interesse bei der Mutter waren frühzeitige Aborte, Präeklampsie, Gestationsdiabetes, Anämie und neurologische und neuropsychiatrische Symptome. Outcomes von Interesse beim Kind waren Frühgeburtlichkeit, niedriges Geburtsgewicht, Small-for-Gestational-Age, intrauterine Wachstumsretardierung, angeborene Herzfehler, Neuralrohrdefekte, Hypospadie, Fütterungsprobleme, neurologische Symptome, Anämie, Wachstum, fein- und grobmotorische Fähigkeiten, Asthma und kognitive Funktionen. Es wurde ein systematischer Review der Literatur durchgeführt. Im Falle von ausreichender Studienzahl und geeignetem Studiendesign wurden Metaanalysen für die jeweiligen Outcomes erstellt.

113 Publikationen erfüllten die Einschlusskriterien. Die Ergebnisse der Metaanalysen zeigten eine signifikante Assoziation zwischen Einhaltung der mediterranen Diät und einem verringerten Risiko für Gestationsdiabetes und Frühgeburtlichkeit. Frauen, die einer mediterranen Diät folgten, entwickelten außerdem seltener weitere Komplikationen wie Schwangerschaftshypertonie oder Small-for-Gestational-Age-Feten, intrauterine Wachstumsretardierung und niedriges Geburtsgewicht. Allerdings waren diese Assoziationen nicht statistisch signifikant. Es konnte ein Zusammenhang zwischen Einhaltung der mediterranen Diät und einem verringerten Risiko für Übergewicht und Adipositas bei Kindern und Jugendlichen gezeigt werden. Zudem konnte bei Kindern, die einer mediterranen Diät folgten, eine Tendenz zu einem geringerem Body Mass Index, einem verminderten Risiko für die Entwicklung von Asthma und bessere kognitive Funktionen ermittelt werden. Unsere Analysen zu vegetarischer, veganer und fleischarmer Ernährung und der Gesundheit von Mutter und Kind kamen zu keinen eindeutigen Ergebnissen. Nur die Assoziation zwischen vegetarischer Ernährung und einem niedrigeren mittleren BMI bei Kindern und Jugendlichen war statistisch signifikant.

Unsere Ergebnisse zeigen, dass die mediterrane Diät ein wesentlicher Bestandteil einer stoffwechselgesunden Schwangerschaft und die Grundlage für eine frühzeitige Prävention von Stoffwechselerkrankungen bei Kindern und Jugendlichen sein könnte. Die mediterrane Diät als kosteneffiziente, risikoarme Intervention sollte in künftigen Empfehlungen und Leitlinien nicht vernachlässigt werden. In Anbetracht der vorliegenden Erkenntnisse über vegetarische Ernährungsformen wäre es unangebracht, schwangeren Frauen von einer vegetarischen oder veganen Ernährung abzuraten, solange der Bedarf an Nährstoffen gedeckt ist. Weitere Untersuchungen sind erforderlich, um die Ergebnisse zu bestätigen.

2 Introduction

The interest in practicing plant-based diets is growing worldwide especially in young people (Vergeer et al., 2020; Mensink et al., 2016). Apart from ethical, cultural, and religious reasons for avoiding animal source foods, there is also an increasing interest in the connection between various diet forms and health (Fox, Ward, 2008). A rising number of women in childbearing age following a plant-based diet will face the question if their nutrition can provide their growing child with sufficient nutrients to fulfill the requirements for growth and development. The maternal diet before and during pregnancy has long-term effects on maternal and offspring health considering not only pregnancy complications like gestational diabetes (Mijatovic-Vukas et al., 2018), hypertensive disorders (Schoenaker et al., 2015a), and low birth weight (Chia et al., 2019) but also the development of atopic diseases (Y Zhang et al., 2019) and overweight in childhood and adolescence (Troiano, Flegal, 1998). The mother's choice between various types of diets results in a fetus being exposed to certain amounts of macronutrients and micronutrients. This crucial period of pregnancy and early childhood has wide-ranging consequences for the health outcomes in mother and child. The maternal diet can be considered as a template for the offspring's mindset towards nutrition, especially with regard to the consumption of animal-based foods.

There is controversial data on potential harms or benefits of a vegetarian diet during pregnancy. This could be due to heterogeneous forms of the vegetarian diet, geographical differences and lifestyles strongly associated with adherence to a vegetarian diet. The heterogeneity of the observational studies and the lack of randomized controlled trials weaken the evidence supporting the recommendation of a vegetarian diet for pregnant women. In contrast, an increasing number of studies show data to support the thesis that adherence to the Mediterranean diet (MD) can protect against some adverse health outcomes. The present Health Technology Assessment (HTA) aimed at evaluating the existing studies and synthesizing evidence with regard to the association between alternative diet forms and health outcomes in mother and child.

2.1 Definitions

In the literature, there are several types of diets that endorse the reduction or avoidance of foods of animal origin (table 2). An omnivorous diet is characterized by the regular consumption of meat. The term ”vegetarian diet” includes any type of diet that avoids foods of animal origin. This includes the vegan diet, lacto-ovo-vegetarian (LOV), lacto-vegetarian (LV), ovo-vegetarian (OV), macrobiotic diet, and for our purpose also the low-meat diet, hereinafter all of them referred to as ”vegetarian diet” if not further specified. The Mediterranean diet was treated separately from the vegetarian diet in the following.

Table 1: Definitions of diets

Diet	Included foods	Excluded foods
vegetarian	vegetables, fruits, grains, pulses	meat, fish, dairy products, eggs, honey
LOV	dairy products, eggs, vegetables, fruits, grains, pulses	meat, fish
LV	dairy products, vegetables, fruits, grains, pulses	meat, fish, eggs
OV	eggs, vegetables, fruits, grains, pulses	meat, fish, dairy products
low-meat diet	meat to a certain extent, fish, dairy products, eggs, vegetables, fruits, grains, pulses	depending on definition meat consumption less than 3 times per week or 50 grams per day
Mediterranean diet	emphasizes vegetables, fruits, nuts, grains, olive oil, fish and seafood, white meat	soda drinks, sweets and pastries, commercial bakery goods, spread fats, red and processed meat are avoided
macrobiotic diet	whole grains, vegetables, including sea vegetables like seaweed, fruits, beans, nuts and seeds, occasionally fish; organic and locally grown products are preferred	poultry, meat, dairy products, eggs, processed foods, refined sugars, tropical fruits, fruit juice, and certain vegetables like asparagus, eggplant, spinach, tomatoes, and zucchini are avoided
omnivorous diet	all foods	

2.2 Epidemiology and associated factors of alternative diets

The estimated proportion of vegetarians in Germany varies between studies. According to a survey in Germany in 2019, 3% of the men and 5% of the women claimed to be vegetarian (Yougov, 2019). The proportion of vegetarians in women between 18 and 29 years was even estimated to be 9.2% (Mensink et al., 2016). The results of a SKOPOS market research showed that 1.3 million Germans followed a vegan diet, 81% of them were women and 60% of the vegans were between 20 and 39 years old (SKOPOS, 2008). Another survey reported on a higher proportion of German vegetarians of 10% (VEBU, 2015). In the United States the number of people following plant-based diets is growing as well. According to a survey by the Vegetarian Resource Group in 2016 5.3% of the adults between 18 and 34 subsisted on a vegetarian diet (Vegetarian Resource Group, 2016).

Studies showed that the parental attitude towards nutrition can have an important impact on their children's eating behavior (Benton, 2004; Story et al., 2002). The number of children following plant-based diets in the Western World is unknown, but vegetarian and vegan parents probably raise their children without meat or without foods of animal origin.

In the Western World most of the people make a conscious decision about becoming vegetarian driven by ethical, environmental and health concerns (Hoffman et al., 2013; Radnitz et al., 2015). But for example, in India a substantial proportion (35%) of the population has been vegetarian for many generations. This proportion varies between 10% and 62% according to the geographical region (Arnold et al., 2009). A publication from 2010 estimated that there were 1.5 billion vegetarians worldwide. Only 75 million were vegetarians of choice, a number that would gradually grow with increasing affluence and education according to the author. The other 1450 million vegetarians were vegetarians of necessity (Leahy et al., 2010).

Adherence to a vegetarian diet in western countries is associated with higher education (Davey et al., 2003; Mensink et al., 2016), whereas vegetarianism in some countries such as India is related to a low socioeconomic status due to higher costs of animal-based foods. Critical differences have been reported between vegetarians from Europe and North America who consume a LOV diet (Davey et al., 2003), while Indian vegetarians are mostly LVs (Jayanthi, 2001). Chinese vegetarians consume considerably smaller amounts of dairy products than Western vegetarians (Lee et al., 2000).

Multiple lifestyle factors are associated with following a vegetarian diet. Vegetarians and vegans, for example, are less likely to be smokers than meat-eaters (Key et al., 1999; Waldmann et al., 2003). Moreover, vegetarians and vegans tend to drink less alcohol than the general population (Haddad, Tanzman, 2003) and also the rate of non-drinkers is higher in vegetarians (Key et al., 1999), especially in vegans (Dyett et al., 2013). Furthermore, vegetarianism is associated with higher physical activity (Orlich et al., 2013; Tonstad et al., 2013). These findings show that vegetarianism cannot be viewed in isolation but it has to be considered as a multifactorial lifestyle.

2.3 Sustainability issues

Apart from health aspects, the environmental impact and the use of resources has to be considered for a comprehensive evaluation of a form of nutrition. About 18% of the global greenhouse gas emissions are caused by livestock production (Steinfeld et al., 2006). Therefore, the consumption of meat and dairy products is a major driver of climate change (Bailey et al., 2014). An estimate of differences in dietary greenhouse gas emissions between self-selected meat-eaters, fish-eaters, vegetarians and vegans in the United Kingdom showed that dietary greenhouse gas emissions in self-selected meat-eaters were approximately twice as high as those in vegans (Scarborough et al., 2014). It is likely that reductions in meat consumption would lead to reductions in dietary greenhouse gas emissions (Scarborough et al., 2014). However, the worldwide demand for meat and dairy is expected to increase by 68% for meat and 57% for dairy by 2030 (McLeod et al., 2011). In 2013, 36% of the calories produced by the world's crops were used for animal feed, and only 12% of those feed calories ultimately contribute to the human diet in the form of meat and other animal products (Cassidy et al., 2013). Given the current crop use, growing food exclusively for direct human consumption could increase available food calories by about 70%, which could feed an additional 4 billion people (Cassidy et al., 2013). Around 70% of the world's arable land is used as pasture and around 30% as cropland. Of this 30% of cropland, about one third is used for the production of animal feed, mainly cereals and soybeans. Therefore, a total of about 80% of the world's arable land is used for the production of animal food (Fritz, 2011). If the entire world population practiced a diet as the average German does, the entire habitable area of the earth, including forests, scrubland and settlements, would have to be used as agricultural land. A diet like it is practiced in the USA would even require about 138% of the available habitable area and would therefore not be possible (Ritchie, 2017). Moreover, the livestock production can cause pollution of air, water and soil due to fertilizers, pesticides, and veterinary drugs (Baroni et al., 2007). Also the destruction of fertile soils, especially through overuse, monocultures and unfavorable tillage are a point of concern (Leitzmann, Keller, 2020).

The burden on the environment and the consequences for the climate is a complex issue and cannot be presented in full here. Nevertheless, there is a consensus within environmental science that a reduction of meat and dairy products can have a significant positive impact on the climate change.

2.4 Benefits and harms of plant-based nutrition

Consuming a vegetarian diet is associated with lower blood lipids (F Wang et al., 2015), blood pressure (Berkow, Barnard, 2005), and body mass index (M Rosell et al., 2006). Therefore, consuming a vegetarian diet could be associated with a decrease in the risk of cardiovascular diseases. Moreover, vegetarian diets tend to have a protective effect against certain types of cancer, such as colorectal and prostate cancer, compared with omnivorous diets which could be related to consuming no meat and more fiber (Fraser, 1999).

In terms of nutritional aspects vegetarians and omnivores do not only differ in consumption of foods of animal origin. Compared to omnivores, vegetarians consume less saturated fat and cholesterol, but have a higher intake of magnesium and potassium, vitamin C and E, folate, carotenoids, flavonoids, and other phytochemicals. (Deriemaeker et al., 2010; Kristensen et al., 2015; Rizzo et al., 2013; Schüpbach et al., 2017; Sobiecki et al., 2016) These nutritional differences may explain some of the health advantages of a varied, balanced vegetarian diet.

The Mediterranean diet consists of fish, monounsaturated fats from olive oil, fruits, vegetables, whole grains, legumes, nuts, and moderate alcohol consumption. It showed protective effects on multiple adverse outcomes in several studies. A meta-analysis of observational studies and clinical trials has shown that adherence to the Mediterranean diet is associated with reduced risk of metabolic syndrome (Esposito et al., 2013). Results from clinical studies revealed the protective role of the Mediterranean diet on the single components of metabolic syndrome, like waist circumference, plasma concentrations of high-density lipoprotein cholesterol, triglycerides and glucose, and systolic and diastolic blood pressure (Kastorini et al., 2011).

However, it is not clear whether the lower risk of diseases associated with plant-based diets is due to the diet itself or to lifestyle accompanying factors such as less smoking and higher physical activity which could equally have protective roles on health.

Due to the restricted food selection, vegetarians and in particular vegans have low or insufficient intakes of critical nutrients (Finkelstein et al., 2015), i.e., protein, iron, calcium, vitamin D (Tucker, 2014), vitamin B12 (Pawlak et al., 2014), and long chain n-3 fatty acids

(MS Rosell et al., 2005). Thus, depending on the reasons of practicing the diet, socioeconomic status and education, vegetarians may have insufficient intake of several nutrients and generally low intake of proteins and amino acids, but a high intake of carbohydrates (Deriemaeker et al., 2010; Rizzo et al., 2013).

2.5 Changes in the understanding of the role of plant-based diets in human health

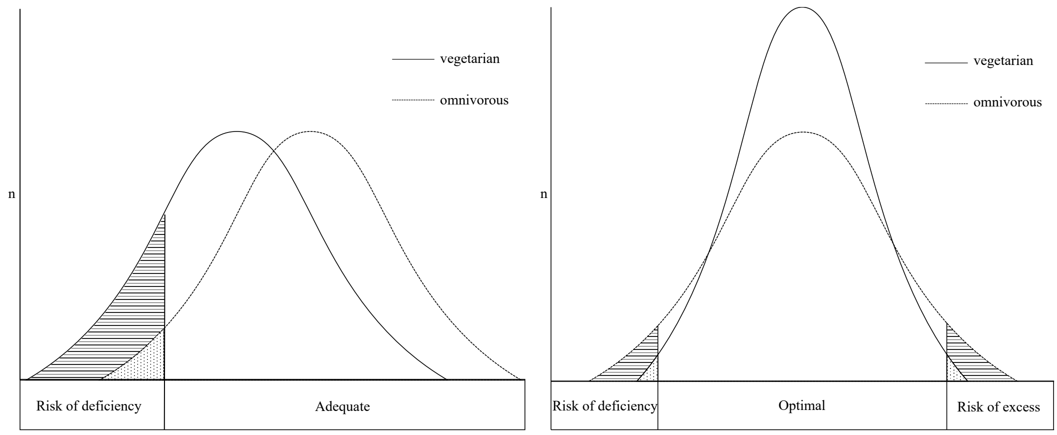
Epidemiological, clinical, and basic science research on the health effects of several plant-based foods is greatly expanding scientists' understanding of the role foods have on human health and nutrition (Sabaté, 2003). Up to the 1970s the majority of the publications assessing the relation between vegetarian diet and health focused on potential risks of an insufficient supply of micronutrients. In the 1990s the focus on the nutrients and potential deficiency symptoms shifted to preventive and therapeutical aspects of nutrition. This approach led to new perceptions about the association between nutrition and health. Not only the lack but also the excess of nutrients became subject of scientific investigation (Leitzmann, Keller, 2020). Numerous epidemiological studies show that vegetarian and other plant-based diets are associated with a reduced risk of several chronic diseases like overweight, type 2 diabetes, hypertension, ischemic heart disease, and some types of cancer (Melina et al., 2016). Findings from large cross-sectional and prospective cohort studies in western countries with a high proportion of vegetarian participants demonstrated that overall mortality was similar for vegetarians and comparable non-vegetarians, but vegetarian groups compared favorably with the general population. Also the long-term health of vegetarians appeared to be generally good, and for some diseases and medical conditions it may be better than that of comparable omnivores (Appleby, Key, 2016). These changes in the understanding of the role of plant-based diets in human health considering not only nutritional deficiency but also the risk of nutritional excess are shown in figure 1.

2.6 Plant-based diets during pregnancy, lactation, and early childhood

The safety of a plant-based diet in young women of childbearing age has been questioned due to many case reports on neonates and infants with serious and partly irreversible impairments owing to vitamin B12 deficiency. For example, psychomotor regression (Bousselamti et al., 2018), (Gowda et al., 2018), (Agrawal, Nathani, 2009), cerebral atrophy (Kocaoglu et al., 2014), poor weight gain, feeding difficulties, severe pallor, muscle hypotonia and somnolence (Guez et al., 2012), and megaloblastic anemia (Rodrigues et al., 2011) occurred in infants of vegan or vegetarian mothers.

Some scientists argue that a well-planned vegan or vegetarian diet during pregnancy and lactation may be considered safe if the unbalanced nutrients and deficiencies can be avoided (Piccoli et al., 2015). However, the evidence supporting this statement is not straightforward due to many interfering factors that were not accounted for in available studies. The

Figure 1: (a) Model of the 1960s on the adequacy of vegetarian diets. The area under the curve represents the proportion of a population for which a given diet may be adequate or deficient. (b) Model on risks and benefits of vegetarian and meat-based diets. The area under the curve represents the proportion of a population for which a diet pattern may be a risk or benefit. (Sabaté, 2003)

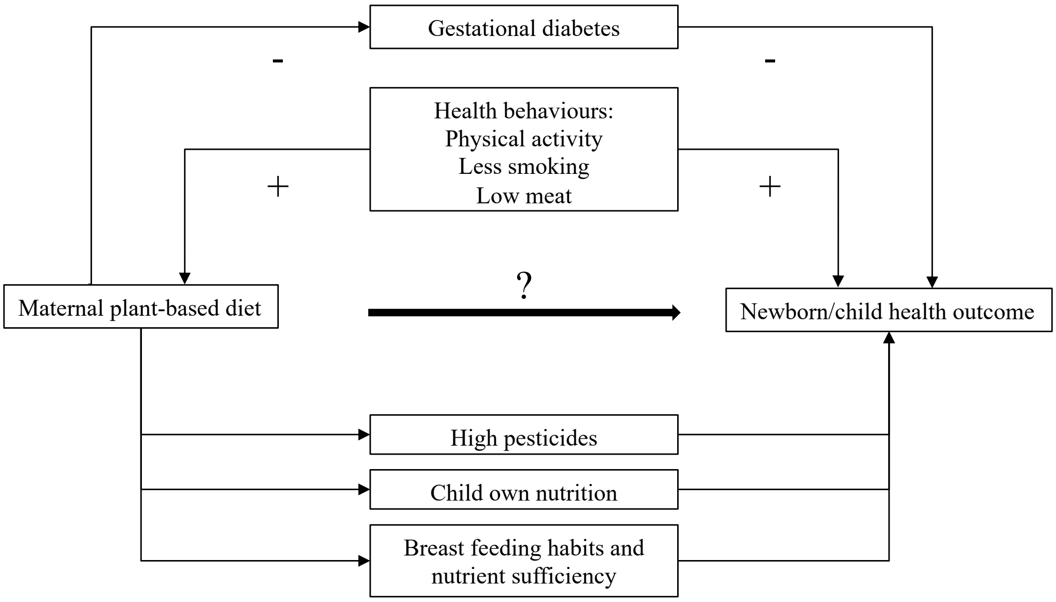


(a) (b)

traditional thinking of maternal diet as a modifier of child health endpoints should take into account other dietary and non-dietary components that could influence the role of maternal diet in child health. Child nutrition in the pre-school age is strongly correlated with and predicted by maternal nutrition. For example, maternal health behavior can potentiate or create an association between maternal plant-based diet and child health. Lower risk of gestational diabetes, breast-feeding, and child own nutrition mediate the association. Whereas, high pesticides in plant-based diet could counteract any beneficial effect. (Obeid, Pannenbäcker, 2020) (figure 2).

A main point of concern is the higher amount of required macronutrients and micronutrients during pregnancy and lactation. Especially an insufficient intake of docosahexaenoic acid (DHA), vitamin B12, iron, iodine, and folate is associated with adverse birth outcomes (Biesalski, 2016; Cetin et al., 2010; Hans, Jana, 2018).
DHA is a polyunsaturated fatty acid that plays an important role in brain development (Brenna, Carlson, 2014; Eilander et al., 2007). It can be found in fish and algae (Ackman, 1989) but it can also be synthesized from the vegetable alpha-linoleic acid (ALA) which is contained in walnuts, canola, several legumes, flaxseed, and green leafy vegetables (Gebauer et al., 2006). This explains why the breastmilk of vegetarian mothers, especially vegan mothers, contains less DHA but more ALA than the breastmilk of omnivores (Sanders, 2009). A supplementation with DHA during pregnancy showed protective effects on gestation duration and birth size (Carlson et al., 2013) but it is unclear if lower DHA-concentrations in vegetarian pregnant women cause adverse outcomes in their offspring.
Vitamin B12 is contained in several foods of animal origin such as meat, milk, egg, fish, and shellfish (Watanabe, 2007). Therefore, vitamin B12 deficiency occurs more frequently in vegans and vegetarians, especially during pregnancy (Pawlak et al., 2013). For this

Figure 2: Conceptualization of mediators and confounding factors of the relationship between maternal plant-based diet and child health.



reason, vitamin B12 supplementation is recommended to vegetarians (Craig, Mangels, 2009). Moreover, low cobalamin concentrations and hyperhomocysteinemia as a result of low vitamin B12 intake during pregnancy are associated with a higher risk of congenital heart defects (CHDs), small for gestational age (SGA), preterm delivery, preeclampsia, and neural tube defects (Bergen et al., 2012; Mignini et al., 2005; Van Der Put et al., 2001; Verkleij-Hagoort et al., 2006).

Despite the absence of menstruation, iron requirements increase during the second half of pregnancy because of the expansion of the red blood cell mass and the transfer of increasing amounts of iron to both the growing fetus and the placental structures (Bothwell, 2000). Although a considerable amount of studies suggest an association between iron deficiency during pregnancy and a higher risk of placental insufficiency, preterm delivery, intrauterine growth retardation (IUGR) (Breymann, 2015; Scholl, Reilly, 2000; Pavlova et al., 2007), it is still unclear if the treatment of mild and moderate anemia during pregnancy provides more benefits than harms (Reveiz et al., 2011). The iron intake of vegans is often higher than the iron intake of LOVs and omnivores (Larsson, Johansson, 2002; Deriemaeker et al., 2010; Sobiecki et al., 2016), but vegans and vegetarians tend to have lower iron stores (Elorinne et al., 2016; Schüpbach et al., 2017). There is an open issue as to whether vegetarian women are at higher risk of adverse birth outcomes due to iron deficiency than omnivores.

Several foods of animal origin such as fish, dairy products, and eggs have a high iodine level, but it can also be found in some types of vegetables in lower concentrations (Haldimann et al., 2005). In moderate-to-severely iodine-deficient areas, studies demonstrated that iodine supplementation before or during early pregnancy can prevent cases of cretinism, increases birthweight, reduces rates of perinatal and infant mortality and generally increases developmental scores in young children (Zimmermann, 2012). Even though severe iodine deficiency nowadays predominantly can be found in developing countries (Elmadfa, Leitzmann, 2019), vegans are at risk of iodine deficiency (Krajčovičová-Kudláčková et al., 2003). A strict vegan diet during pregnancy can lead to transient neonatal hypothyroidism (Shaikh et al., 2003) and the maternal dietary iodine intake during lactation determines the sufficient iodine intake of the infant (Dror, Allen, 2018).

In contrast, the average folate intake of vegetarians and vegans is higher than the intake of omnivores (Koebnick et al., 2001; Gilsing et al., 2010). Low folate levels are associated with the occurrence of neural tube defects (NTDs) and folate supplementation during early pregnancy can lower the risk of NTDs (Berry et al., 1999). Regardless of the type of diet, a maternal folate supplementation from four weeks before pregnancy until the end of the first trimester is recommend (DGE, 2013).

While there is proof for several relations between deficiency of micronutrients and adverse birth outcomes, the evidence for associations between plant-based diets and birth outcomes is less straightforward. There are some studies showing better mother and child health endpoints if the mothers consumed basic foods such as vegetables and fruits that are enriched in a plant-based diet (Chia et al., 2019), but this does not answer the question on the association between an exclusively plant-based diet and health. The safety of maternal vegetarian diet during pregnancy with relevance to maternal and fetal outcomes has been investigated in multiple studies. Vegetarian pregnancies showed a trend towards an association with low birth weight. In other studies, the weighted mean difference of birth weight suggested no difference between vegetarians and omnivores. Due to heterogeneity of the identified studies, no conclusion was possible on the risk of hypospadias, intrauterine growth retardation, maternal anemia, and gestational diabetes. (Tan et al., 2019)

The health benefits of the Mediterranean diet are better established than those of vegan-vegetarian diets. This could be due to the diversity of the Mediterranean diet and a more balanced amount of macronutrients and micronutrients compared to a vegetarian diet. Moreover, epidemiological studies have often used a clear definition of the dietary components of the Mediterranean diet by using diet scores (Panagiotakos et al., 2006; Trichopoulou et al., 2003), which could enable detecting systematic differences between low- and high-adherence subgroups. In addition, dietary components that are enriched in the Mediterranean diet, but deprived in a vegan-vegetarian diet such as fish and dairy products could have independent health benefits. Even though the majority of the studies are observational, there are some randomized controlled trials (RCTs) that have used components or whole concept of the Mediterranean diet and investigated the health benefits.

Several studies support the evidence that a higher Mediterranean diet score (MDS) or consumption of certain components of the Mediterranean diet such as fish and dairy products may improve the clinical pregnancy and live births in women undergoing in vitro fertilization (IVF) (Karayiannis et al., 2018), (Gaskins et al., 2019), but the generalizability of the individual studies is not certain. On the other hand, there are studies suggesting that periconceptional intake of pesticide residues in fruits and vegetables can negatively influence achieving pregnancy in women with fertility problems (Chiu et al., 2018). This factor could compromise a beneficial effect of consuming fruits and vegetables.

A systematic review and meta-analysis stated that several studies from their literature search indicated that a Mediterranean diet may be protective and possibly reduce the risk of gestational diabetes (GDM) (Mijatovic-Vukas et al., 2018). Consuming a Mediterranean diet is the most consistent dietary pattern associated with a lower risk of GDM. The risk reduction varies depending on the diet scoring system and adherence degree (Tobias et al., 2012), (Schoenaker et al., 2016), (Karamanos et al., 2014), (Schoenaker et al., 2015b), (Izadi et al., 2016). When additional risk factors were taken into account such as physical activity, non smoking, and normal BMI, the risk reduction associated with a Mediterranean diet even increases (C Zhang et al., 2014). It has been estimated that the four risk factors in combination (smoking, inactivity, overweight, and poor diet) are responsible for almost half of all cases with GDM in the population (C Zhang et al., 2014).

Furthermore a protective effect of high adherence to the Mediterranean diet during pregnancy on the incidence of wheeze in the first 12 months of life and an inverse association between the Mediterranean diet during childhood and the incidence of wheeze in the history and current wheeze was shown. However, no significant associations between high adherence of the Mediterranean diet in pregnancy and childhood and any of the other asthma-and-wheezing-related end points could be demonstrated so far. (Y Zhang et al., 2019)

The strength of the associations varies in the different health outcomes, and the level of evidence is affected by the high heterogeneity among the study designs (Biagi et al., 2019). Despite the present evidence it cannot be ruled out that lifestyle accompanying factors such as less smoking and higher physical activity formed a significant part of the detected associations.

The requirements for energy and nutrients are high during growth phase for infants, children, and adolescents. Thus, children constitute a risk group for nutrient inadequacies. Up to now, there is no consensus between international dietary expert associations, as to whether vegetarian and vegan diets are appropriate for the young. According to the American Academy of Nutrition and Dietetics appropriately planned vegetarian, including vegan, diets are healthful, nutritionally adequate, and may provide health benefits for the prevention and treatment of certain diseases. These diets are appropriate for all stages of the life cycle, including pregnancy, lactation, infancy, childhood, adolescence, older adulthood, and for athletes (Melina et al., 2016). While the German Nutrition Association (Deutsche Gesellschaft für Ernährung) also considers a LOV diet as appropriate they do not recommend a vegan diet in infancy, childhood, and adolescence due to the higher risk of nutrient deficiencies (Richter et al., 2016).

The number of recent studies is low and the existing studies are heterogeneous and often have a small number of participants (Leitzmann, Keller, 2020). The available evidence suggests tendencies towards favorable total energy intake and intake of macronutrients, vitamins and minerals in vegetarian and vegan children but lower intake of vitamin B12, zinc, calcium, iron, and vitamin D (Keller, Müller, 2016). Moreover, vegetarian and vegan children can have a sufficient intake of macronutrients and normal growth in early childhood (Weder et al., 2019). However, the associations with health outcomes that manifest at later age and a potentially negative impact if the child shifts from a vegan diet to an omnivorous diet at an older age remain unclear.

Maternal plant-based diets have been studied in relation to many health aspects of the mother and the child. Moreover, there are reports on health conditions in infants and children who were fed a plant-based diet. Maternal diet could have an impact on the growth and development of the child. The evidence is mixed and the quality of many studies is low or the generalizability is limited. It is not clear whether a plant-based diet is associated with favorable or undesirable health outcomes compared with an omnivorous diet. Thus, no clear recommendations can be made for women who plan a pregnancy, pregnant women, or parents who decide to feed their children a plant-based diet. An additional point of uncertainty is the lack of a perfect control group when accessing the risk of diseases associated with a plant-based diet. An omnivorous diet could be classified in many ways but the heterogeneity of omnivorous dietary patterns as well as the heterogeneity of plant-based dietary patterns complicates the comparability of intervention and control group.

2.7 Objectives

The overall objective of this study was to conduct a HTA to evaluate the evidence and provide recommendations on following a plant-based diet during critical life phases such as in pregnancy, lactation and early childhood. The specific objectives of this thesis were the following:

- Is a maternal plant-based diet (vegan, LOV, LV, OV, Mediterranean diet, macrobiotic diet, low-meat diet) during pregnancy associated with adverse health outcomes in the women?
- Is a maternal plant-based diet during pregnancy associated with adverse health outcomes in the child?
- Is a plant-based diet during childhood associated with adverse health outcomes in the child/adolescent?

Information retrieval for this HTA was based on a systematic review of the available literature followed by a critical appraisal and meta-analysis.

3 Methods

3.1 Sources and search strategy

This HTA was conducted according to a priori study protocol. The systematic review and meta-analysis study was registered at the international prospective register of systematic reviews (PROSPERO); ID: CRD42020211102. A systematic review of evidence to address the research question was performed. Meta-analyses to generate a pooled effect size were conducted if study designs allowed it. A search in *PubMed* was carried out. The keywords included in the search strategy were related to the forms of nutrition (including vegetarian diet, vegan diet, macrobiotic diet, low meat diet, and Mediterranean diet) and the stages of life of mother and child which were relevant for the research question (including pregnancy, fetal development, lactation, child health, and adolescent health). A combined search term was developed. For the identification of relevant publications, the term "AND" was used to combine one form of nutrition with one stage of life and the term "OR" was used for the avoidance of duplications by creating only one term instead of conducting multiple single searches. Studies were not excluded on the basis of publication date. For the full search term see appendix 2. The full text search was performed using the institutional access of the *Saarland University*. If publications were not available, the corresponding author was contacted by email and the full text was requested. Additionally, the author was contacted via the online portal *Researchgate* for a full text request. If the email was not answered within 4 weeks, the publication was excluded and the process was documented.

3.2 Study selection

The evaluation of the publications for eligibility was conducted by Arved Pannenbäcker and supervised by Prof. Dr. rer. med. Rima Obeid in a three-step process. In step one, all identified titles and abstracts were screened. In step two, a full-text review was performed on all the publications that met the predefined inclusion criteria. In step three, full texts were reevaluated for data extraction and quality assessment. The two reviewers had regular meetings to discuss the search results. Discrepancies in the evaluation were resolved through discussion in the reviewer team.

3.2.1 Inclusion/exclusion criteria

Studies and publications investigating associations between one of the above-named diets and predefined health outcomes in the mother and the child were eligible for inclusion. Only articles published in English language were included.

Eligible study designs were meta-analyses, case-control studies, cohort studies, cross-sectional studies, randomized and non-randomized, blinded and non-blinded, and controlled and non-controlled intervention studies. Case reports and case series were not considered for the general evaluation of the scientific evidence. However, these two types of publications were included to evaluate the safety of alternate diets. Systematic reviews were not included in the analysis, but their references were checked for eligible studies. Non-systematic reviews, expert opinions and consensus papers were excluded. Experimental studies with animals and cell cultures were also excluded.

3.2.2 Target population

Pregnant women, pregnant women and their offspring, infants, children, and adolescents up to 17 years (also without data on maternal diet) were considered as target population. Studies were excluded if they investigated mothers and/or children that followed an alternate diet due to metabolic or systemic diseases like chronic kidney disease, type I diabetes mellitus, coeliac diseases, phenylketonuria or cancer.

3.2.3 Exposures

Studies were included if one of the predefined alternate diet forms (vegetarian diet, vegan diet, macrobiotic diet, low meat diet, Mediterranean diet) was practiced by the mothers and/or the children. Moreover, studies were included if children and adolescents were previously fed one of the suitable diets at earlier stages of their childhood.

3.2.4 Outcomes

The study must have reported at least one clinical outcome in the mother or the child. Studies not reporting clinical outcomes such as those reporting serum/plasma concentrations of markers of deficiency without symptoms or signs were excluded unless the serum/plasma concentration was an essential component of the outcome's definition.

Outcomes of interest in the mother were: early abortion, preeclampsia, gestational diabetes, anemia, neurological and neuropsychiatric symptoms including pregnancy depression.

Outcomes of interest in the child were: preterm birth, low birth weight, small for gestational age/intrauterine growth restriction, congenital heart defects, neural tube defects, hypospadias, feeding difficulties, neurological symptoms, anemia, child physical growth markers (weight, length and body mass index or their z-scores), fine and gross motor skills, asthma and wheezing, cognitive function including school performance.

3.2.5 Dealing with multiple publications from the same cohort

Exceptions that needed careful interpretation were double publications from the same cohort or register. Multiple publications from the same cohort dealing with different outcomes were included. In case of multiple publications from the same cohort dealing with the same outcome the most relevant publication was included. Relevance was determined by the following criteria from high to low priority: congruence between the primary question of the study and our question, number of participants included in the study (larger sample size was preferred), date of publication (the most recent publication was preferred). Outcomes that we did not plan to examine were documented but were not evaluated in detail.

3.3 Data extraction

Key information about the included interventional and observational studies was extracted using a standardized data extraction table. Extracted data included information on the first author, year of publication, study design, geographic location (country, setting), study population (age, gender distribution, characteristics), methods (inclusion/exclusion criteria, measurement of dietary intake, statistical methods and adjustment for confounders), the studied exposure (diet), the outcome, the study results, and the author's conclusion. The binary outcomes were collected in a fourfold table if data for study groups with high MD adherence versus (vs) low MD adherence or plant-based vs omnivorous diet as a measurement of exposure and data for study members with or without the adverse outcome for the different exposure groups were available, respectively. The extracted data from the meta-analyses were captured separately in a second data extraction table with modified parameters.

3.4 Quality assessment

The assessment tools by the National Heart, Lung, and Blood Institute (NHLBI) suitable for each study type were used. Any disagreement in quality assessment was clarified by the reviewer team. For quality assessment of cohort studies and cross-sectional studies the Quality Assessment Tool for Observational Cohort and Cross-Sectional Studies (NHLBI, Cited on 03.06.2020) was used. For quality assessment of case-control studies the tool Quality Assessment of Case-Control Studies (NHLBI, Cited on 03.06.2020) was used and for randomized controlled trials the tool Quality Assessment of Controlled Intervention Studies (NHLBI, Cited on 03.06.2020) was used. In case of non-controlled interventional studies we used the Quality Assessment Tool for Before-After (Pre-Post) Studies With No Control Group (NHLBI, Cited on 03.06.2020). For quality assessment of meta-analyses the tool Quality Assessment of Systematic Reviews and Meta-Analyses (NHLBI, Cited on 03.06.2020) was used. Studies that obtained more than 50% of the maximum number of points were rated as fair quality studies. Studies that obtained more than 80% were rated as good quality studies. Studies with a score of up to 50% were considered as poor quality studies. All articles were included in the analysis regardless of their quality.

3.5 Data synthesis

The objective was to conduct a meta-analysis of comparable studies for each predefined outcome. To perform a meta-analysis at least three combinable studies concerning the same outcome were required. Combinability is further defined in section 4 for each outcome, respectively. The following hypotheses were reviewed:

- H_0: The odds for women/children with high adherence to the Mediterranean diet to have a negative outcome are not different from those with low adherence to the Mediterranean diet.
- H_1: The odds for women/children with high adherence to the Mediterranean diet to have a negative outcome are different from those with low adherence to the Mediterranean diet.
- H_0: The odds for vegetarian women/children to have a negative outcome are not different from omnivorous women/children.
- H_1: The odds for vegetarian women/children to have a negative outcome are different from omnivorous women/children.

3.5.1 Calculation of effect sizes

For every included study an effect size was calculated. In case of dichotomous outcomes, odds ratios (ORs) and their 95% confidence intervals (CIs) were computed. If the publications provided data to create a fourfold table, the following equations were used to calculate the OR and its 95% CI:

$$OR = \frac{\frac{a}{c}}{\frac{b}{d}} = \frac{a}{c} \times \frac{d}{b} = \frac{a}{b} \times \frac{d}{c}$$

$$lower\ 95\%\ CI\ limit = e^{ln(OR)-1.96\times SE(ln(OR))}$$

$$upper\ 95\%\ CI\ limit = e^{ln(OR)+1.96\times SE(ln(OR))}$$

If the publications with dichotomous outcomes did not provide data to create a fourfold table, the given ORs were applied for the meta-analysis. If the publications neither provided data for a fourfold table nor a computed OR but a risk ratio (RR), the RR was treated like an OR and included in the analysis. If studies met the inclusion criteria but no usable effect size for meta-analysis was presented, the results were discussed separately as an addition to the meta-analysis. If studies dealt with multiple definitions of one outcome within the same study group, data of the outcome which was most similar to the predefined outcome criteria were used for meta-analysis.

In the event of studies that investigated continuous outcomes, mean values were extracted. When performing a meta-analysis of multiple studies assessing a continuous outcome the difference in means was calculated to pool the results.

If the full text assessment produced less than three combinable studies concerning the same outcome, the results of the individual studies were tabulated and discussed in the form of a systematic review.

3.5.2 Software for analysis

All analyses were conducted in *Comprehensive Meta-Analysis* (version 3, ©2006-2020 Biostat, Inc.). Since a certain heterogeneity between studies was expected, the random effects model was used. The random effects model allows that the true effect could vary from study to study. Cochran's Q test and I^2 statistics were used to estimate the extent of heterogeneity between studies. The results of the analysis were displayed in a forest plot - a plot that shows the effect size and precision for each study as well as the combined effect.
Publication bias was assessed by visual inspection of a funnel plot and Egger's regression. Where necessary (Egger's regression: $p < 0.05$), the funnel plot was complemented by the 'trim and fill' method (Duval, Tweedie, 2000) to identify and correct for funnel plot asymmetry arising from publication bias.

3.5.3 Subgroup analysis

The potential sources of heterogeneity were evaluated by inspecting the distribution of the studies in the forest plot and identifying mutual factors, trends, time or groups of studies that agreed or disagreed. Due to the small number of studies no subgroup analysis was conducted.

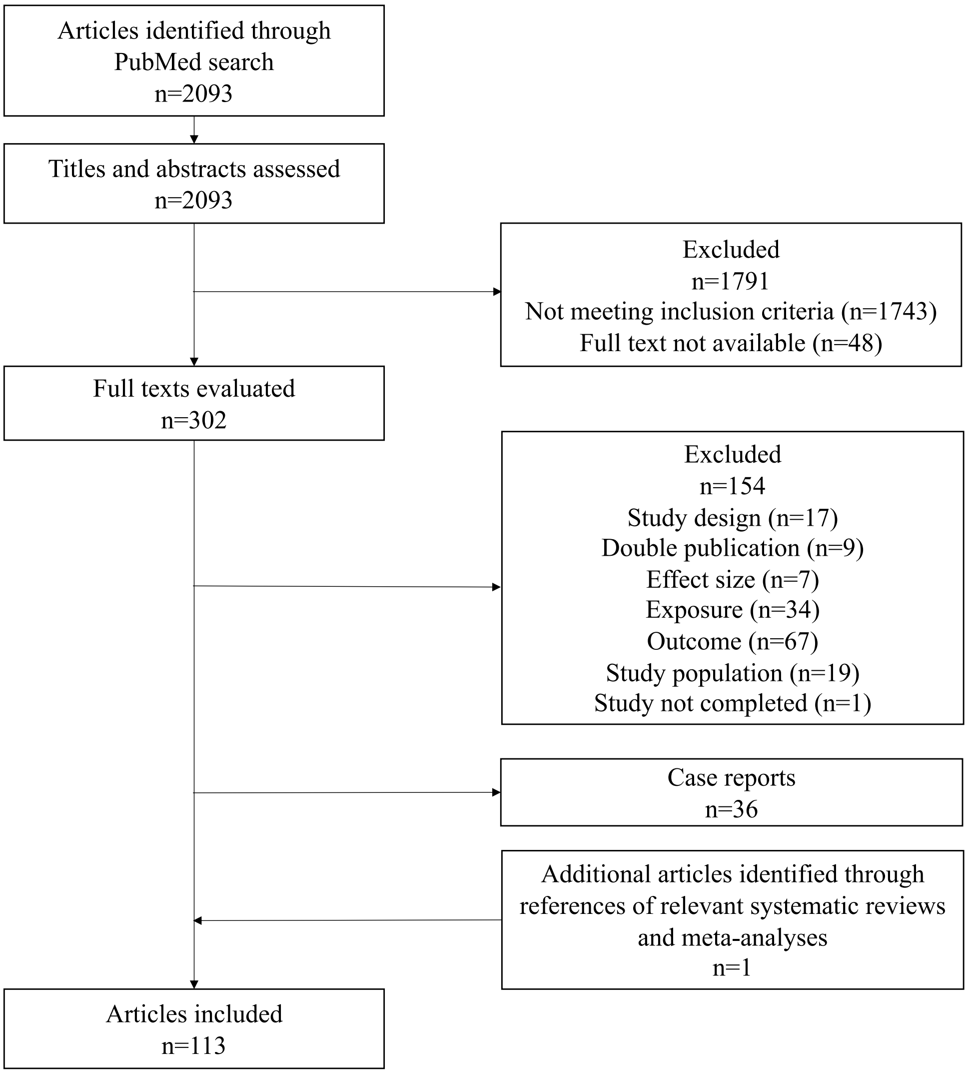
3.5.4 Sensitivity analysis

To assess the impact of each study on the combined effect a sensitivity analysis was conducted by running the analysis with one study removed at a time.

4 Results

4.1 Search results

Figure 3: Flow chart of study selection



The systematic literature search was conducted on 18 September 2019. 2093 abstracts from *PubMed* were identified and screened for eligibility. The screening process was completed on 29 November 2019 and led to 1743 excluded abstracts not meeting the inclusion criteria. Additional 48 articles were excluded after unsuccessful attempt to contact the corresponding author. For full text evaluation, 302 publications remained. In the course of full text assessment, one additional article was identified through references of relevant systematic reviews and meta-analyses. By mutual agreement, 154 studies were excluded and 36 case reports were detected. The full text evaluation was completed on 25 April 2020 and resulted in 113 included publications. The study selection process is shown in figure 3.

4.2 Quality assessment

The quality of 12 case-control studies, 37 cohort studies, 55 cross-sectional studies, 6 interventional studies, and 3 meta-analyses was rated. Overall, a good quality was attributed to 28 studies, fair quality to 82 studies, and 3 studies were considered as studies with poor quality. The rating and quality score of each individual study were tabulated (table 18-23). Since none of the predefined quality assessment tools was appropriate for the interventional study by Garcia de la Torre et al., the study was rated by using a modified version of the tool for quality assessment of controlled intervention studies.

4.3 Meta-analyses existing in the field

Of the 113 included studies, 3 publications were meta-analyses addressing our research question. The results of the identified meta-analyses are summarized in table 2.

4.3.1 Birth outcomes

Among other birth-related outcomes, Chia et al. assessed the association between maternal dietary patterns and SGA/FGR/LBW and preterm birth in a systematic review and meta-analysis. The authors did not investigate one particular dietary pattern, but multiple healthy dietary patterns characterized by high intakes of vegetables, fruits, wholegrains, low-fat dairy, and lean protein foods including the Mediterranean diet. Pooling six observational studies showed that women in the top tertile of healthy dietary patterns had a lower risk of preterm birth compared to women in the bottom tertile [OR = 0.79; (0.68-0.91)]. The meta-analysis of 10 observational studies showed a trend towards a lower risk of SGA/FGR/LBW in women in the top tertile of healthy dietary patterns [OR = 0.86; (0.73-1.01)].

4.3.2 Asthma and wheezing

The systematic review and meta-analysis by Y Zhang et al. investigated the association between maternal adherence to the Mediterranean diet as well as Mediterranean diet adherence in children and the risk of asthma and wheezing. There was an inverse association

Table 2: Meta-analyses existing in the field

Author & year	Exposure	Outcome	Studies n	Pooled estimate (95% CI)	I^2
Chia 2019	maternal healthy patterns	preterm birth	6	OR = 0.79 (0.68-0.91)	32%
		SGA/FGR/LBW	10	OR = 0.86 (0.73-1.01)	34%
Eaton 2019	animal source food intervention in children	linear growth	5	difference in means = 0.24 (-0.09-0.56)[1]	99%
		weight gain	5	difference in means = 0.22 (0.06-0.39)[2]	93%
Zhang 2019	MD pregnancy	asthma	2	OR = 1.01 (0.94-1.09)	0%
	MD pregnancy	wheeze 12 first months	3	OR = 0.92 (0.88-0.95)	0%
	MD pregnancy	current wheeze	3	OR = 0.76 (0.45-1.29)	78%
	MD childhood	asthma	7	OR = 0.87 (0.72-1.04)	72%
	MD childhood	severe asthma	2	OR = 0.97 (0.89-1.06)	25%
	MD childhood	exercise-induced asthma	1	OR = 1.16 (0.97-1.39)	0%
	MD childhood	wheeze in the history	3	OR = 0.51 (0.37-0.70)	0%
	MD childhood	current wheeze	8	OR = 0.97 (0.95-0.99)	4%
	MD childhood	atopic wheeze in childhood	3	OR = 1.00 (0.95-1.05)	0%

CI = confidence interval; FGR = fetal growth restriction; HAZ = height-for-age z-score; LAZ = length-for-age z-score; LBW = low birth weight; MD = Mediterranean diet; OR = odds ratio; SGA = small for gestational age; WAZ = weight-for-age z-score

[1] linear growth assessed using HAZ/LAZ

[2] weight gain assessed using WAZ

between Mediterranean diet adherence during pregnancy and the incidence of wheezing in the first 12 months of life [OR = 0.92; (0.88-0.95)]. High Mediterranean diet adherence during childhood was associated with a reduced incidence of wheezing in the history [(OR = 0.51; 0.37-0.70)] and current wheeze [OR = 0.97; (0.95-0.99)]. Further meta-analyses showed no significant relations between Mediterranean diet adherence during pregnancy and any other end point (asthma, current wheeze) or Mediterranean diet adherence during childhood and any other end point (asthma, severe asthma, exercise-induced asthma, atopic wheeze).

4.3.3 Child growth

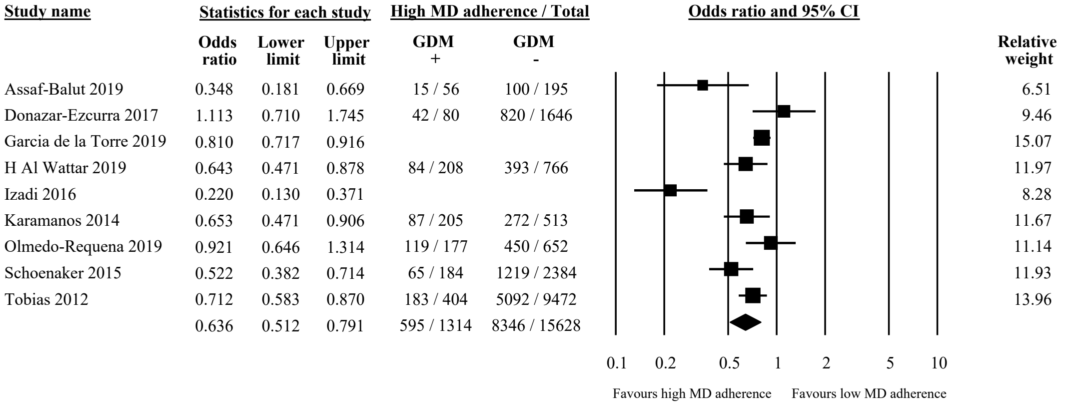
The Cochrane review by Eaton et al. examined the effectiveness of animal-source foods compared to other feeding interventions or no intervention in improving growth and developmental outcomes in children aged 6 to 59 months. Meta-analyses were conducted for the associations between animal-source food interventions and linear growth and weight gain including 5 studies per outcome. The analyses showed a higher weight gain in children receiving an animal-source food intervention [difference in means = 0.22; (0.06-0.39)] and no significantly higher linear growth [difference in means = 0.24 (-0.09-0.56)]. The authors criticized the low quality of evidence and requested more adequately powered trials.

4.4 Plant-based diet during pregnancy and maternal outcomes

Twenty-two studies assessing the relation between maternal diet during pregnancy and one of the predefined maternal outcomes met the inclusion criteria. The findings of the systematic reviews and meta-analyses of every outcome are described in detail in the following sections. The listed effect sizes in the tables refer to the comparison of high vs low Mediterranean diet adherence or vegetarian vs omnivorous diet, respectively.

4.4.1 Mediterranean diet and gestational diabetes

Figure 4: Forest plot for the association between Mediterranean diet adherence and GDM



Study name	Statistics for each study			High MD adherence / Total		Relative weight
	Odds ratio	Lower limit	Upper limit	GDM +	GDM -	
Assaf-Balut 2019	0.348	0.181	0.669	15 / 56	100 / 195	6.51
Donazar-Ezcurra 2017	1.113	0.710	1.745	42 / 80	820 / 1646	9.46
Garcia de la Torre 2019	0.810	0.717	0.916			15.07
H Al Wattar 2019	0.643	0.471	0.878	84 / 208	393 / 766	11.97
Izadi 2016	0.220	0.130	0.371			8.28
Karamanos 2014	0.653	0.471	0.906	87 / 205	272 / 513	11.67
Olmedo-Requena 2019	0.921	0.646	1.314	119 / 177	450 / 652	11.14
Schoenaker 2015	0.522	0.382	0.714	65 / 184	1219 / 2384	11.93
Tobias 2012	0.712	0.583	0.870	183 / 404	5092 / 9472	13.96
	0.636	0.512	0.791	595 / 1314	8346 / 15628	

Cochran's Q Test I^2 = 79.18% (p = 0.00); Egger's regression: p = 0.12

Nine studies evaluated the association between Mediterranean diet adherence and GDM. The studies are summarized in table 3. A meta-analysis was conducted to generate a pooled effect size of the detected publications. The study by Izadi et al. did not provide sufficient data to create a fourfold table so that their computed OR was used in the meta-analysis. Due to the interventional design of their study, Garcia de la Torre et al. calculated a RR to present the effect of Mediterranean diet adherence on the risk of GDM. The RR was treated as an OR in our analysis. In total, the analysis included 1444 participants with GDM and 16430 participants without GDM as well as 325 participants from the study by Izadi et al. who can not be allocated to one of the groups for lack of data.

The meta-analysis resulted in a combined OR and 95% CI of 0.64 (0.51-0.79) (figure 4).

Therefore a statistically significant association between a high Mediterranean diet adherence and a lower risk of GDM was shown.
The included studies showed a high heterogeneity (Cochran's Q Test I^2 = 79.18%, p = 0.00). No publication bias was detected (Egger's regression: p = 0.12; appendix 4).
Sensitivity analysis showed no effect on the combined result to a large extent (data not shown).

Table 3: Studies assessing the association between Mediterranean diet adherence and GDM

Author & year	Design	Outcome definition	Effect size (95% CI)
Assaf-Balut 2019	cohort	IADPSG criteria[1]	OR = 0.35 (0.18-0.67)
Donazar-Ezcurra 2017	cohort	self-reported diagnosis, confirmed by medical doctors	OR = 1.11 (0.71-1.75)
García de la Torre 2019	interventional	IADPSG criteria[1]+ WHO criteria[2]	RR = 0.81 (0.72-0.92)
H Al Wattar 2019	RCT	IADPSG criteria[1]	OR = 0.64 (0.47-0.88)
Izadi 2016	case-control	FG > 95 mg/dL or 1-h post-prandial glucose > 140 mg/dL	OR = 0.22 (0.13-0.37)
Karamanos 2014	cohort	IADPSG criteria[1]	OR = 0.65 (0.47-0.91)
Olmedo-Requena 2019	case-control	NDDG criteria[3]	OR = 0.92 (0.65-1.31)
Schoenaker 2015	cohort	self-reported diagnosis	OR = 0.52 (0.38-0.71)
Tobias 2012	cohort	self-reported diagnosis	OR = 0.71 (0.58-0.87)

CI = confidence interval; FG = fasting glucose; IADPSG = International Association of the Diabetes and Pregnancy Study Groups; NDDG = National Diabetes Data Group; OR = odds ratio; RCT = randomized controlled trial; RR = risk ratio; WHO = World Health Organization

[1] IADPSG criteria: fasting plasma glucose value $\geq$ 5.1 mmol/L, or 2-hour values $\geq$ 8.5 mmol/L following a 75-g oral glucose tolerance test

[2] WHO criteria: fasting plasma glucose value of 5.1-6.9 mmol/l, 2-hour plasma glucose 8.5-11.0 mmol/l following a 75g oral glucose tolerance test

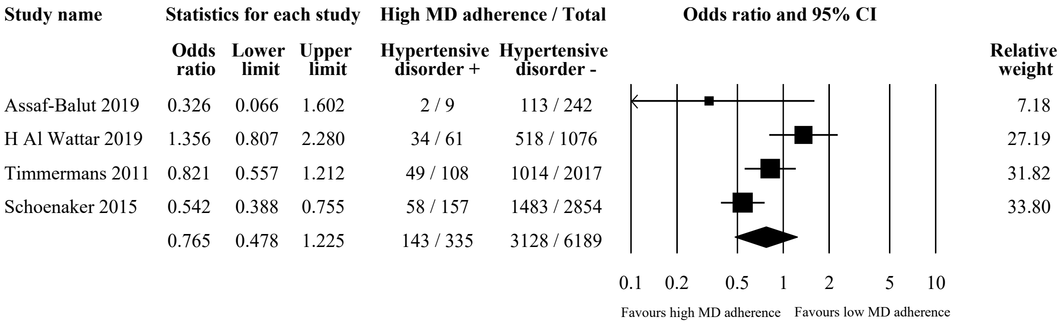
[3] NDDG criteria: fasting plasma glucose value of 105 mg/dL; 1-hour value of 190 mg/dL; 2-hour value of 165 mg/dL; 3-hour value 145 mg/dL

4.4.2 Mediterranean diet and hypertensive disorders

The search produced four studies reporting on the association between maternal Mediterranean diet adherence and hypertensive disorders during pregnancy (table 5).
The meta-analysis of the RCT by H. Al Wattar et al. and three cohort studies by Assaf-Balut et al., Timmermans et al., and Schoenaker et al. showed that pregnant women with high Mediterranean diet adherence had a lower OR for developing a pregnancy-induced hypertension, but the result was not statistically significant [0.77; (0.48-1.23); figure 5].
The included studies showed a high heterogeneity (Cochran's Q Test I^2 = 69.72%, p =

0.02). No publication bias was detected (Egger's regression: p = 0.95; data not shown). Removing one study at a time for sensitivity analysis showed that the association became statistically significant when the study by H. Al Wattar et al. was removed [0.64; (0.44-0.91)]. Being the only interventional study might be one reason for this result. The intervention consisted of a dietary advice which can not be equated with a high adherence to the Mediterranean diet.

Figure 5: Forest plot for the association between Mediterranean diet adherence and hypertensive disorders



Study name	Statistics for each study			High MD adherence / Total		Relative weight
	Odds ratio	Lower limit	Upper limit	Hypertensive disorder +	Hypertensive disorder -	
Assaf-Balut 2019	0.326	0.066	1.602	2 / 9	113 / 242	7.18
H Al Wattar 2019	1.356	0.807	2.280	34 / 61	518 / 1076	27.19
Timmermans 2011	0.821	0.557	1.212	49 / 108	1014 / 2017	31.82
Schoenaker 2015	0.542	0.388	0.755	58 / 157	1483 / 2854	33.80
	0.765	0.478	1.225	143 / 335	3128 / 6189	

Cochran's Q Test I^2 = 69.72% (p = 0.02); Egger's regression: p = 0.95 (no publication bias)

Table 5: Studies assessing the association between Mediterranean diet adherence and hypertensive disorders

Author & year	Design	Outcome definition	Effect size (95% CI)
Assaf-Balut 2019	cohort	gestational hypertension: BP ≥140/90 mmHg after 20 GW	OR = 0.33 (0.07-1.60)
H Al Wattar 2019	RCT	preeclampsia[1]	OR = 1.36 (0.81-2.28)
Timmermans 2011	cohort	gestational hypertension: BP ≥140/90 mmHg after 20 GW	OR = 0.82 (0.56-1.21)
Schoenaker 2015	cohort	self-reported diagnosis	OR = 0.54 (0.38-0.76)

BP = blood pressure; CI = confidence interval; GW = gestational weeks; OR = odds ratio; RCT = randomized controlled trial

[1] preeclampsia: onset of hypertension (BP ≥140/90 mmHg) and new onset proteinuria (spot urine protein creatinine ratio > 30 mg/mmol or 24-hour urine protein > 300 mg or 2+ or more on urine dipstick) after 20 GW

4.4.3 Mediterranean diet and gestational weight gain

The search produced three studies reporting on the association between Mediterranean diet adherence and gestational weight gain (GWG). Due to significant differences in study design, a meta-analysis was not conducted. Details of the studies are summarized in table 6.
In a cross-sectional study by Koutelidakis et al. including 1432 mothers, moderate to high Mediterranean diet adherence compared to low to very low Mediterranean diet adherence before pregnancy was associated with a lower risk of excessive GWG [0.53; (0.42-0.66)].
In a RCT, KM Renault et al. evaluated the effect of a Mediterranean diet intervention and a physical activity intervention or a physical activity intervention alone on GWG in 342 obese pregnant women. The combined intervention of Mediterranean diet and physical activity resulted in a RR of 0.73 (0.57-0.94) and the physical activity intervention alone resulted in a RR of 0.86 (0.68-1.08) for an excessive GWG. In a cross-sectional study with 170 participants by Silva-del Valle et al., women in the third tertile of Mediterranean diet adherence also had a lower risk of excessively high weight gain compared to women in the first tertile of Mediterranean diet adherence [OR = 0.82 (0.23-2.92)].
Even though it was not possible to conduct a meta-analysis due to the heterogeneity between the three studies, the results indicate that a high Mediterranean diet adherence might be favorable for pregnant women to reduce the risk of excessive GWG.

Table 6: Studies assessing the association between Mediterranean diet adherence and gestational weight gain

Author & year	Design	Outcome definition	Effect size (95% CI)
Koutelidakis 2018	cross-sectional	GWG outside the IOM recommendations[1]	OR = 0.56 (0.45-0.69)
Renault 2015	RCT	GWG > 9kg	RR = 0.73 (0.57-0.94)
Silva-del Valle 2013	cross-sectional	GWG > 9kg	OR = 0.82 (0.23-2.92)

CI = confidence interval; GWG = gestational weight gain; IOM = Institute of Medicine; OR = odds ratio; RCT = randomized controlled trial; RR = risk ratiol

[1] GWG outside the IOM recommendations: < 18.5 kg/m^2 (underweight): 12.7–18.1 kg, 18.5–24.9 kg/m^2 (normal weight): 11.3–15.9 kg, 25.0–29.9 kg/m^2 (overweight): 6.8–11.3 kg, $\geq$ 30 kg/m^2 (obese): 5.0–9.1 kg

4.4.4 Vegetarian diet and anemia in pregnant women

The search generated three studies evaluating the association between low meat consumption or vegetarian diet and anemia during pregnancy (table 7). The study by Abriha et al. including 619 Ethiopian pregnant women and the study by Baig-Ansari et al. including 1366 Pakistani women compared low meat eaters to women consuming meat on a regular basis. Sharma et al. inspected 1150 Indian women for anemia with regard to being vegetarian or eating halal meat.
The data of the three studies were pooled in a meta-analysis. No statistically significant

effect could be shown [1.38 (0.86-2.23); appendix 5]. The included studies showed a moderate heterogeneity (Cochran's Q Test I^2 = 54.79%, p = 0.11). No publication bias was detected (Egger's regression: p = 0.74; data not shown).
Due to the small number of studies, no sensitivity analysis was conducted.

Table 7: Studies assessing associations between vegetarian diet forms during pregnancy and anemia in pregnant women

Author & year	Design	Outcome definition	Effect size (95% CI)
Abriha 2014	cross-sectional	Hb < 11 g/dl	OR = 2.43 (1.27-4.65)
Baig-Ansari 2008	cross-sectional	Hb < 11 g/dl	OR = 1.17 (0.82-1.69)
Sharma 2003	cross-sectional	Hb < 11 g/dl	OR = 0.99 (0.49-1.99)
CI = confidence interval; Hb = hemoglobin; OR = odds ratio			

4.4.5 Vegetarian diet and gestational diabetes

Two cohort studies and one cross-sectional study were found that reported on the relation between adherence to a vegetarian diet during pregnancy and GDM (table 8).
The identified studies used different criteria for diagnosing GDM. Moreover, the exposures differed between studies. Jali et al. included 325 Indian women and compared vegetarians to non-vegetarians. Mak et al. assessed the adherence to a plant-based dietary pattern in 1337 Chinese pregnant women, whereas Mari-Sanchis et al. compared the lowest quartile to the highest quartile of meat consumption in 3298 Spanish women.
A meta-analysis was conducted to generate a pooled estimate of the single results. No statistically significant effect could be shown [0.63 (0.31-1.28); appendix 6]. The included studies showed a high heterogeneity (Cochran's Q Test I^2 = 86.11%, p = 0.00). No publication bias was detected (Egger's regression: p = 0.20; data not shown).

Table 8: Studies assessing associations between vegetarian diet forms during pregnancy and gestational diabetes mellitus

Author & year	Design	Outcome definition	Effect size (95% CI)
Jali 2011	cross-sectional	WHO criteria[1]	OR = 0.31 (0.17-0.58)
Mak 2018	cohort	IADPSG criteria[2]	OR = 1.17 (0.81-1.69)
Mari-Sanchis 2018	cohort	self-reported diagnosis	OR = 0.61 (0.40-0.94)
CI = confidence interval; IADPSG = International Association of the Diabetes and Pregnancy Study Groups; OR = odds ratio; WHO = World Health Organization			

[1] WHO criteria: fasting plasma glucose value of 5.1-6.9 mmol/l, 2-hour plasma glucose 8.5-11.0 mmol/l following a 75g oral glucose tolerance test

[2] IADPSG criteria: fasting plasma glucose value $\geq$ 5.1 mmol/L, or 2-hour values $\geq$ 8.5 mmol/L following a 75-g oral glucose tolerance test

4.4.6 Vegetarian diet and other pregnancy-related outcomes

The maternal outcomes with a low number of available studies are summarized in table 9. The search generated one study dealing with the association between maternal vegetarian diet during pregnancy and excessive GWG. The US American cohort study by Stuebe et al. included 1388 pregnant women. Compared to omnivorous women, women who followed a vegetarian diet during first trimester of pregnancy had a lower risk of excessively gaining weight during pregnancy [OR = 0.45; (0.27-0.76)]. A vegetarian diet during second semester was not associated with a significantly lower risk of excessive GWG [OR = 0.70; (0.40-1.20)].

The case-control study by Kaur et al. assessed the association between maternal vegetarian diet and pregnancy-induced hypertension. Women suffering from pregnancy induced hypertension were more likely to be vegetarian [OR = 2.54; (1.76-3.67)].

The search yielded one study by Santos Vaz et al. investigating the relation between following a vegetarian diet and anxiety during pregnancy. In the cohort study including 9530 British women, vegetarians showed an increased likelihood of high anxiety symptoms [OR = 1.25; (1.08-1.45)].

Table 9: Studies assessing associations between vegetarian diet forms during pregnancy and gestational weight gain, hypertensive disorders, and neuropsychiatric symptoms

Author & year	Design	Outcome definition	Effect size (95% CI)
Gestational weight gain			
Stuebe 2009	cohort	GWG outside the IOM recommendations[1]	OR = 0.45 (0.27-0.76)[2] OR = 0.70 (0.40-1.20)[3]
Hypertensive disorders			
Kaur 2013	case-control	BP $\geq$ 140/90 + significant proteinuria	OR = 2.54 (1.76-3.67)
Neuropsychiatric symptoms			
Santos Vaz 2013	cohort	anxiety symptoms during pregnancy	OR = 1.25 (1.08-1.45)

BP = blood pressure; CI = confidence interval; GWG = gestational weight gain; IOM = Institute of Medicine; OR = odds ratio

[1] GWG outside the IOM recommendations: < 18.5 kg/m^2 (underweight): 12.7–18.1 kg, 18.5–24.9 kg/m^2 (normal weight): 11.3–15.9 kg, 25.0–29.9 kg/m^2 (overweight): 6.8–11.3 kg, $\geq$ 30 kg/m^2 (obese): 5.0–9.1 kg

[2] vegetarian diet during first trimester of pregnancy

[3] vegetarian diet during second trimester of pregnancy

4.5 Plant-based diet during pregnancy and outcomes in the child

Twenty-nine studies assessing the relation between maternal diet during pregnancy and one of the predefined outcomes in the child met the inclusion criteria. The findings of the systematic reviews and meta-analyses of every outcome are described in detail in the following sections.

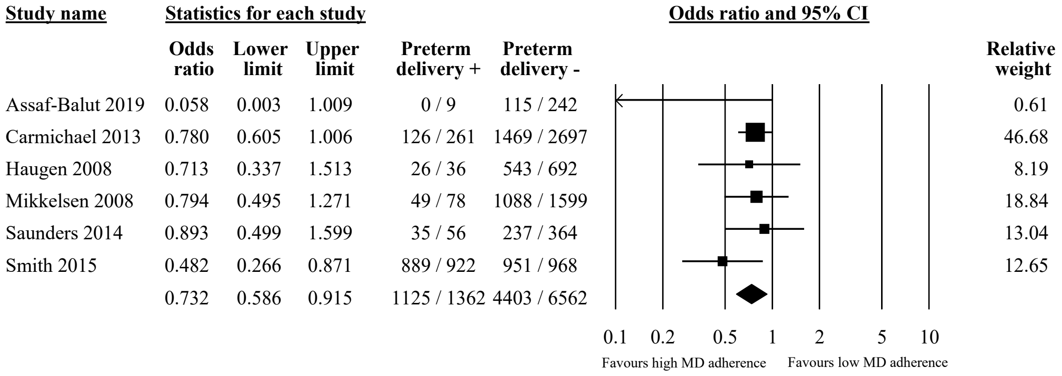
4.5.1 Mediterranean diet and preterm delivery

The search identified six studies reporting on the association between maternal Mediterranean diet adherence and preterm delivery which are summarized in table 9. All the authors defined the outcome preterm delivery as delivery before 37 weeks of gestation. Only Smith et al. defined late and moderately preterm delivery as birth after 32 and before 37 weeks of gestation. Carmichael et al. assessed the maternal Mediterranean diet adherence during the year before pregnancy whereas the remaining studies assessed the Mediterranean diet adherence during pregnancy.

The meta-analysis of the six studies resulted in a statistically significant combined OR and 95% CI of 0.73 (0.59-0.92) (figure 6). From this result can be deduced that compared to a low Mediterranean diet adherence, pregnant women with high Mediterranean diet adherence had a 42% lower probability for preterm delivery. The included studies showed a low heterogeneity (Cochran's Q Test I^2 = 12.78%, p = 0.33). No publication bias was detected (Egger's regression: p = 0.14; appendix 7).

Sensitivity analysis showed no considerable effect when removing one study at a time (data not shown).

Figure 6: Forest plot for the association between Mediterranean diet adherence and preterm delivery



Study name	Odds ratio	Lower limit	Upper limit	Preterm delivery +	Preterm delivery -	Relative weight
Assaf-Balut 2019	0.058	0.003	1.009	0 / 9	115 / 242	0.61
Carmichael 2013	0.780	0.605	1.006	126 / 261	1469 / 2697	46.68
Haugen 2008	0.713	0.337	1.513	26 / 36	543 / 692	8.19
Mikkelsen 2008	0.794	0.495	1.271	49 / 78	1088 / 1599	18.84
Saunders 2014	0.893	0.499	1.599	35 / 56	237 / 364	13.04
Smith 2015	0.482	0.266	0.871	889 / 922	951 / 968	12.65
	0.732	0.586	0.915	1125 / 1362	4403 / 6562	

Cochran's Q Test I^2 = 12.78% (p = 0.33); Egger's regression: p = 0.14 (no publication bias)

Table 9: Studies assessing the association between Mediterranean diet adherence and preterm delivery

Author & year	Design	Outcome definition	Effect size (95% CI)
Assaf-Balut 2019	cohort	preterm delivery: birth before 37 GW	OR = 0.06 (0.00-1.01)
Carmichael 2013	cross-sectional	preterm delivery: birth before 37 GW	OR = 0.78 (0.61-1.01)
Haugen 2008	cohort	preterm delivery: birth before 37 GW	OR = 0.71 (0.34-1.51)
Mikkelsen 2008	cohort	preterm delivery: birth before 37 GW	OR = 0.79 (0.50-1.27)
Saunders 2014	cohort	preterm delivery: birth before 37 GW	OR = 0.89 (0.50-1.60)
Smith 2015	case-cohort	preterm delivery: birth after 32 and before 37 GW	OR = 0.48 (0.27-0.87)

CI = confidence interval; GW = gestational weeks; OR = odds ratio

4.5.2 Mediterranean diet and small for gestational age, intrauterine growth retardation, fetal growth restriction and low birth weight

The search generated ten individual studies reporting on potential associations between maternal Mediterranean diet adherence and small for gestational age (SGA) infants, intrauterine growth retardation (IUGR), fetal growth restriction (FGR) or low birth weight (LBW) (table 10). The authors defined their outcome as a birth weight below the tenth percentile of the reference population with the exception of Monteagudo et al. (gestational age-adjusted birth weight below percentile 2.3 in the study cohort) and Timmermans et al. (birth weight below 2500 g). Five studies provided sufficient data to create fourfold tables. In other cases, the ORs computed by the authors were extracted. The publications by Chatzi et al. and Poon et al. supplied RRs that were treated as ORs in the analysis. A meta-analysis was conducted pooling eight studies after exclusion of the studies by Gómez Roig et al. and Peraita-Costa et al. due to asymmetric CIs. Their results are presented separately in narrative form.
Combining the results led to a pooled estimate and 95% CI of 0.87 (0.58-1.31) (appendix 8). The included studies showed a high heterogeneity (Cochran's Q Test I^2 = 70.94%, p = 0.00). No publication bias was detected (Egger's regression: p = 0.62; appendix 8).
Sensitivity analysis indicated no significant impact of one study when removing one study at a time (data not shown).
The studies, that could not be included in the meta-analysis, showed varying results. Gómez Roig et al. assessed differences in dietary habits between pregnant women with SGA fetuses and those with appropriate for gestational age (AGA) fetuses. Examining the data of 46 mothers with SGA and 81 mothers with AGA fetuses showed that women following a Mediterranean diet were more likely to have an AGA fetus ($p < 0.05$). Peraita-Costa et al.

investigated the association between maternal Mediterranean diet adherence during pregnancy and the risk of SGA fetuses in a cross-sectional study of 492 Spanish mothers. Their findings indicated that newborns of women with low Mediterranean diet adherence had a higher risk of being SGA when adjusting for parental BMI and multiple gestation, but not when adjusting for all confounders.

In total, the results of the meta-analysis and the single studies show that there is no clear relation between maternal Mediterranean diet adherence and the risk of giving birth to SGA children. Nevertheless, the findings implicate a slight trend towards a protective effect of the Mediterranean diet.

Table 10: Studies assessing the association between Mediterranean diet adherence and SGA, FGR, IUGR and LBW

Author & year	**Design**	**Outcome definition**	**Effect size (95% CI)**
Assaf-Balut 2019	cohort	BW < 10th percentile	OR = 0.05 (0.00-0.81)
Chatzi 2012	cohort	BW < 10th percentile	RR = 0.97 (0.42-2.25)[1] RR = 0.50 (0.28-0.90)[2] RR = 1.96 (0.90-4.26)[3]
Gomez Roig 2017	cross-sectional	BW < 10th percentile	OR = 0.18 (0.07-0.50)
H Al Wattar 2019	RCT	BW < 10th percentile	OR = 0.78 (0.53-1.14)
Martinez-Galiano 2018	case-control	BW < 10th percentile	OR = 0.85 (0.50-1.44)
Monteagudo 2016	cohort	BW < 2500 g	OR = 6.16 (1.44-26.40)
Peraita-Costa 2018	cross-sectional	BW < 10th percentile	OR = 1.03 (0.43-2.00)
Poon 2013	cohort	BW < 10th percentile	RR = 0.94 (0.48-1.83)
Saunders 2014	cohort	BW < 10th percentile	OR = 1.34 (0.72-2.50)
Timmermans 2012	cohort	BW < 2.3 percentile of study population	OR = 0.35 (0.20-0.60)

BW = birth weight; CI = confidence interval; OR = odds ratio; RCT = randomized controlled trial; RR = risk ratio

[1] INMA Atlantic cohort
[2] INMA Mediterranean cohort
[3] RHEA cohort

4.5.3 Mediterranean diet and birth defects

Four of the identified studies assessed the association between maternal Mediterranean diet adherence and birth defects. Due to a lack of studies reporting on the same outcome, a meta-analysis was not performed. Key points of the studies are summarized in table 11.

In their case-control study including 9885 cases and 9468 controls, Botto et al. evaluated the association between maternal Mediterranean diet adherence and congenital heart defects.

No significantly lower OR was observed neither for conotruncal [0.98; (0.84-1.14)] nor for septal defects [0.93; (0.82-1.06)] comparing the highest to the lowest quartile of maternal Mediterranean diet adherence. Carmichael et al. investigated the association between maternal Mediterranean diet adherence and hypospadias in their offspring in a case-control study with 1250 cases and 3118 controls. This study showed that there was no significant relation between maternal high Mediterranean diet adherence and the occurrence of hypospadias [0.9; (0.7-1.1)]. Another case-control study by Carmichael et al. assessed the association between maternal Mediterranean diet adherence and anencephaly and spina bifida including 291 anencephaly cases, 645 spina bifida cases, and 6147 controls. The authors showed that a high Mediterranean diet adherence was associated with a significantly lower risk of anencephaly [0.64; (0.45-0.92)] but not of spina bifida [0.88; (0.68-1.13)]. The fourth identified case-control study assessed the connection between maternal Mediterranean diet adherence and the occurrence of spina bifida. Vujkovic et al. analyzed data of 50 cases and 81 controls resulting in an OR of 0.4 (0.2-1.1) for high versus low Mediterranean diet adherence.

Table 11: Studies assessing the association between Mediterranean diet adherence birth defects

Author & year	Design	Outcome definition	Effect size (95% CI)
Botto 2016	case-control	conotruncal CHDs	OR = 0.98 (0.84-1.14)
		septal CHDs	OR = 0.93 (0.82-1.06)
Carmichael 2012a	case-control	hypospadias	OR = 0.9 (0.7-1.1)
Carmichael 2012b	case-control	anencephaly	OR = 0.64 (0.45-0.92)
		spina bifida	OR = 0.88 (0.68-1.13)
Vujkovic 2009	case-control	spina bifida	OR = 0.4 (0.2-1.1)

CHD = congenital heart defect; CI = confidence interval; OR = odds ratio

4.5.4 Vegetarian diet and small for gestational age, intrauterine growth retardation, fetal growth restriction and low birth weight

The search generated seven studies investigating potential associations between maternal vegetarian diet and SGA infants, IUGR, FGR or LBW. The exposure was defined as vegetarian diet by all authors apart from Zulyniak et al. who used a plant-based pattern and Ibanez et al. who compared low to high maternal meat consumption. The majority of the articles defined the outcome as birth weight below the tenth percentile of the reference population or birth weight below 2500 g, whereas Kaur et al. investigated IUGR as fetal weight below 500 g and placental insufficiency. A meta-analysis was performed to combine the extracted data in a pooled estimate. The studies by Grieger et al. and Zulyniak et al. were not included in the analysis because they calculated their ORs per one-standard deviation (SD)-increase and per one-unit-increase in dietary pattern adherence, respectively.
Combining the results of the single studies led to a pooled estimate of 0.97 (0.55-1.71) (appendix 9). The studies showed a high heterogeneity (Cochran's Q Test I^2 = 77.42%, p = 0.00). No publication bias was found (Egger's regression: p = 0.42; appendix 9).

Sensitivity analysis indicated no significant impact of one study when removing one study at a time (data not shown).

The studies that were not included in the meta-analysis demonstrated similar results. Grieger et al. performed a cross-sectional study including 309 Australian mothers. Their aim was to identify relations between maternal dietary patterns in the 12 months before conception and fetal growth. A one-SD-increase in adherence to the vegetarian dietary pattern was associated with a higher risk of having a SGA fetus [OR = 1.08; (0.78-1.48)].

Zulyniak et al. recruited 3997 Canadian pregnant women for their cohort study with the objective to detect links between maternal diet and birth weight. Ethnically stratified analyses showed that among white Europeans, a one-unit-increase in maternal adherence to the plant-based pattern was associated with a higher risk of SGA fetuses [OR = 1.46; (1.08-1.54)].

Overall, the results of the meta-analysis and the single studies show no correlation between a vegetarian diet during pregnancy and an increased risk of SGA, IUGR, FGR or LBW.

Table 12: Studies assessing the association between vegetarian diet and SGA, IUGR, FGR and LBW

Author & year	**Design**	**Outcome definition**	**Effect size (95% CI)**
Fikree 1994	cohort	BW < 10th percentile	OR = 0.35 (0.18-0.70)
Grieger 2014	cross-sectional	BW < 10th percentile	OR = 1.08 (0.78-1.48)
Ibanez 2019	cross-sectional	BW < 10th percentile	OR = 1.15 (0.78-1.70)
Kaur 2013	case-control	fetal weight < 500 g + placental insufficiency	OR = 1.90 (1.22-2.95)
Koirala 2015	cross-sectional	BW < 2500 g	OR = 1.33 (0.53-3.36)
Misra 2015	cohort	BW < 2500 g	OR = 0.72 (0.30-1.67)
Zulyniak 2017	cohort	BW < 10th percentile	OR = 1.46 (1.08-1.54)

BW = birth weight; CI = confidence interval; OR = odds ratio

4.5.5 Vegetarian diet and birth defects

Four articles assessing the association between maternal vegetarian diet and the development of congenital malformations in their offspring were included (table 13).

Two case-control studies and one cohort study investigated the potential relation between maternal vegetarian diet and hypospadias. Akre et al. included 719 Swedish and Danish mother-infant pairs in their case-control study. Carmichael et al. contrasted the diet before pregnancy of 1250 US American case mothers and 3118 controls. The cohort study by North et al. including 6296 British mothers also assessed the risk of hypospadias.

A meta-analysis was conducted to generate a pooled estimate. The result signaled that children of mothers who did not consume meat might be at higher risk to be born with hypospadias, but the result was not statistically significant [1.88 (0.70-5.08); appendix 10]. The included studies showed a high heterogeneity (Cochran's Q Test I^2 = 78.24%, p = 0.01). No publication bias was detected (Egger's regression: p = 0.33; data not shown). Due to the small number of studies, no sensitivity analysis was conducted.

J Yang et al. investigated the association between maternal vegetarian diet and the risk of congenital heart defects in a case-control study including 1422 Chinese mothers and their offspring (474 cases, 948 controls). A high adherence to a vegetarian diet pattern was associated with an increased likelihood of congenital heart defects [OR = 1.56; (1.13-2.15)].

Table 13: Studies assessing the association between vegetarian diet and birth defects

Author & year	Design	Outcome definition	Effect size (95% CI)
Akre 2008	case-control	hypospadias	OR = 2.65 (1.10-6.39)
Carmichael 2012	case-control	hypospadias	OR = 0.75 (0.37-1.53)
North 2000	cohort	hypospadias	OR = 3.58 (1.58-8.09)
Yang 2019	case-control	CHDs	OR = 1.56 (1.13-2.15)

CHD = congenital heart defect; CI = confidence interval; OR = odds ratio

4.5.6 Vegetarian diet and preterm delivery

One study investigating the relation between maternal vegetarian diet and preterm delivery was found. The cross-sectional analysis of 309 Australian mothers by Grieger et al. indicated that there was no significant association between preterm delivery (birth before 37 weeks of gestation) and an increase in adherence to the vegetarian dietary pattern per one SD [OR = 1.08; (0.74-1.57)].

4.6 Plant-based diet during childhood and outcomes in children

Sixty-one studies assessing the relation between maternal diet during pregnancy and one of the predefined outcomes in the child met the inclusion criteria. The findings of the systematic reviews and meta-analyses of every outcome are described in the following sections.

4.6.1 Mediterranean diet and asthma and wheezing

The search produced ten studies and one meta-analysis reporting on the association between Mediterranean diet adherence during pregnancy or childhood and asthma symptoms in children (table 14). Only three studies provided sufficient data to create a fourfold table. In other cases, the ORs and RRs computed by the authors were used for meta-analysis. Since Garcia-Marcos et al. and Grigoropoulou et al. did not compare high Mediterranean diet adherence with low adherence, but a continuous one-point-increase of the diet score to calculate an effect size, their results were not combined with the other studies. Gonzalez Barcala et al. presented their results of two different age groups divided into boys and girls separately. Both groups were included in the analysis. Studies with a patient collective aged three years or younger assessed maternal Mediterranean diet adherence during pregnancy whereas studies with older participants assessed the children's diet. Furthermore, there was a certain heterogeneity of asthma and wheezing definitions.

The meta-analysis including eight studies resulted in a statistically significant combined effect size and 95% CI of 0.82 (0.68-0.97) (appendix 12). The studies showed a high heterogeneity (Cochran's Q Test I^2 = 70.50%, p = 0.00). Moreover, a potential publication bias was detected (Egger's regression: p = 0.03). After applying Duval and Tweedie's trim and fill method the combined effect size shifted to 0.92 (0.75-1.12) (appendix 12).

In the sensitivity analysis the pooled estimate lost its statistical significance when removing Lange et al. or Pellegrini-Belinchon et al. from the analysis (data not shown).

The studies that could not be included in the analysis showed similar results. In their cross-sectional study, Garcia-Marcos et al. spoke of an OR of 0.97 (0.92-1.01) for current occasional asthma in girls and an OR of 0.98 (0.95-1.04) for current occasional asthma in boys per one-point-increase of Mediterranean diet score. Grigoropoulou et al. reported on an OR of 0.84 (0.77-0.91) per one-point-increase of Mediterranean diet score in Greek school children.

In total, the results of our meta-analysis and the single studies indicate that there might be a protective effect of the Mediterranean diet on developing asthma or wheezing, but no firm conclusions can be drawn.

Table 14: Studies assessing the association between Mediterranean diet and asthma and wheezing

Author & year	Design	Outcome definition	Effect size (95% CI)
Castro-Rodriguez 2008	cross-sectional	current wheezing	OR = 0.54 (0.33-0.88)
Castro-Rodriguez 2016	cohort	current wheezing	OR = 0.85 (0.51-1.40)
Chatzi 2008	cohort	persistent wheezing	OR = 0.46 (0.10-2.14)
Chatzi 2013	cohort	wheezing ever	RR = 0.97 (0.76-1.23)
de Batlle 2008	cross-sectional	asthma ever	OR = 0.61 (0.37-1.00)
Garcia-Marcos 2007	cross-sectional	current wheezing	OR = 0.97 (0.92-1.01)[1] OR = 0.98 (0.95-1.04)[2]
Gonzalez Barcala 2010	cross-sectional	asthma ever	OR = 0.98 (0.82-1.71)[3] OR = 1.02 (0.85-1.23)[4] OR = 0.93 (0.70-1.24)[5] OR = 1.20 (0.94-1.53)[6]
Grigoropoulou 2011	cross-sectional	asthma symptoms	OR = 0.84 (0.77-0.91)
Lange 2010	cohort	recurrent wheezing	OR = 0.64 (0.43-0.95)
Pellegrini-Belinchon 2016	cross-sectional	recurrent wheezing	OR = 0.43 (0.30-0.62)

CI = confidence interval; OR = odds ratio; RR = risk ratio

[1] boys
[2] girls
[3] boys 6-7 years old
[4] girls 6-7 years old
[5] boys 13-14 years old
[6] girls 13-14 years old

4.6.2 Mediterranean diet and anthropometrics

The studies examining the association between Mediterranean diet adherence in children and anthropometrics were divided into three groups of outcomes: overweight and obesity, BMI and its z-score, and studies that monitored child growth over a certain period of time. Basic data and effect sizes are summarized in table 15.

Table 15: Studies assessing the association between Mediterranean diet adherence and anthropometrics in children and adolescents

Author & year	Design	Outcome definition	Effect size (95% CI)
Overweight and obesity			
Antonogeorgos 2013	cross-sectional	overweight/obesity: IOTF cut-off values[1]	OR = 0.77 (0.46-1.30)
Archero 2018	cross-sectional	overweight/obesity: IOTF cut-off values[1]	OR = 0.92 (0.48-1.78)
Bacopoulou 2017	interventional	overweight: IOTF cut-off values[1] obesity: IOTF cut-off values[1]	20.5% overweight before, 18.5% after intervention 5.7% obese before, 5.5% after intervention
Esfahani 2016	cross-sectional	obesity: weight $\geq$ 95th percentile	OR = 0.48 (0.15-0.80)
Fernandez-Barres 2016	cohort	overweight/obesity: BMI z-score $\geq$ 85th percentile	OR = 1.08 (0.85-1.38)
Lazarou 2010	cross-sectional	obesity: IOTF cut-off values[1]	OR = 0.33 (0.12-0.95)
Mistretta 2017	cross-sectional	overweight/obesity: IOTF cut-off values[1]	OR = 0.72 (0.50-1.04)
Muros 2017a	cross-sectional	overweight/obesity: IOTF cut-off values[1]	OR = 0.03 (0.00-0.22)
Rosi 2017	cross-sectional	overweight/obesity: IOTF cut-off values[1]	OR = 1.02 (0.56-1.89)
Tambalis 2018	cross-sectional	obesity: IOTF cut-off values[1]	OR = 0.87 (0.82-0.92) OR = 0.89 (0.83-0.96)
Tognon 2014	cross-sectional	overweight/obesity: IOTF cut-off values[1]	OR = 0.83 (0.76-0.91)
Voltas 2016	cross-sectional	overweight/obesity: IOTF cut-off values[1]	OR = 0.94 (0.25-3.52)
BMI			
Chatzi 2017	cohort	BMI z-score	β = -0.13 [-0.24-(-0.01)][2] β = -0.13 [-0.28-(-0.02)][3]
Farajian 2011	cross-sectional	mean BMI	difference in means = 0.00 (-0.56-0.56) kg/m^2
Galan-Lopez 2018	cross-sectional	mean BMI	difference in means[4]= -2.49[-4.18-(-0.80)] kg/m^2

			difference in means[5]= -0.33 (-1.86-1.20) kg/m^2
Goni 2018	cross-sectional	BMI z-score	β = -0.011 (p = 0.676)
Jennings 2011	cross-sectional	BMI z-score	β = -0.03 (SE = 0.03)
Julian 2018	cross-sectional	mean BMI	difference in means = 0.20 (-0.81-1.21) kg/m^2
Kontogianni 2008	cross-sectional	mean BMI	difference in means = -0.60 (-1.51-0.31) kg/m^2
Monjardino 2014	cross-sectional	mean BMI mean BMI	difference in means[4]= -0.40 (-1.01-0.28) kg/m^2 difference in means[5]= -0.30 (-0.96-0.36) kg/m^2
Muros 2017b	cross-sectional	mean BMI	difference in means = -2.73 [-5.44-(-0.02)] kg/m^2
Child growth			
Fernandez-Barres 2019	cohort	BMI trajectories[6] BMI trajectories[7] BMI trajectories[8] BMI trajectories[9]	RR = 0.68 (0.47-0.99) RR = 0.98 (0.74-1.28) RR = 0.91 (0.64-1.28) RR = 0.79 (0.55-1.12)
Martin-Calvo 2016	cohort	BMI change	β = -0.30 [-0.40-(-0.20)]
Poon 2013	cohort	weight-for-length z-score change	β = 0.06 (-0.03-0.14)
Wolters 2018	cohort	BMI gains >75th percentile during primary school	OR = 0.92 (0.47-1.79)

β = regression coefficient; BMI = body mass index; CI = confidence interval; IOTF = International Obesity Task Force; OR = odds ratio; RR = risk ratio; SE = standard error

[1] The IOTF provides tables defining BMI cut-off values for overweight and obesity adjusted for sex and age in months

[2] VIVA cohort

[3] RHEA cohort

[4] boys

[5] girls

[6] larger birth size with subsequent accelerated BMI gain

[7] larger birth size with subsequent slower BMI gain

[8] smaller birth size with subsequent accelerated BMI gain

[9] smaller birth size with subsequent slower BMI gain

Overweight and obesity

Twelve studies assessed the association between children's Mediterranean diet adherence and overweight and obesity. A meta-analysis was conducted to generate a pooled estimate including ten studies. The publications by Bacopoulou et al. and Esfahani et al. were not combined with the other studies due to their divergent effect sizes. Since Tambalis et al. presented their results in subgroups of boys and girls, both groups were included separately. Six studies provided sufficient data to create fourfold tables. In other cases, the ORs computed by the authors were used. The analysis included data of more than 350000 children and adolescents.

Combining the results of the single studies led to a pooled estimate of 0.87 (0.79-0.94) (figure 7). The studies showed a moderate heterogeneity (Cochran's Q Test I^2 = 50.54%, p = 0.03). No publication bias was found (Egger's regression: p = 0.22) (appendix 11).

Sensitivity analysis did not affect the combined result considerably, but the CI widened clearly when removing the studies by Tambalis et al. or Tognon et al. due to their large study population (data not shown).

The findings of the publications reporting on overweight and obesity that had to be excluded from the meta-analysis are compatible with the pooled estimate. In their pre-post interventional study, Bacopoulou et al. provided an educational intervention regarding nutrition according to the principles of Mediterranean diet, regular physical activity, healthy body image, and healthy eating behaviors to 1032 Greek high schoolers. Before the intervention 20.5% of the children were overweight and 5.7% were obese, whereas after the intervention only 18.5% were overweight and 5.5% were obese (p = 0.03). Esfahani et al. assessed the relation between Mediterranean diet adherence and overweight and obesity in 840 Iranian high schoolers. Comparing the 4th with the 1st quartile of Mediterranean diet adherence the students following a Mediterranean diet had a lower risk for overweight and obesity [OR = 0.65; (0.37-0.93); OR = 0.48; (0.15-0.80)].

Overall, the Mediterranean diet showed a protective effect on the development of overweight and obesity in children and adolescents.

Body mass index

Ten studies investigated the association between Mediterranean diet adherence and mean body mass index (BMI) or its z-score of children and adolescents. The studies having mean BMI as their outcome were pooled in a meta-analysis and the difference in means was calculated. Data of 4244 study participants were included in the analysis.

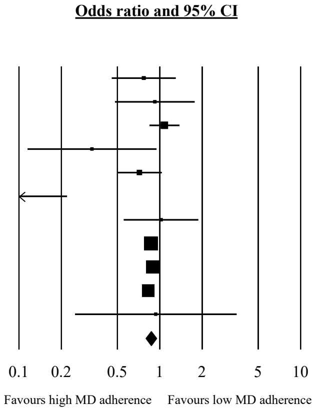
The meta-analysis resulted in a difference in means of -0.42 (-0.86-0.02) kg/m^2 comparing children and adolescents with high Mediterranean diet adherence to ones with low adherence (appendix 13). The studies showed a low heterogeneity (Cochran's Q Test I^2 = 42.09%, p = 0.01). A potential publication bias was detected (Egger's regression: p = 0.04). Applying Duval and Tweedie's trim and fill the pooled effect estimate changed to -0.23 (-0.78-0.32) kg/m^2 (appendix 13).

In the sensitivity analysis the pooled estimate did not change considerably when one study was removed from the analysis (data not shown).

The studies having children's BMI z-scores as their outcome could not be pooled in a

Figure 7: Forest plot for the association between Mediterranean diet adherence and overweight and obesity in children

Study name	Statistics for each study			High MD adherence / Total		
	Odds ratio	Lower limit	Upper limit	Overweight/Obesity +	Overweight/Obesity -	Relative weight
Antonogeorgos 2013	0.770	0.455	1.304			2.47
Archero 2018	0.923	0.480	1.775	23 / 44	108 / 199	1.64
Fernandez-Barres 2016	1.080	0.845	1.381			8.89
Lazarou 2010	0.330	0.115	0.950	4 / 75	44 / 302	0.65
Mistretta 2017	0.718	0.497	1.036	71 / 344	79 / 297	4.71
Muros 2017	0.029	0.004	0.220	69 / 117	49 / 50	0.18
Rosi 2017	1.022	0.555	1.884	70 / 88	175 / 221	1.87
Tambalis 2018 I	0.868	0.822	0.917			28.71
Tambalis 2018 II	0.893	0.831	0.959			26.53
Tognon 2014	0.830	0.759	0.908			23.94
Voltas 2016	0.938	0.250	3.521	3 / 19	20 / 120	0.42
	0.865	0.793	0.942	240 / 687	475 / 1189	



Cochran's Q Test I^2 = 50.54% (p = 0.03); Egger's regression: p = 0.24 (no publication bias)

meta-analysis due to lack of data. In their cross-sectional analysis, Goni et al. assessed the association between Mediterranean diet adherence and BMI z-score of 619 Spanish preschoolers in a linear regression. No statistically significant association could be shown (β = -0.011; p = 0.676). Chatzi et al. inspected data of 997 children from the US American VIVA cohort and 569 children from the Greek RHEA cohort for relations between Mediterranean diet adherence and BMI z-scores. They pooled the data of both cohorts resulting in a regression coefficient β of -0.13; [-0.13-(-0.12)] per three-point-increase in Mediterranean diet score. Jennings et al. examined the association between Mediterranean diet adherence and BMI z-score in 1700 British school children. Their findings indicated that there was no significant reduction in BMI z-score per one-standard-deviation-increase in Mediterranean diet score (β = -0.03; p > 0.05).

In sum, the results of the meta-analysis and the single studies show a trend towards a lower BMI and a lower BMI z-score in children following a Mediterranean diet.

Child growth

Four studies assessed the relation between Mediterranean diet adherence and child growth over a certain period of time. In consequence of insufficient data and different effect sizes, no meta-analysis was conducted.

Fernandez-Barres et al. evaluated the association between maternal adherence to the Mediterranean diet during pregnancy and their offspring's longitudinal BMI development in 2195 mother-child pairs. The findings indicated that high Mediterranean diet adherence during pregnancy was associated with a lower risk of larger birth size, followed by accel-

erated BMI gain compared to the reference trajectory group (children with average birth size and subsequent slower BMI gain). No significant relations were observed for other predefined growth trajectories. Martin-Calvo et al. prosecuted the change in Mediterranean diet adherence and BMI over 7 years of follow-up in 3942 US American children. A significantly lower BMI two-year-increase comparing the fourth quartile of Mediterranean diet adherence with the first quartile [β = -0.30; -0.40-(-0.20)] was observed. The third study by Wolters et al.found no significantly lower risk for excessive gains in BMI was found [OR = 0.92; (0.47-1.79)] analyzing data of 298 German children.
In their cohort study, Poon et al. observed the changes in weight-for-length z-score in 426 infants from 4 to 6 months of life. In this period of time, no significant association between maternal Mediterranean diet adherence and child growth was detected.

All in all, and despite some discrepancies in the results, the findings indicate that a high Mediterranean diet adherence leads to a lower risk for overweight and obesity and a lower mean BMI in children and adolescents.

4.6.3 Mediterranean diet and cognitive functions

The search generated six studies evaluating the association between Mediterranean diet adherence and cognitive functions in children. Due to the broad definition of cognitive functions, the outcomes of the identified studies varied substantially, so that a meta-analysis was not conducted and the results were reviewed in the following paragraph and summarized in table 15.
In a cross-sectional study, Chacon-Cuberos et al. assessed the relation between Mediterranean diet adherence and several parameters for cognitive functions in 1059 Spanish high schoolers. Their results showed no significant association between Mediterranean diet adherence and anxiety or value of task, whereas significant positive associations ($p < 0.001$) between Mediterranean diet adherence and elaboration strategies, organizational strategies, critical thinking, self-regulation, time and study habits, self-regulation of effort, and goals of intrinsic orientation were found.
House et al. conducted a cohort study in the USA with 325 mother-infant pairs to evaluate the association between maternal periconceptional Mediterranean diet adherence and social and emotional scores in the second year of life. The offspring of women with high Mediterranean diet scores had decreased odds for atypical behaviors, for maladaptive behaviors, and for an index of autism spectrum disorder behaviors. Moreover, they were less likely to exhibit depressive and anxiety behaviors and showed increased odds for social relatedness behaviors in comparison to children of low Mediterranean diet adherence mothers.
Henriksson et al. investigated the association of dietary patterns with attention capacity in 384 European adolescents. No significant connection between Mediterranean diet adherence per one-unit-increase and attention capacity was detected.
The cohort study by Haapala et al. assessed the association between Mediterranean diet adherence and academic achievement in Finnish school children from grade one to three. Only one positive relation was found between Mediterranean diet adherence and reading

Table 15: Studies assessing the association between Mediterranean diet and cognitive functions

Author & year	Design	Outcome definition	Effect size (95% CI)
Chacon-Ruberos 2018	cross-sectional	elaboration strategies	4.10 ± 0.90 vs 3.53 ± 1.28
		organizational strategies	4.08 ± 0.93 vs 4.00 ± 1.54
		critical thinking	3.75 ± 0.98 vs 2.78 ± 0.50
		self-regulation	3.78 ± 0.88 vs 3.73 ± 1.54
		time and study habits	3.91 ± 0.87 vs 3.72 ± 1.33
		self-regulation of effort	4.16 ± 0.82 vs 3.61 ± 1.35
		intrinsically orientated goals	4.24 ± 0.87 vs 3.58 ± 1.28
House 2018	cohort	atypical behavior	OR = 0.40 (0.17-0.92)
		maladaptive behavior	OR = 0.42 (0.18-0.95)
		autism spectrum disorders behavior	OR = 0.35 (0.15-0.80)
		depressive behavior	OR = 0.28 (0.12-0.64)
		anxiety behavior	OR = 0.42 (0.18-0.97)
		social relatedness	OR = 2.31 (1.04-5.19)
Henriksson 2017	cross-sectional	attention capacity	β = 0.39 (-1.49-2.26)
Haapala 2017	cohort	reading fluency	β = -0.03 (-0.18-0.12)[1]
			β = 0.08 (-0.08-0.12)[2]
			β = 0.04 (-0.12-0.21)[3]
		reading comprehension	β = 0.01 (-0.15-0.16)[1]
			β = 0.13 (-0.03-0.28)[2]
			β = 0.17 (0.02-0.32)[3]
		arithmetic skills	β = 0.10 (-0.06-0.25)[1]
			β = 0.00 (-0.16-0.16)[2]
			β = -0.04 (-0.21-0.12)[3]
Leventakou 2016	cross-sectional	verbal ability	β = -0.31 (-1.55-0.92)
		perceptual performance	β = -0.97 (-2.18-0.24)
		quantitative ability	β = -0.46 (-1.73-0.81)
		general cognitive ability	β = -0.70 (-1.90-0.49)
		memory	β = -0.31 (-1.59-0.97)
		motor ability	β = -1.39 [2.37-(-0.05)]
		executive function	β = -0.40 (-1.61-0.81)
		cognitive function of posterior cortex	β = -0.99 (-2.21-0.23)
Vassiloudis 2014	cohort	school performance	β = 0.140; p = 0.001

β = regression coefficient; CI = confidence interval; OR = odds ratio

[1] children grade 1
[2] children grade 2
[3] children grade 3

comprehension in third-graders. An increase in Mediterranean diet adherence was not associated with arithmetic skills or reading fluency in all age groups.

Leventakou et al. conducted a multivariable analysis for the relation between several dietary patterns and neurodevelopmental test scores at 4 years of age in Greek children. A higher Mediterranean diet adherence was not associated with significantly better results regarding verbal ability, perceptual performance, quantitative ability, general cognitive ability, memory, motor ability, executive function, and cognitive functions of posterior cortex.

A cross-sectional study by Vassiloudis et al. examined possible links between Mediterranean diet adherence and academic performance in 528 Greek primary school children. Linear regression analysis showed that Mediterranean diet adherence was a significant factor in positively predicting academic performance.

4.6.4 Vegetarian diet and anthropometrics

The studies assessing the associations between vegetarian diet forms and body dimensions in children and adolescents were assigned to groups of studies of similar outcome definitions. The defined groups were overweight and obesity, stunting and wasting, and child growth.

Overweight and obesity

Five studies investigated the potential connection between vegetarian diet during childhood and the presence of overweight and obesity. A meta-analysis was performed to generate a pooled estimate of the single results. Weder et al. examined vegetarian and vegan children separately. These two groups were combined and compared to the omnivorous group for the meta-analysis. The age of the participants ranged from infancy to adolescence between studies.

Combining data of 2753 children and adolescents led to a pooled estimate of 0.81 (0.49-1.32) (appendix 14). The studies showed a low heterogeneity (Cochran's Q Test I^2 = 0.00%, p = 0.89). No publication bias was found (Egger's regression: p = 0.94) (appendix 14).

Sensitivity analysis showed no considerable differences in the result when removing one study at a time (data not shown).

Stunting and wasting

Five studies examined the potential effect of a vegetarian diet on stunting in children, two of them additionally assessed the outcome wasting. The authors consistently defined stunting as length-for-age z-score (LAZ) or height-for-age z-score (HAZ) < 2 except from Shull et al. who defined stunting as height < 25% of Harvard standards. Vegetarian and vegan children of the study by Weder et al. were combined and compared to the omnivorous group for the meta-analysis. The RCT by Krebs et al. including 1064 mother-infant pairs was not combined with the other studies. Infants receiving a multimicronutrient-fortified cereal intervention had a lower risk of being stunted than infants who received a meat intervention of 30 to 45 g of meat per day [OR = 0.78; (0.61-0.99)].

The four remaining studies were pooled in a meta-analysis. The calculations resulted in a statistically insignificant effect size of 1.41 (0.61-3.26) (appendix 15). The studies showed a high heterogeneity (Cochran's Q Test I^2 = 97.87%, p = 0.00). No publication bias was detected (Egger's regression: p = 0.63; data not shown).

Sensitivity analysis showed no considerable differences in the combined result when removing one study at a time (data not shown).

Two studies further provided data on wasting. In the RCT by Krebs et al., infants that received the cereal intervention were not more likely to be wasted than infants who received the meat intervention [OR=1.43; (0.87-2.36)]. The same applies to the German cross-sectional analysis by Weder et al., who did not detect and increased risk of being wasted neither in vegetarian [OR = 0.43; (0.02-10.58)] nor in vegan infants OR = [6.08; (0.70-52.70)].

Child growth

Eight studies investigated potential relations between meatless diet forms and mean growth parameters in children. Four studies that compared the mean BMI of vegetarian children to the mean BMI of non-vegetarians were pooled in a meta-analysis. The analyzed data of 278 vegetarians and 12801 omnivores demonstrated a significant difference in means of -0.92 [-1.34-(-0.49)] kg/m^2 comparing vegetarian children to non-vegetarians (appendix 16). The studies showed a high heterogeneity (Cochran's Q Test I^2 = 87.47%, p = 0.00). No publication bias was detected (Egger's regression: p = 0.445; data not shown).

A RCT by Sheng et al. included 180 Chinese infants from high poverty areas. The participants received 50 g per day of pork (meat group), an equicaloric micronutrient-fortified rice cereal-based supplement (fortified cereal group), or a local non-fortified rice cereal supplement (local cereal group) for one year. No significant differences in LAZ, weight-for-length z-score (WLZ) and weight-for-age z-score (WAZ) were found when comparing the three study arms.

Leung et al. performed a cross-sectional analysis to examine the nutritional status of 51 Chinese vegetarian children. The mean height for age, weight for age and weight for height of boys and girls demonstrated no significant differences compared to Hong Kong growth reference charts.

In their cross-sectional study, O'Connell et al. assessed the association between nutritional factors and growth parameters in 373 vegetarian children living in a US American rural community. At age five or younger, the HAZ of the community children was significantly decreased in comparison to the US American reference population. This association was not observed in the older participants. Furthermore no significant differences in WAZ were found, except from the vegetarian children between 9 and 10 years, who had a lower WAZ than the reference population.

Rona et al. explored the relation between vegetarian status and growth of children in Great

Britain in a cross-sectional study. Body measurements of 369 primary school children with in Urdu, Gujarati, and Punjabi ethnicity were collected. No differences in weight for height were detected when comparing vegetarian to non-vegetarian children.
P Dagnelie et al. investigated the association between macrobiotic diet during lactation and infancy and weight and height growth in a Dutch cohort of 110 children. During the observation period from 4 to 18 months of life, the macrobiotic children showed a significantly lower height gain and weight gain per year than the omnivorous reference group (13.2 cm vs 16.7 cm; 3.1 kg vs 4.4 kg; $p < 0.001$).

Table 16: Studies assessing association between vegetarian diet forms and anthropometrics in children

Author & year	Design	Outcome definition	Effect size (95% CI)
Overweight and obesity			
Alizadeh 2015	cross-sectional	overweight: IOTF cut-off values[1] obesity: IOTF cut-off values[1]	OR = 0.82 (0.35-1.90) OR = 0.99 (0.14-7.18)
Larsson 2002	cross-sectional	overweight: BMI > 24.3 (males), > 23.7 (females)	OR = 1.05 CI (0.48-2.32)
Shull 1977	cohort	overweight/obesity: weight > 75% of Harvard standards	OR = 0.57 (0.23-1.38)
Weder 2019	cross-sectional	overweight/obesity: WHZ > 2 SD	OR = 0.73 (0.22-2.44)
Yen 2008	cross-sectional	obesity: weight-for-height-index > 1,2	OR = 0.88 (0.13-5.78)
Stunting and wasting			
Krasavec 2017	cross-sectional	stunting: LAZ < 2	OR = 2.15 (2.01-2.30)
Krebs 2012	RCT	stunting: LAZ < 2 wasting: WAZ < 2	OR = 0.78 (0.61-0.99) OR = 1.43 (0.87-2.36)
Melaku 2018	cross-sectional	stunting: HAZ < 2	OR = 0.74 (0.63-0.88)
Shull 1977	cohort	stunting: height < 25% of Harvard standards	OR = 1.07 (0.47-2.43)
Weder 2019	cross-sectional	stunting: HAZ < 2 wasting: WAZ < 2	OR = 10.82 (0.62-188.69) OR = 3.12 (0.36-26.97)
Child growth			
Ambroszkiewicz 2018	cross-sectional	mean BMI	difference in means = -0.10 (-0.62-0.42) kg/m^2
Dagnelie 1989	cohort	mean height growth per year	13.2 cm (MBD), 16.7 cm (OMN)

		mean weight gain per year	3.1 kg (MBD), 4.4 kg (OMN)
Grant 2008	cross-sectional	mean BMI	difference in means = -1.40 [-1.63-(-1.17)] kg/m^2
Haddad 2003	cross-sectional	mean BMI	difference in means = -1.20 [-1.23-(-1.17)] kg/m^2
Leung 2001	cross-sectional	mean height for age	0.08 ± 1.10 (boys) 0.36 ± 0.85 (girls)
		mean weight for height	0.51 ± 1.02 (boys) 0.08 ± 0.95 (girls)
		mean weight for age	0.41 ± 1.07 (boys) 0.32 ± 0.85 (girls)
O'Connell 1989	cross-sectional	HAZ	-0.09 (<1 y), -0.67 (1-2 y), -0.55 (3-4 y), -0.39 (5-6 y), -0.13 (7-8 y), -0.11 (9-10 y)
		WAZ	-0.10 (<1 y), -0.09 (1-2 y), -0.13 (3-4 y), -0.18 (5-6 y), -0.06 (7-8 y), -0.27 (9-10 y)
Persky 1992	cross-sectional	mean BMI	difference in means = 0.6 (-1.24-2.44) kg/m^2
Rona 1987	cross-sectional	mean weight-for-height SDS	-0.65 ± 1.20 vs -0.38 ± 1.27 -0.68 ± 1.29 vs -0.69 ± 1.08 -0.35 ± 1.16 vs -0.37 ± 1.24
Sheng 2019	RCT	mean LAZ	-1.5 ± 1.0 (meat) -1.8 ± 0.9 (fortified cereal) -1.6 ± 1.1 (local cereal)
		mean WLZ	-0.3 ± 0.9 (meat) -0.2 ± 0.8 (fortified cereal) -0.1 ± 0.9 (local cereal)
		mean WAZ	-0.9 ± 0.9 (meat) -1.0 ± 0.9 (fortified cereal) -0.8 ± 1.0 (local cereal)

BMI = body mass index; CI = confidence interval; HAZ = height-for-age z-score; IOTF = International Obesity Task Force; LAZ = length-for-age z-score; MBD = macrobiotic diet; OMN = omnivorous; OR = odds ratio; RCT = randomized controlled trial; SD = standard deviation; SDS = standard deviation score; WAZ = weight-for-age z-score; WHZ = weight-for-height z-score

[1] The IOTF provides tables defining BMI cut-off values for overweight and obesity adjusted for sex and age in months

4.6.5 Vegetarian diet and other outcomes in children

The outcomes with a low number of available studies that are summarized in table 17. Four studies dealt with the relation between meatless diet forms and anemia in infants and children. Since the studies showed a major heterogeneity in study design, outcome definition, and exposure, no meta-analysis was conducted.

Table 17: Studies assessing the association between vegetarian diet and anemia, cognitive development and motor skills in children

Author & year	Design	Outcome definition	Effect size (95% CI)
Anemia in children			
George 2000	cross-sectional	Hb < 8.8 g/dl	OR = 0.74 (0.58-0.95)
Goswmai 2015	cross-sectional	Hb 10.0-10.9 g/dl	OR = 1.13 (1.04-1.22)
		Hb 7.0-9.9 g/dl	OR = 1.32 (1.23-1.42)
		Hb < 7.0 g/dl	OR = 3.35 (2.92-3.66)
Krajcovicova 1997	cross-sectional	Hb < 12 g/dl	OR = 9.30 (1.04-83.13)
Krebs 2012	RCT	Hb < 11g/dl	OR = 0.60 (0.44-0.81)
Cognitive development and motor skills			
Sheng 2019	RCT	mean cognitive score	21.3 ± 1.9 (meat)
			21.2 ± 2.0 (fortified)
			20.4 ± 2.0 (local)
		mean fine motor score	18.0 ± 1.1 (meat)
			18.3 ± 1.1 (fortified)
			18.3 ± 1.0 (local)
		mean gross motor score	20.1 ± 1.4 (meat)
			20.1 ± 1.4 (fortified)
			20.2 ± 1.1 (local)
Dagnelie 1994	cohort	fine motor development	$\bar{x}$ = -0.13; p = 0.49[1]
		gross motor development	$\bar{x}$ = -0.63; p < 0.001[1]
		speech and language development	$\bar{x}$ = -0.42; p = 0.03[1]
Larsen 2014	cohort	age at sitting	HR = 1.01 (0.89-1.14)[2]
			HR = 0.95 (0.64-1.42)[3]
		age at walking	HR = 1.16 (0.99-1.34)[2]
			HR = 1.25 (0.86-1.81)[3]

CI = confidence interval; Hb = hemoglobin; HR = hazard ratio; OR = odds ratio; RCT = randomized controlled trial

[1] Difference in standard deviation score between macrobiotic and omnivorous children

[2] vegetarian

[3] vegan

George et al. performed a cross-sectional analysis including 3633 Indian preschoolers. Vegetarian children were less likely to be anemic (Hb < 8.8 g/dl) than non-vegetarian children [OR = 0.74; (0.58-0.95)].

In their cross-sectional study, Goswmai, Das showed that compared to infants of omnivorous mothers, children of vegetarian mothers had a significantly higher risk of mild anemia

[OR = 1.13; (1.04-1.22)]. This association became even stronger for moderate and severe anemia [OR = 1.32; (1.23-1.42); OR = 3.35; (2.92-3.66)].

Krajcovicova-Kudlaakova et al. conducted a cross-sectional analysis with a small sample size of 58 Slovakian pupils. Comparing the prevalence of anemia (Hb < 12 g/dl), vegetarian children were more likely to be anemic than children following an omnivorous diet.

Krebs et al. performed a RCT including 1064 mother-infant pairs in the Democratic Republic of Congo, Zambia, Guatemala, and Pakistan. They provided an intervention of 30 to 45 g of meat per day and a control intervention of multimicronutrient-fortified cereal from 6 to 18 months of age. Infants receiving the cereal intervention had a lower risk of anemia (Hb < 11 g/dl) than infants who received the meat intervention.

The search generated three studies investigating associations between plant-based diet forms and cognitive development and fine and gross motor skills in infants. No meta-analysis was performed due to immense differences with respect to study design, exposure, and outcome definition.

The approach of the RCT by Sheng et al. was already described in section 4.6.4. Toddlers in the meat group and toddlers in the fortified cereal group reached significantly better results in the cognitive score than the local cereal group. No differences in fine and gross motor skills were observed.

In their cohort study, PC Dagnelie, Staveren recruited 106 Dutch infants following a macrobiotic diet. Macrobiotic children had significantly lower standard deviation scores in gross motor development ($\bar{x}$ = -0.63; $p < 0.001$) and speech and language development ($\bar{x}$ = -0.42; p = 0.03). No differences between groups were found for fine motor development ($\bar{x}$ = -0.13; p = 0.49).

Larsen et al. analyzed data of 55185 Danish children from the national birth cohort with the aim to examine the association between maternal vegetarianism and the risk of impaired neurodevelopment. A hazard ratio (HR) below one indicated delayed sitting or walking status. Children of LOV mothers were not at higher risk of delayed sitting or walking status [HR = 1.01; CI (0.89-1.14); HR = 1.16; (0.99-1.34)]. The same applied to the children of vegan mothers [HR = 0.95; (0.64-1.42); HR = 1.25; (0.86-1.81)].

4.6.6 Safety of vegetarian and vegan diet

To the evaluate the safety of vegetarian diet forms, 36 case reports and case series were identified (appendix 18). In the majority of cases, severe vitamin B12 deficiency and its clinical symptoms such as hypotonia, developmental regression, macrocytic anemia and cerebral atrophy were described. Some authors reported on vitamin D deficiency and rachitic signs. Moreover, isolated cases of sudden death (Cundiff, Harris, 2006) (Rinaldo et al., 1997), acute small bowel obstruction (Amoroso et al., 2018) and transient neonatal hypothyroidism (Shaikh et al., 2003) were observed but those findings were not clearly attributable to the mother's diet. The majority of the the children was between 6 and 18 months old. Many authors did not clearly state the composition of the mother's diet and referred to vegan diet as strict vegetarian diet. Overall, a vegan diet during lactation period appeared to be potentially harmful, if mothers neglected to compensate the lack of vitamin B12 and vitamin D in their vegan diet.

5 Discussion

We aimed to assess the association between plant-based diets and maternal and offspring health. The search identified 113 eligible articles.

5.1 Mediterranean diet

Pregnant women who followed a Mediterranean diet had a 38.9% lower probability to develop GDM compared to women with low Mediterranean diet adherence [OR = 0.636 (0.51-0.79)]. To our knowledge, this is the first analysis that quantifies the association between maternal Mediterranean diet adherence and the risk of GDM. Our findings are in line with results of previous systematic reviews that attributed the Mediterranean diet a positive impact on GDM (Amati et al., 2019) and described the Mediterranean diet as the most consistently reported protective dietary pattern against GDM risk (Mijatovic-Vukas et al., 2018). One reason for the favorable effects of the Mediterranean diet might be the reduced intake of saturated fatty acids (Bo et al., 2001; Park et al., 2013) and the increased consumption of polyunsaturated fatty acids which was shown to be linked to improved glycemia, insulin resistance, and insulin secretion capacity (Imamura et al., 2016; Ying, DF Wang, 2006). The mechanisms behind these effects are still poorly understood. A positive effect of polyunsaturated fatty acids on hepatic telomere length and liver metabolism could be one possible mechanism (Gao et al., 2019).

Moreover, the low consumption of red meat and animal fat which is part of the Mediterranean diet showed beneficial effects of the development on GDM (Bao et al., 2013; Bowers et al., 2012). Further confirmation of these results was shown by the findings regarding the association between Mediterranean diet adherence and gestational weight gain. The review of the single studies showed a clear trend towards a lower risk of excessive gestational weight gain in women who followed a Mediterranean diet. Maternal obesity is an established risk factor for the development of GDM (Torloni et al., 2009) and excessive gestational weight gain is associated with a higher risk of pregnancy complications such as cesarean section and macrosomia (National Research Council, 2010), but also pregnancy-induced hypertension and preeclampsia (Gaillard et al., 2013; Roberts et al., 2003). Our analysis showed a lower risk of hypertensive disorders in women who followed a Mediterranean diet. The association was not statistically significant which might be explained by the small amount of studies. Even though the results of our analysis showed some significant associations, no causality can be concluded. However, our findings implicate that a Mediterranean diet during pregnancy can positively influence the reciprocal relationship between complications such as GDM, excessive gestational weight gain and hypertensive disorders.

Compared to women with low Mediterranean diet adherence, pregnant women with high Mediterranean diet adherence had a 42.2% lower probability of preterm delivery. This result validates the findings of a previous systematic review and meta-analysis that found a lower risk of preterm delivery in women in the top tertile of healthy dietary patterns in general (including Mediterranean diet) compared to women in the bottom tertile (Chia et al., 2019). Therefore, our analysis was a more specific approach to evaluate the role of the Mediterranean diet in the occurrence of preterm delivery. The etiology of preterm delivery is a multifactorial process, but healthy dietary patterns characterized by high intake of foods with antioxidative and antiinflammatory qualities such as vegetables, fruits, wholegrains, fish, legumes and pulses, could reduce inflammation contributing to reduce risk of preterm birth (Romero et al., 2003; Casanueva et al., 2005; Chia et al., 2019). The low heterogeneity between studies of our analysis strengthens the evidence that a high Mediterranean diet adherence during pregnancy could have a protective effect on preterm delivery.

The outcome small for gestational age/fetal growth restriction/intrauterine growth retardation/low birth weight was not significantly associated with maternal Mediterranean diet adherence. However, a trend towards a lower risk in women with high Mediterranean diet adherence was observed. These findings substantiate the assumption that following the Mediterranean diet may benefit pregnant women.

According to our analysis, a high Mediterranean diet adherence was associated with a lower risk of asthma and wheezing in infants and children. This result should be interpreted with caution due to heterogeneity of exposure and outcome definitions and different time points of outcome assessment. Additionally, the association lost its statistical significance after adjustment for publication bias. However, the effect of plant-based diets in reduction of pro-inflammatory molecules and increase of anti-inflammatory markers has been shown (Schwingshackl, Hoffmann, 2014) which are part of the pathogenesis of asthma. The results of our analysis were similar to a previous systematic review and meta-analysis. Y Zhang et al. (2019) conducted multiple analyses by creating more detailed outcome definitions of asthma and wheezing. The authors showed that Mediterranean diet during pregnancy was associated with a reduced risk of wheezing in the offspring in the first 12 months and there was an inverse association between the exposure during childhood and the risk of wheeze in the history in children. A relationship between Mediterranean diet and pediatric asthma was not confirmed. Therefore, no explicit conclusions regarding a potentially protective effect of Mediterranean diet on asthma and wheezing in children can be drawn in consideration of the present evidence.

The meta-analysis assessing the relation between Mediterranean diet adherence during childhood and adolescence and overweight and obesity resulted in a 13.5% lower probability of being overweight or obese when following a Mediterranean diet. This result only partially confirms previous findings. Although systematic reviews showed beneficial effects of Mediterranean diet adherence on overweight and obesity in adults (Buckland et al., 2008; Grosso et al., 2014), so far a previous systematic review could not explicitly confirm a transferability of these findings to children and adolescents (Idelson et al., 2017). Additionally, our meta-analysis showed no significant difference in mean BMI between children and adolescents with different levels of Mediterranean diet adherence. Also, the results of the single studies that assessed the role of Mediterranean diet in child growth allowed no clear conclusions. However, our findings implicate a certain potential of the Mediterranean diet in the prevention of overweight and obesity in early stages of life.

The single studies examining the relation between Mediterranean diet and cognitive functions presented inconsistent results as well. Some studies detected advantages of high Mediterranean diet adherence regarding cognitive development and school performance whereas other results showed no differences.

In sum, the systematic review and meta-analysis of the role of the Mediterranean diet in adverse outcomes in mothers and their offspring showed promising results. However, the results should be interpreted with caution. Our findings were mainly based on observational studies, in particular cross-sectional studies. Therefore, no causalities but only associations can be concluded. There was considerable heterogeneity between studies included in the review. Study methods varied widely with respect to design, population, dietary assessment, exposure measures and outcome definition. There is, for example, no scientific consensus on the measurement of the Mediterranean diet adherence. Several different diet scores coexist equally and even within one diet score two people who consume different foods can reach the same score. Moreover, the results of many studies were based on self-reported data. Since it was impossible to adjust the results for potential confounders, it cannot be ruled out that lifestyle accompanying factors such as less smoking and higher physical activity formed a significant part of the detected associations.

To our knowledge, this is the first study to systematically review the potential role of Mediterranean diet in maternal and offspring health to this extent. Despite all limitations, our findings represent a progress in the stated question. No indications were found that high Mediterranean diet adherence during pregnancy and childhood is associated with adverse health outcomes in the mother or the child. Especially our analyses with regard to multiple beneficial effects of the Mediterranean diet on maternal metabolic health during pregnancy represent a key finding.

5.2 Vegetarian diet

Our results allowed no solid conclusions in terms of the relation between vegetarian diet forms and maternal health. The lack of studies and and the high heterogeneity between studies restricted the implementation of high-quality meta-analyses. Study methodology varied widely regarding design, socioeconomic status of the study population, dietary assessment, exposure measurement and outcome definition. Even though tendencies towards a slightly higher risk of anemia in pregnant women consuming a vegetarian diet were detected, our results do not suggest harms of a vegetarian diet during pregnancy. Despite some controversy in the evidence, even potential benefits of a vegetarian diet during pregnancy in terms of excessive gestational weight gain and GDM were found. Our findings are in line with the results of a previous systematic narrative review that assessed vegan and vegetarian diets and pregnancy outcomes (Piccoli et al., 2015). The authors also observed a scarcity of evidence and concluded that when vegan-vegetarian diets were the result of a free choice and were not linked with limited access to food or with poverty, pregnancy outcomes were similar to those reported in the omnivorous population.

We found a tendency towards a slightly higher risk of hypospadias, but the single studies provided contradictory results. The etiology of most cases of hypospadias is still unknown (Kalfa et al., 2010). One potential explanation of the origin of hypospadias is the consumption of phytoestrogens (North et al., 2000), which are contained in soy foods. On the other hand, studies consistently show that eating soy foods does not raise estrogen levels, upset hormonal balance or reduce testosterone concentrations in men and no adverse effects on fertility or sexual health have been reported (Hamilton-Reeves et al., 2010). Thus, a vegetarian diet is unlikely to be a risk factor in the origin of hypospadias, but further research is required to explain the observed associations.

The results of the studies assessing associations between vegetarian diet forms and adverse health outcomes in children and adolescents neither showed consistent harms nor benefits of vegetarian diet forms in comparison to an omnivorous diet. Slight trends towards a higher risk of stunting in vegetarian children were found whereas a lower risk of being overweight or obese was observed, but none of these associations was statistically significant. A majority of the individual studies found no differences between the two exposure groups.

Our results are similar to the findings of a previous systematic review that investigated the role of vegetarian diet forms in children and adolescents. The review included 24 individual studies. The authors summed up that their systematic review showed that the literature available was insufficient to draw up-to-date conclusions on health effects of vegetarian or vegan diets in infants, children, and adolescents in developed countries. Additionally, they remarked that the included studies did not show harmful effects of vegetarian diets in children but even suggested potentially beneficial health outcomes compared to omnivorous diets, such as favorable lipid profile, antioxidant status, or dietary fiber intake as well as tendencies towards a lower risk of overweight. (Schürmann et al., 2017)

The safety concerns in terms of vegetarian diet forms during pregnancy and lactation were only partially confirmed. Although multiple case reports described severe consequences of vitamin B12 deficiency in infants of vegan mothers, these deficiency symptoms probably could have been avoided by regular supplementation.

The studies assessing vegetarian diet forms and adverse outcomes provided less insights due to the lack of studies and and the high heterogeneity between studies. Nevertheless, we provided an overview of the current evidence. Our findings and the results of comparable literature confirm the recommendations of the Academy of Nutrition and Dietetics who declared that a well-planned vegetarian, including vegan diet, was appropriate for all stages of the life cycle, including pregnancy, lactation, infancy, childhood, and adolescence (Melina et al., 2016). The German Nutrition Association (Deutsche Gesellschaft für Ernährung) also considers a LOV diet as appropriate, but they do not recommend a vegan diet during pregnancy, infancy, childhood, and adolescence due to the higher risk of nutrient deficiencies (Richter et al., 2016). Considering the present evidence, it would be inappropriate to discourage pregnant women from following a vegetarian or vegan diet as long as macronutrient and micronutrient requirements are fulfilled.

5.3 Limitations

Since the literature search was limited to *Pubmed*, it cannot be ruled out that relevant articles were not collected. To address this concern, references of identified systematic reviews were searched for missed publications. Not all full texts were available in the institutional access of the *Saarland University*. Even though the corresponding authors were contacted for full text request, some potentially relevant articles were not obtained. Only publications in English language were considered, which might have reduced the comprehensiveness of the search. However, a study showed no evidence of a systematic bias from the use of language restrictions in systematic reviews and meta-analyses (Morrison et al., 2012).

The exclusion of full texts and the documentation of extracted data were controlled by the second reviewer to minimize potential mistakes during the process of full text evaluation and data extraction. Discrepancies were resolved through discussion in the reviewer team.

Another limitation of the meta-analyses was the treatment of varying symptoms as one outcome. Asthma and wheezing were combined in one analysis despite differences in their definitions. Due to the small numbers of studies, an analysis stratified by more precise outcome definitions was not possible. Also, small for gestational age, fetal growth restriction, intrauterine growth retardation, and low birth weight were combined although there were slightly different definitions.

RRs were included in the analysis and treated like an OR when there were not enough data to compute an OR. This might have generated a potential source of error. However, RR and OR are approximately the same in case of rare diseases.

Since a certain heterogeneity between studies regarding study design and study population was expected, the random effects model was applied. The random effects model assumes that effect sizes are estimates of their own true effect sizes, distributed around an average true effect.

Moreover, the pooled effect sizes might be distorted by quality defects of the individual studies because the publications were included regardless of their quality. In consequence of the small number of studies per each individual outcome, it was impossible to conduct a more detailed analysis including only high quality studies.

5.4 Conclusions, recommendations and perspectives

One of the essential perceptions is that the current evidence does not allow the study questions to be answered with certainty. Consequently, strict evidence-based recommendations in terms of plant-based diets during pregnancy and childhood cannot be made. Further research is needed to verify our findings. Well-designed prospective cohort studies and RCTs are most appropriate as the next step. Standardized questionnaires for dietary assessment and consistent diet scores are required to increase the comparability of the single studies. Regular updates of the evidence are necessary to enable meta-analyses with lower heterogeneity and higher statistical power in the future.

However, the present study situation does not indicate any harms of the Mediterranean diet during pregnancy and childhood. Despite the small number of studies per outcome, it even shows significant benefits in terms of multiple pregnancy-related outcomes such as GDM and preterm delivery. Moreover, the significantly lower risk of overweight and obesity in children constitutes an important finding. Our results suggest that the Mediterranean diet could be an essential component of metabolically healthy pregnancies and the basis of early prevention of metabolic disorders in children and adolescents. The Mediterranean diet as a sustainable, cost-effective, low-risk intervention should not be neglected in future dietary recommendations and guidelines.

The findings in terms of vegetarian diet forms revealed a tremendous scarcity and heterogeneity of studies. The present study situation showed an under-representation of vegetarian diet forms, especially vegan diet, in current research when considering the growing importance of plant-based nutrition over the past years. When considering the significant advantages of vegetarian diet forms with respect to sustainability, large prospective cohort studies and RCTs are needed to assess harms and benefits as well as long-term effects of vegetarian diet forms. However, our findings indicate that a vegetarian diet does not pose a risk to pregnant women and children as long as requirements of macronutrients and micronutrients are fulfilled. Moreover, the results suggest that vegetarian diet forms might even have a beneficial potential, but no firm conclusions can be made on the basis of heterogeneous and inconsistent evidence, especially with regard to long-term effects.

6 Appendix

Appendix 1: Study quality

Table 18: Study quality of cross-sectional studies

Author & year	Score	Quality
Abriha 2014	10/14	fair
Alizadeh 2015	9/14	fair
Ambroszkiewicz 2018	8/14	fair
Antonogeorgos 2013	11/14	fair
Archero 2018	10/14	fair
Baig-Ansari 2008	10/14	fair
Carmichael 2013	9/14	fair
Castro-Rodriguez 2008	9/14	fair
Chacon-Ruberos 2018	9/14	fair
de Batlle 2008	9/14	fair
Esfahani 2016	11/14	fair
Farajian 2011	10/14	fair
Galan-Lopez 2018	9/14	fair
Garcia-Marcos 2007	8/14	fair
George 2000	9/14	fair
Gomez Roig 2017	11/14	fair
Goni 2018	10/14	fair
Gonzalez Barcala 2010	9/14	fair
Goswmai 2015	8/14	fair
Grant 2008	8/14	fair
Grieger 2014	12/14	good
Grigoropoulou 2011	10/14	fair
Haddad 2003	8/14	fair
Henriksson 2017	10/14	fair
Jali 2011	6/14	poor
Jennings 2011	10/14	fair
Julian 2018	8/14	fair
Koirala 2015	8/14	fair
Kontogianni 2008	7/14	fair
Koutelidakis 2018	10/14	fair
Krajvcovivcova-Kudlaakova 1997	5/14	poor

Krasevec 2017	7/14	fair
Larsson 2002	6/14	poor
Lazarou 2010	9/14	fair
Leung 2001	7/14	fair
Leventakou 2016	10/14	fair
Melaku 2018	11/14	fair
Mistretta 2017	10/14	fair
Monjardino 2014	9/14	fair
Muros 2017a	9/14	fair
Muros 2017b	10/14	fair
O'Connell 1989	10/14	fair
Pellegrini-Belinchon 2016	8/14	fair
Peraita-Costa 2018	8/14	fair
Persky 1992	8/14	fair
Rona 1987	8/14	fair
Rosi 2017	9/14	fair
Sharma 2003	8/14	fair
Silva-del Valle 2013	9/14	fair
Tambalis 2018	10/14	fair
Tognon 2014	10/14	fair
Vassiloudis 2014	10/14	fair
Voltas 2016	9/14	fair
Weder 2019	11/14	fair
Yen 2008	8/14	fair

Table 20: Study quality of meta-analyses

Author & year	Score	Quality
Chia 2019	8/8	good
Zhang 2019	7/8	good
Eaton 2019	8/8	good

Table 21: Study quality of interventional studies

Author & year	Score	Quality
Bacopoulou 2017	9/12	fair
Garcia de la Torre 2019	-/-	fair
H Al Wattar 2019	12/14	good
Krebs 2012	11/14	fair
Renault 2015	10/14	fair
Sheng 2019	12/14	good

Table 22: Study quality of case-control studies

Author & year	Score	Quality
Akre 2008	8/12	fair
Botto 2016	10/12	good
Carmichael 2012a	9/12	fair
Carmichael 2012b	10/12	good
Ibanez 2019	10/12	good
Izadi 2016	8/12	fair
Kaur 2013	7/12	fair
Martinez-Galiano 2018	8/12	fair
Olmedo-Requena 2019	10/12	good
Smith 2015*	8/12	fair
Vujkovic 2009	10/12	good
Yang 2019	8/12	fair
**case-cohort study*		

Table 23: Study quality of cohort studies

Author & year	Score	Quality
Assaf-Balut 2019	11/14	fair
Castro 2016	10/14	fair
Chatzi 2008	12/14	good
Chatzi 2012	12/14	good
Chatzi 2013	10/14	fair
Chatzi 2017	11/14	fair
Dagnelie 1989	12/14	good
Dagnelie 1994	12/14	good
Donazar-Ezcurra 2017	13/14	good
dos Santos 2013	10/14	fair
Fernandez-Barres 2016	14/14	good
Fernandez-Barres 2019	12/14	good
Fikree 1994	9/14	fair
Haapala 2017	12/14	good
Haugen 2008	12/14	good
House 2018	11/14	fair
Karamanos 2014	10/14	fair
Lange 2010	10/14	fair
Larsen 2014	11/14	fair
Mak 2018	11/14	fair
Mari-Sanchis 2018	13/14	good
Martin-Calvo 2016	10/14	fair
Mikkelsen 2008	12/14	good
Misra 2015	12/14	good
Monteagudo 2016	10/14	fair
North 2000	9/14	fair
Poon 2013	10/14	fair
Saunders 2014	9/14	fair
Schoenaker 2015a	11/14	fair
Schoenaker 2015b	11/14	fair
Shull 1977	10/14	fair
Stuebe 2009	12/14	good
Timmermans 2011	12/14	good
Timmermans 2012	12/14	good
Tobias 2012	10/14	fair
Wolters 2018	12/14	good
Zulyniak 2017	12/14	good

Appendix 2: Terms of the search on *PubMed*

The following terms were combined in one search term. The brackets were removed for the purpose of transparency.

vegetarian AND pregnancy OR
vegetarian AND fetal development OR
vegetarian AND lactation OR
vegetarian AND child health OR
vegetarian AND newborn OR
vegetarian AND infant health OR
vegetarian AND adolescent health OR
vegan AND pregnancy OR
vegan AND fetal development OR
vegan AND lactation OR
vegan AND child health OR
vegan AND newborn OR
vegan AND infant health OR
vegan AND adolescent health OR
macrobiotic diet AND pregnancy OR
macrobiotic diet AND fetal development OR
macrobiotic diet AND lactation OR
macrobiotic diet AND child health OR
macrobiotic diet AND newborn OR
macrobiotic diet AND infant health OR
macrobiotic diet AND adolescent health OR
low meat diet AND pregnancy OR
low meat diet AND fetal development OR
low meat diet AND lactation OR
low meat diet AND child health OR
low meat diet AND newborn OR
low meat diet AND infant health OR
low meat diet AND adolescent health OR
mediterranean diet AND pregnancy OR
mediterranean diet AND fetal development OR
mediterranean diet AND lactation OR
mediterranean diet AND child health OR
mediterranean diet AND newborn OR
mediterranean diet AND infant health OR
mediterranean diet AND adolescent health

Appendix 3: Summary of our meta-analyses

Table 24: Summary of meta-analyses assessing Mediterranean diet

Outcome	Studies n	Pooled estimate (95% CI)	I^2	Egger's regression
GDM	9	OR = 0.64; (0.51-0.79)	79.18%; p = 0.00	p = 0.12
Hypertensive disorders	4	OR = 0.77; (0.48-1.23)	69.72%; p = 0.02	p = 0.95
Preterm delivery	6	OR = 0.73; (0.59-0.92)	12.78%; p = 0.33	p = 0.14
SGA/FGR/ IUGR/LBW	8	OR = 0.87; (0.58-1.31)	70.94%; p = 0.00	p = 0.62
Asthma/ wheezing	8	OR = 0.82; (0.68-0.97) OR = 0.92; (0.75-1.12)[1]	70.50%; p = 0.00	p = 0.03
Overweight/ obesity	10	OR = 0.87; (0.79-0.94)	50.54%; p = 0.03	p = 0.24
Mean BMI	6	-0.42; (-0.86-0.02)[2] -0.23; (-0.78-0.32)[3]	42.09%; p = 0.10	p = 0.04

BMI = body mass index; CI = confidence interval; FGR = fetal growth restriction; GDM = gestational diabetes mellitus; IUGR = intrauterine growth retardation; LBW = low birth weight; OR = odds ratio; SGA = small for gestational age

[1] adjusted OR after applying Duval and Tweedie's trim and fill
[2] difference in means in kg/m^2
[3] adjusted difference in means after applying Duval and Tweedie's trim and fill

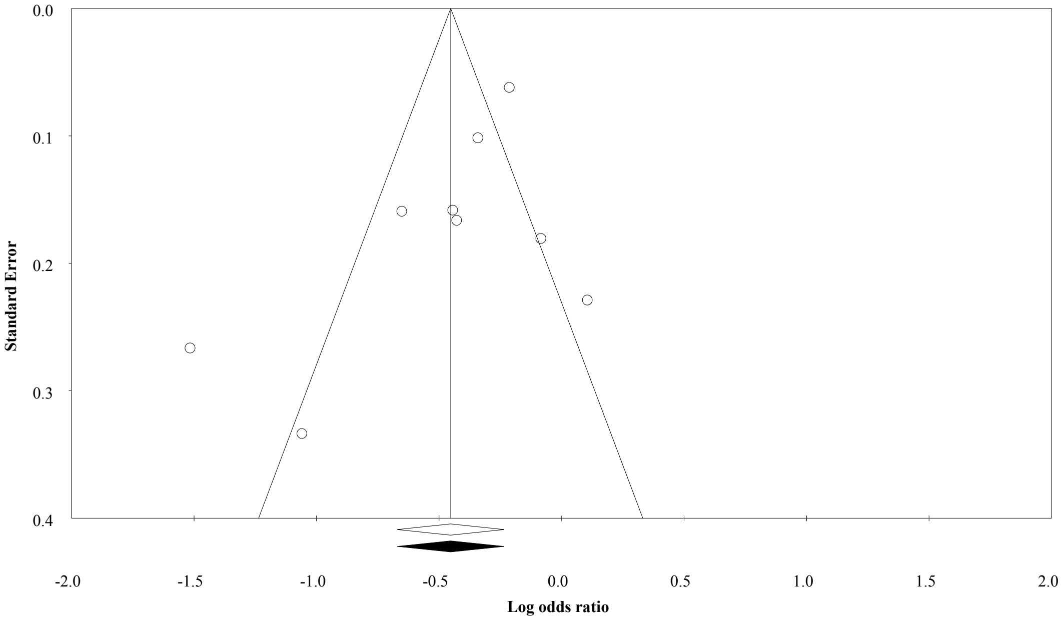
Table 25: Summary of meta-analyses assessing vegetarian diet forms

Outcome	Studies n	Pooled estimate (95% CI)	I^2	Egger's regression
Anemia	3	OR = 1.38; (0.86-2.23)	54.79%; p = 0.11	p = 0.74
GDM	3	OR = 0.63; (0.31-1.28)	86.11%; p = 0.00	p = 0.20
Hypospadias	3	OR = 1.88; (0.70-5.08)	78.24%; p = 0.01	p = 0.33
SGA/FGR/ IUGR/LBW	5	OR = 0.97; (0.55-1.71)	77.42%; p = 0.00	p = 0.42
Overweight/ obesity	5	OR = 0.81; (0.49-1.32)	0.00%; p = 0.89	p = 0.94
Stunting	4	OR = 1.41; (0.61-3.26)	97.87%; p = 0.00	p = 0.63
Mean BMI	4	-0.92; [-1.34-(-0.49)][1]	87.47%; p = 0.00	p = 0.44

BMI = body mass index; CI = confidence interval; FGR = fetal growth restriction; GDM = gestational diabetes mellitus; IUGR = intrauterine growth retardation; LBW = low birth weight; OR = odds ratio; SGA = small for gestational age

[1] difference in means in kg/m^2

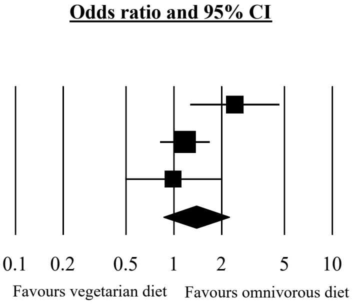
Appendix 4: Mediterranean diet and gestational diabetes



Egger's regression: $p = 0.118$ (no publication bias)

Appendix 5: Vegetarian diet and anemia during pregnancy

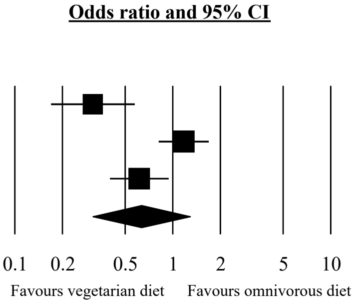
Study name	**Statistics for each study**			**Vegetarian / Total**		
	Odds ratio	**Lower limit**	**Upper limit**	**Anemia mother +**	**Anemia mother -**	**Relative weight**
Abriha 2014	2.427	1.267	4.649	93 / 105	265 / 348	28.59
Baig-Ansari 2008	1.175	0.818	1.688	699 / 1225	69 / 130	44.90
Sharma 2003	0.991	0.494	1.988	504 / 860	20 / 34	26.51
	1.382	0.857	2.229	1296 / 2190	354 / 512	



Cochran's Q Test $I^2 = 54.79\%$ ($p = 0.11$); Egger's regression: $p = 0.74$ (no publication bias)

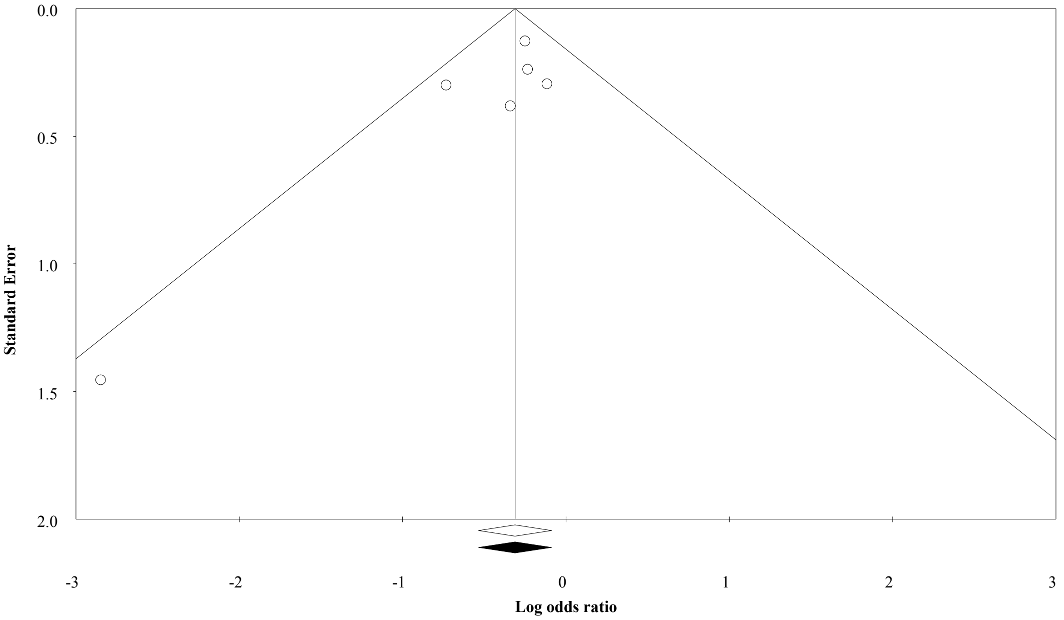
Appendix 6: Vegetarian diet forms and gestational diabetes

Study name	Statistics for each study			Vegetarian / Total		Relative weight
	Odds ratio	Lower limit	Upper limit	GDM +	GDM -	
Jali 2011	0.313	0.169	0.577	20 / 52	182 / 273	30.31
Mak 2018	1.173	0.813	1.694	72 / 135	373 / 756	35.44
Mari-Sanchis 2018	0.614	0.400	0.943	36 / 93	789 / 1556	34.25
	0.629	0.309	1.281	128 / 280	1344 / 2585	



Cochran's Q Test $I^2 = 86.11\%$ *(p = 0.00); Egger's regression: p = 0.20 (no publication bias)*

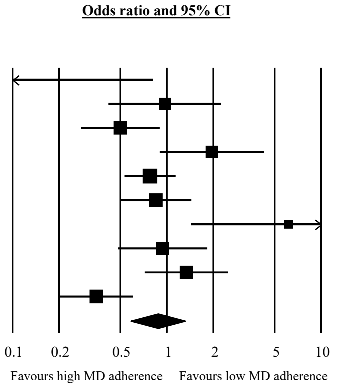
Appendix 7: Mediterranean diet and preterm delivery



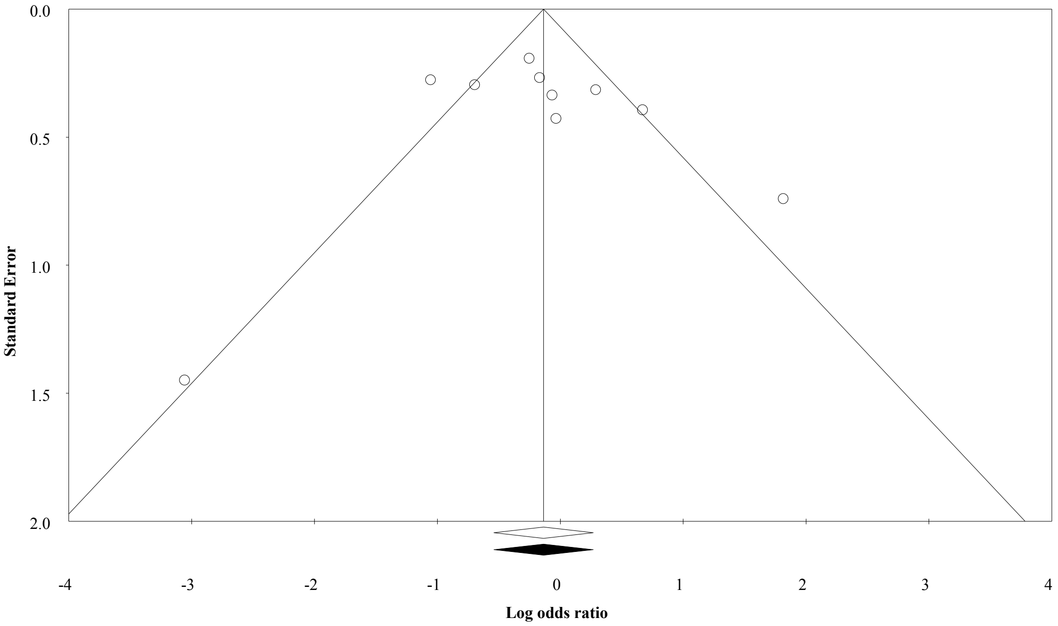
Egger's regression: p = 0.138 (no publication bias)

Appendix 8: Mediterranean diet and SGA, IUGR, FGR, LBW

Study name	Statistics for each study			High MD adherence / Total		
	Odds ratio	Lower limit	Upper limit	SGA/FGR/IUGR/LBW +	SGA/FGR/IUGR/LBW -	Relative weight
Assaf-Balut 2019	0.047	0.003	0.811	0 / 11	115 / 240	1.79
Chatzi 2012 I	0.970	0.418	2.250			9.43
Chatzi 2012 II	0.500	0.279	0.896			11.96
Chatzi 2012 III	1.960	0.902	4.259			10.04
H Al Wattar 2019	0.779	0.532	1.140	52 / 121	479 / 974	13.96
Martinez-Galiano 2018	0.849	0.500	1.439	45 / 81	109 / 183	12.53
Monteagudo 2016	6.162	1.438	26.399			5.20
Poon 2013	0.940	0.484	1.825			11.15
Saunders 2014	1.340	0.719	2.495	38 / 54	234 / 366	11.58
Timmermans 2012	0.349	0.202	0.603	18 / 68	1051 / 2071	12.35
	0.872	0.582	1.306	153 / 335	1988 / 3834	

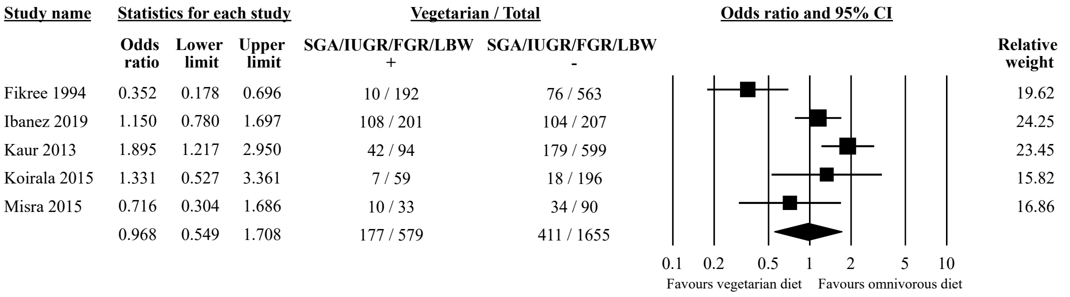


Cochran's Q Test $I^2 = 70.98\%$ *(p = 0.00); Egger's regression: p = 0.62 (no publication bias)*



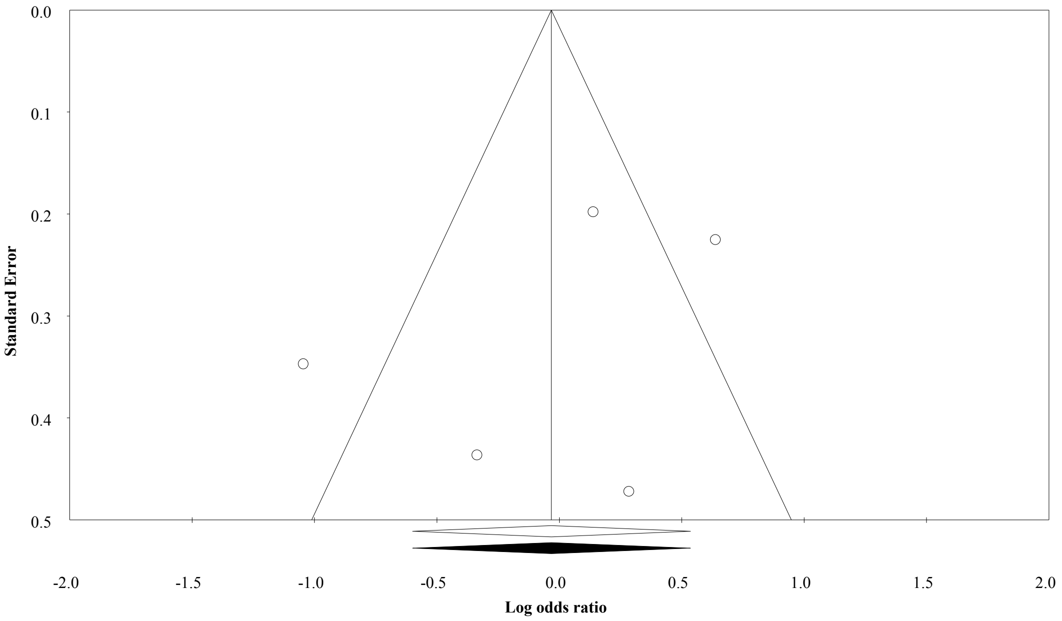
Egger's regression: p = 0.619 (no publication bias)

Appendix 9: Vegetarian diet forms and SGA, IUGR, FGR, LBW



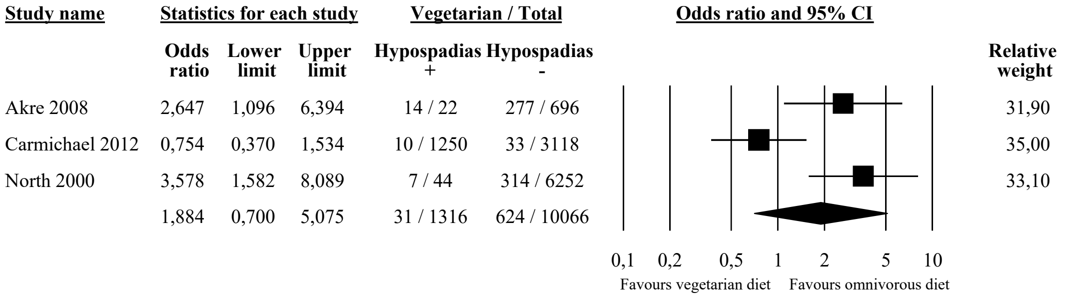
Study name	Statistics for each study			Vegetarian / Total		
	Odds ratio	Lower limit	Upper limit	SGA/IUGR/FGR/LBW +	SGA/IUGR/FGR/LBW -	Relative weight
Fikree 1994	0.352	0.178	0.696	10 / 192	76 / 563	19.62
Ibanez 2019	1.150	0.780	1.697	108 / 201	104 / 207	24.25
Kaur 2013	1.895	1.217	2.950	42 / 94	179 / 599	23.45
Koirala 2015	1.331	0.527	3.361	7 / 59	18 / 196	15.82
Misra 2015	0.716	0.304	1.686	10 / 33	34 / 90	16.86
	0.968	0.549	1.708	177 / 579	411 / 1655	

Cochran's Q Test I^2 *= 77.42% (p = 0.00); Egger's regression: p = 0.42 (no publication bias)*



Egger's regression: p = 0.418 (no publication bias)

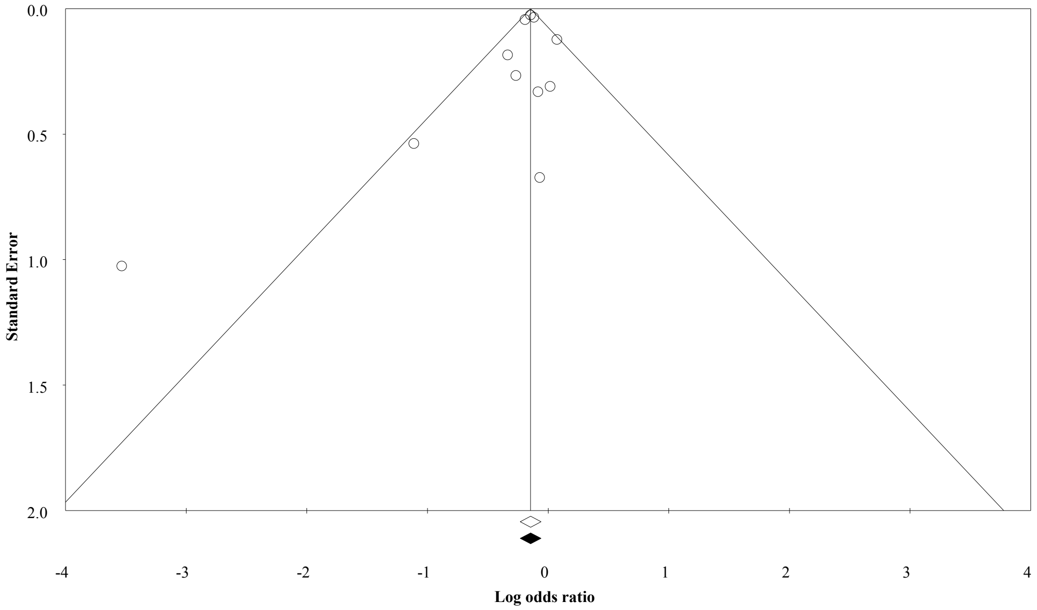
Appendix 10: Vegetarian diet forms and hypospadias



Study name	Statistics for each study			Vegetarian / Total		Relative weight
	Odds ratio	Lower limit	Upper limit	Hypospadias +	Hypospadias -	
Akre 2008	2,647	1,096	6,394	14 / 22	277 / 696	31,90
Carmichael 2012	0,754	0,370	1,534	10 / 1250	33 / 3118	35,00
North 2000	3,578	1,582	8,089	7 / 44	314 / 6252	33,10
	1,884	0,700	5,075	31 / 1316	624 / 10066	

Cochran's Q Test $I^2 = 78.24\%$ *(p = 0.01); Egger's regression: p = 0.33 (no publication bias)*

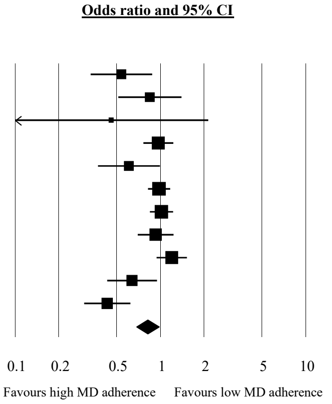
Appendix 11: Mediterranean diet and overweight and obesity



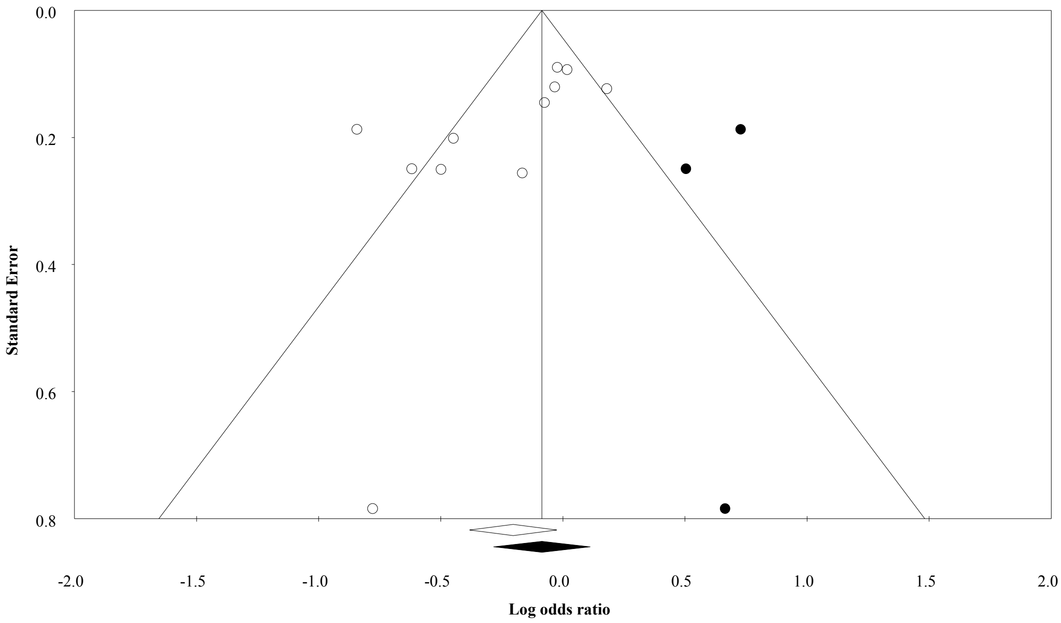
Egger's regression: p = 0.244 (no publication bias)

Appendix 12: Mediterranean diet and asthma and wheezing

Study name	Statistics for each study			High MD adherence / Total		Relative weight
	Odds ratio	Lower limit	Upper limit	Asthma/Wheezing +	Asthma/Wheezing -	
Castro-Rodriguez 2008	0.540	0.331	0.882			7.00
Castro-Rodriguez 2016	0.849	0.513	1.404	24 / 98	128 / 463	6.81
Chatzi 2008	0.460	0.099	2.143			1.23
Chatzi 2013	0.970	0.764	1.231			11.82
de Batlle 2008	0.609	0.372	0.996	24 / 84	347 / 875	6.97
Gonzalez Barcala 2010 I	0.980	0.820	1.171			13.05
Gonzalez Barcala 2010 II	1.020	0.848	1.227			12.91
Gonzalez Barcala 2010 III	0.930	0.699	1.238			10.81
Gonzalez Barcala 2010 IV	1.200	0.941	1.531			11.70
Lange 2010	0.640	0.431	0.951			8.59
Pellegrini-Belinchon 2016	0.431	0.298	0.624	51 / 136	598 / 1028	9.12
	0.816	0.683	0.974	99 / 318	1073 / 2366	



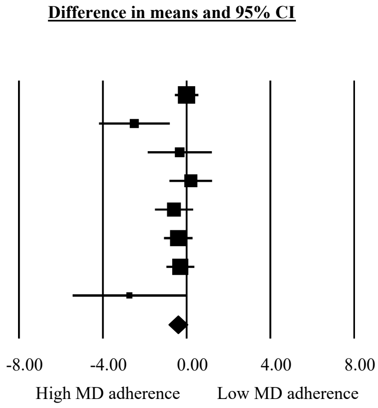
Cochran's Q Test I^2 = 70.50% (p = 0.00); Egger's regression: p = 0.03 (significant publication bias); adjusted OR = 0.92 (0.75-1.12)



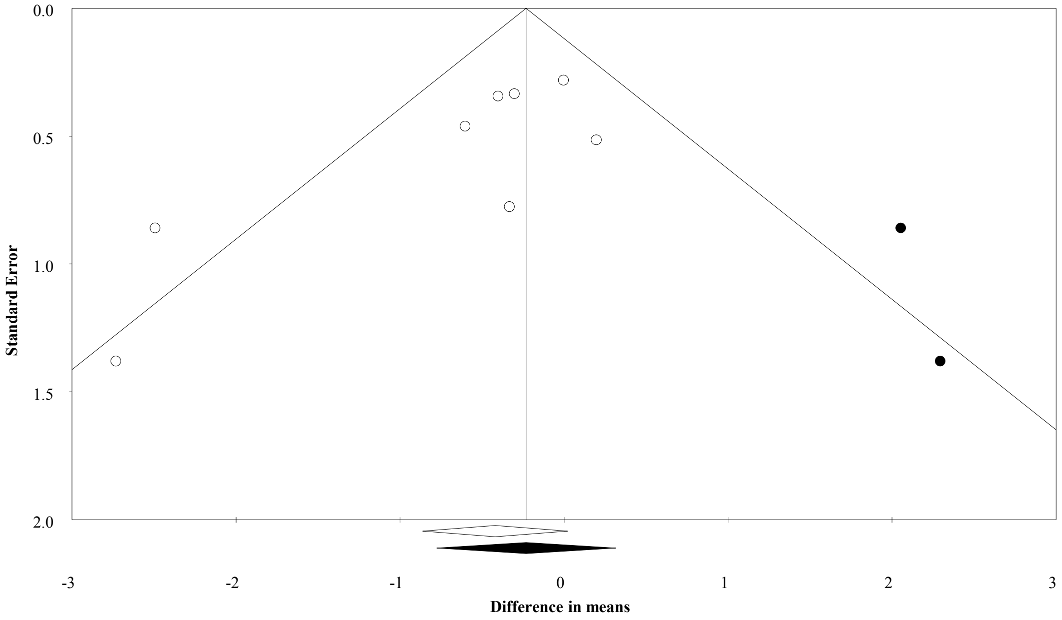
Egger's regression: p = 0.027 (significant publication bias); adjusted OR = 0.917 (0.753-1.117)

Appendix 13: Mediterranean diet and mean BMI

Study name	Statistics for each study			Sample size	
	Difference in means	Lower limit	Upper limit	High MD adherence	Low MD adherence
Farajian 2011	0.000	-0.557	0.557	205	2240
Galan-Lopez 2018 I	-2.490	-4.179	-0.801	94	58
Galan-Lopez 2018 II	-0.330	-1.855	1.195	94	58
Julian 2018	0.200	-0.814	1.214	123	56
Kontogianni 2008	-0.600	-1.507	0.307	85	112
Monjardino 2014 I	-0.400	-1.077	0.277	186	219
Monjardino 2014 II	-0.300	-0.961	0.361	194	247
Muros 2017	-2.730	-5.439	-0.021	265	8
	-0.420	-0.862	0.021	1246	2998



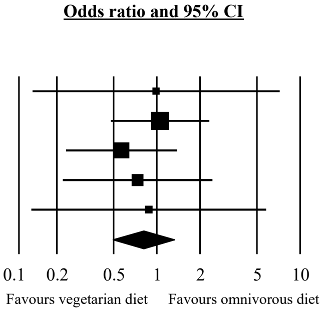
Cochran's Q Test I^2 *= 42.09% (p = 0.10); Egger's regression: p = 0.04 (significant publication bias); adjusted difference in means = -0.23 (-0.78-0.32) kg/m*^{2}



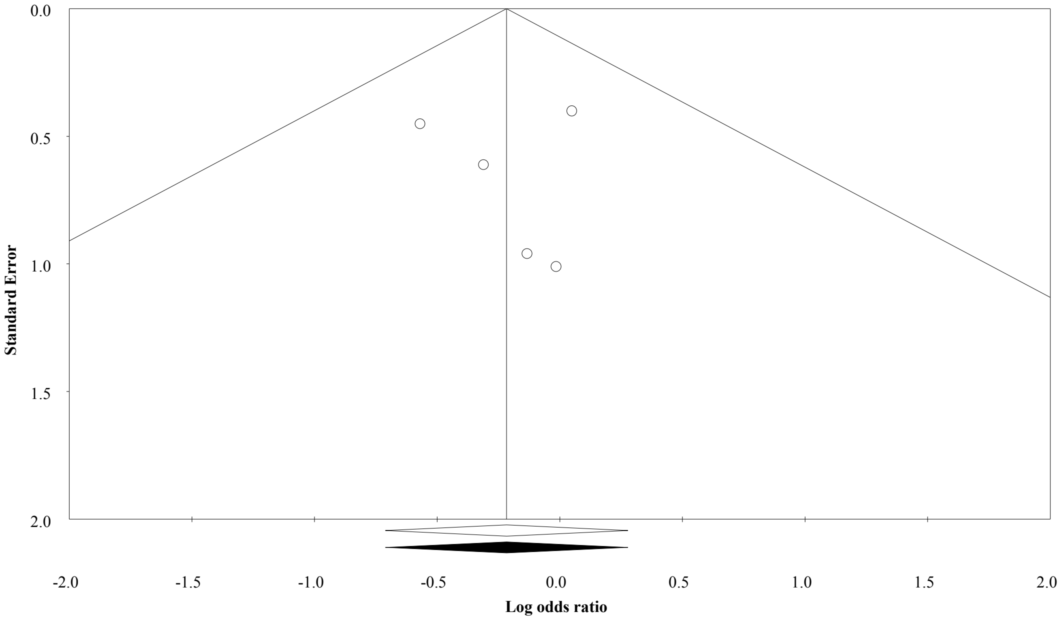
Egger's regression: p = 0.044 (significant publication bias); adjusted difference in means = -0.231 (-0.777-0.315) kg/m^2

Appendix 14: Vegetarian diet forms and overweight and obesity

Study name	Statistics for each study			Vegetarian / Total		
	Odds ratio	Lower limit	Upper limit	Overweight/Obesity +	Overweight/Obesity -	Relative weight
Alizadeh 2015	0.988	0.136	7.184	2 / 4	80 / 159	6.20
Larsson 2002	1.053	0.478	2.321	7 / 90	142 / 1915	39.14
Shull 1977	0.567	0.233	1.379	17 / 29	55 / 77	30.91
Weder 2019	0.734	0.220	2.444	6 / 11	260 / 419	16.88
Yen 2008	0.877	0.133	5.783	2 / 5	19 / 44	6.87
	0.805	0.491	1.319	34 / 139	556 / 2614	



Cochran's Q Test I^2 *= 0.00% (p = 0.89); Egger's regression: p = 0.94 (no publication bias)*

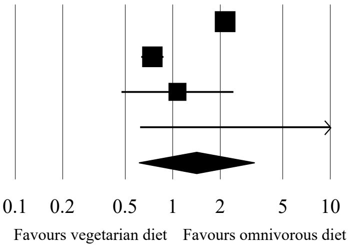


Egger's regression: p = 0.942 (no publication bias)

Appendix 15: Vegetarian diet forms and stunting

Study name	Statistics for each study			Vegetarian / Total			Relative weight
	Odds ratio	Lower limit	Upper limit	Stunting +	Stunting -		
Krasevec 2017	2.151	2.010	2.302	8796 / 9992	18022 / 23293		33.90
Melaku 2018	0.743	0.631	0.875	431 / 960	749 / 1432		33.54
Shull 1977	1.072	0.472	2.435	33 / 48	39 / 58		25.67
Weder 2019	10.818	0.620	188.686	8 / 8	258 / 422		6.89
	1.408	0.607	3.263	9268 / 11008	19068 / 25205		

Odds ratio and 95% CI

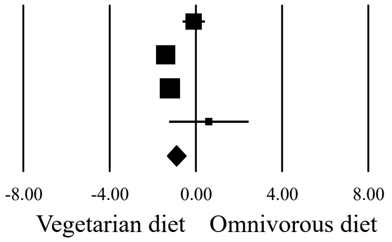


Cochran's Q Test $I^2 = 97.87\%$ (p = 0.00); Egger's regression: p = 0.63 (no publication bias)

Appendix 16: Vegetarian diet forms and mean BMI

Study name	Statistics for each study			Sample size	
	Difference in means	Lower limit	Upper limit	Vegetarian	Omnivorous
Ambroszkiewicz 2018	-0.100	-0.616	0.416	70	60
Grant 2008	-1.400	-1.634	-1.166	53	160
Haddad 2003	-1.200	-1.232	-1.168	120	12543
Persky 1992	0.600	-1.243	2.443	35	38
	-0.918	-1.342	-0.494	278	12801

Difference in means and 95% CI



Cochran's Q Test $I^2 = 87.47\%$ (p = 0.00); Egger's regression: p = 0.45 (no publication bias)

Appendix 17: List of case reports

Table 26: List of case reports referring to deficiency symptoms of vegetarian and vegan children

Author & year	Diet of the mother	Patient's age	Symptoms & findings
Agrawal 2009	strict vegetarian	8 months	cerebral atrophy
	strict vegetarian	10 months	cerebral atrophy
Amoroso 2018	raw vegan	1 year	acute small bowel obstruction
Bousselamti 2018	strict vegetarian	9 months	hypotonia, apathy, psychomotor regression
Casella 2005	low meat	6 months	developmental regression, cerebral atrophy
Ciani 2000	vegan	22 months	metabolic acidosis, hyperammonemia, ketonuria, macrocytic anemia
Cundiff 2006	raw vegan	5 months	sudden death
Curtis 1983	vegan	3.5 years	rachitic signs
	vegan	1.5 years	rachitic signs
	vegan	2.75 years	rachitic signs
de Jong 2005	vegan	7 months	recurrent generalized convulsions, rachitic signs, developmental delay
Doyle 1989	strict vegetarian	8 months	rachitic signs, developmental delay, megaloblastic anemia
	vegetarian	18 months	vomiting, rachitic signs, megaloblastic anemia
Erdeve 2009	vegan	newborn	megaloblastic anemia
Gambon 1986	vegan	11 months	hypotonia, megaloblastic anemia
Gowda 2018 (case series)	46 of 70 were vegetarian	13.2 months	pallor, skin depigmentation, developmental delay, tremor
Guez 2012	vegan	5 months	pallor, skin depigmentation, developmental delay, some with tremor
Grattan 1997	vegetarian	10 months	hypotonia, developmental delay
	vegan	12 months	involuntary movements, megaloblastic anemia
	vegetarian	18 months	hypotonia, cerebral atrophy
Higginbottom 1978	vegan	6 months	neurologic abnormalities, methylmalonic aciduria, homocystinuria, megaloblastic anemia
Idris 2012	low meat	32 years	pancytopenia during pregnancy

Kanra 2005	vegetarian	1 year	weight loss, anemia, psychomotor regression
Kocaoglu 2014	vegetarian	12 months	cerebral atrophy
Kühne 1991	vegan	9 months	psychomotor regression, pancytopenia with megaloblastic anemia
Lampkin 1969	vegetarian	10 months	megaloblastic anemia
Lövblad 1997	strict vegetarian	14 months	cerebral atrophy, developmental delay, megaloblastic anemia
Michaud 1992	strict vegetarian	3 months	vitamin B12 deficiency
Muhammad 2003	vegan	15 months	developmental delay, severe macrocytic anemia
	vegetarian	30 months	developmental delay
Rachmel 2003	vegetarian	9 months	developmental delay, megaloblastic anemia
Reghu 2005	vegetarian	9 months	edema, megaloblastic anemia
	vegetarian	10 months	edema, megaloblastic anemia
Renault 1999	vegetarian	12 months	pallor, edema, severe hypotonia
	vegetarian	10 months	regurgitation, weight loss, pallor, edema, apathy
Rendle-Short 1979	vegan	11 months	hypotonia, developmental regression, macrocytic anemia
	vegan	16 months	hypotonia, developmental regression, macrocytic anemia
Rinaldo 1997	vegetarian	5 days	sudden neonatal death, carnitine transporter deficiency
Rodrigues 2011	vegetarian	10 months	severe megaloblastic anemia
Rudolf 1980	vegan	3 years	rachitic signs
Shaikh 2003	vegan	10 days	transient neonatal hypothyroidism
Shinwell 1982	vegan	6 months	erythematous rash, corneal ulcer, conjunctivitis, blepharitis, partial alopecia, diarrhea
	vegan	3 months	rachitic signs, megaloblastic anemia
Sklar 1986	vegan	7 months	hypotonia, megaloblastic anemia
Stollhoff 1987	vegan	18 months	cerebral atrophy, psychomotor regression
Yoganathan 2017	strict vegetarian	6 months	poor weight gain, feeding difficulties, severe pallor, muscle hypotonia, somnolence
Unknown author 1979	vegan	6 months	hypotonia, developmental delay, severe megaloblastic anemia

Appendix 18: Dietary assessment of studies investigating Mediterranean diet

Table 27: Dietary assessment of studies investigating Mediterranean diet

Author & year	**Diet score**	**Measurement of dietary intake**
Antonogeorgos 2013	KIDMED[1]	FFQ
Archero 2018	KIDMED[1]	KIDMED questionnaire
Assaf-Balut 2019	six-item-score[2]	FFQ
Bacopoulou 2017	KIDMED[1]	KIDMED questionnaire
Botto 2016	MDS based on Trichopoulou et al[3]	FFQ
Carmichael 2012a	MDS based on Trichopoulou et al[3]	FFQ
Carmichael 2012b	MDS based on Trichopoulou et al[3]	FFQ
Carmichael 2013	MDS based on Trichopoulou et al[3]	FFQ
Castro-Rodriguez 2008	MDS based on Psaltopoulou et al[7]	FFQ
Castro-Rodriguez 2016	MDS based on Psaltopoulou et al[7]	FFQ
Chacon-Ruberos 2018	KIDMED[1]	KIDMED questionnaire
Chatzi 2008	MDS based on Trichopoulou et al;[3] KIDMED	FFQ
Chatzi 2012	MDS based on Trichopoulou et al[3]	FFQ
Chatzi 2013	MDS based on Trichopoulou et al[3]	FFQ
Chatzi 2017	MDS based on Trichopoulou et al[3]	FFQ
de Batlle 2008	MDS based on Trichopoulou et al[3]	FFQ
Donazar-Ezcurra 2017	component analysis	FFQ
Esfahani 2016	component analysis	FFQ
Farajian 2011	KIDMED[1]	FFQ
Fernandez-Barres 2016	rMED[4]	FFQ
Fernandez-Barres 2019	rMED[4]	FFQ
Galan-Lopez 2018	KIDMED[1]	KIDMED questionnaire
García de la Torre 2019	MEDAS[5]	FFQ
Garcia-Marcos 2007	MDS based on Psaltopoulou et al[7]	FFQ
Gomez Roig 2017	MDS based on Trichopoulou et al[3]	FFQ
Goni 2018	KIDMED[1]	KIDMED questionnaire
Gonzalez Barcala 2010	MDS by Garcia-Marcos et al[6] (based on Psaltopoulou et al)[7]	FFQ
Grigoropoulou 2011	KIDMED[1]	FFQ

Haapala 2017	MDS based on Trichopoulou et al[3]	4-day dietary record
H Al Wattar 2019	ESTEEM Q[8]	FFQ
Haugen 2008	MDS including 4 components[9]	FFQ
Henriksson 2017	MDS based on Trichopoulou et al[3]	24-hour-recall (2x)
House 2018	MDS based on Trichopoulou et al[3]	FFQ
Izadi 2016	MDS based on Trichopoulou et al[3]	24-hour-recall (3x)
Jennings 2011	MDS based on Trichopoulou et al[3]	4-day dietary record
Julian 2018	MDS-A[10]	24-hour-recall (2x)
Karamanos 2014	MDS based on Trichopoulou et al[3]	FFQ
Kontogianni 2008	KIDMED[1]	KIDMED questionnaire, 24-hour-recall
Koutelidakis 2018	MDS based on Panagiotakos et al[11]	FFQ
Lange 2010	MDS based on Trichopoulou et al[3]	FFQ
Lazarou 2010	KIDMED[1]	KIDMED questionnaire
Leventakou 2016	component analysis	FFQ
Martin-Calvo 2016	KIDMED[1] (modified to m-KM index)[12]	FFQ
Martinez-Galiano 2018	MDS by Trichopoulou et al[3]	FFQ
Mikkelsen 2008	MDS including 4 components[9]	FFQ
Mistretta 2017	KIDMED[1]	FFQ + KIDMED questionnaire
Monjardino 2014	KIDMED[1]	FFQ
Monteagudo 2016	MDS-P[13]	FFQ
Muros 2017a	KIDMED[1]	KIDMED questionnaire
Muros 2017b	KIDMED[1]	KIDMED questionnaire
Olmedo-Requena 2019	MDS based on Trichopoulou et al[3]	FFQ
Pellegrini-Belinchon 2016	no diet score[14]	FFQ
Peraita-Costa 2018	KIDMED[1]	KIDMED questionnaire
Poon 2013	aMED[15]	FFQ
Renault 2015	no diet score	FFQ
Rosi 2017	KIDMED[1]	KIDMED questionnaire
Saunders 2014	MDS based on Trichopoulou et al[3]	FFQ
Schoenaker 2015	component analysis	FFQ
Schoenaker 2015	component analysis	FFQ
Silva-del Valle 2013	MEDAS[5]	FFQ
Smith 2015	MDS including 4 components[9]	interview
Timmermans 2011	component analysis	FFQ
Timmermans 2012	component analysis	FFQ
Tambalis 2018	KIDMED[1]	KIDMED questionnaire
Tobias 2012	aMED[15]	FFQ

Tognon 2014	fMDS[16]	FFQ
Vassiloudis 2014	KIDMED[1]	KIDMED questionnaire
Voltas 2016	Krece Plus food questionnaire[17]	Krece Plus food questionnaire
Vujkovic 2009	component analysis	FFQ
Wolters 2018	FPQ,[18] CEHQ[19]	FFQ

CEHQ = children's eating habits questionnaire; FFQ = food frequency questionnaire; FPQ = food propensity questionnaire; MDS = Mediterranean diet score; MEDAS = Mediterranean diet adherence screener; rMED = relative Mediterranean diet

---

[1] The KIDMED test evaluates the MD adherence in children and adolescents. The 16-item questionnaire ranges from -4 to 12. Questions denoting a negative connotation in terms of MD are assigned a value of -1, and those with a positive aspect +1.(Serra-Majem et al., 2004)

[2] MD adherence based on six criteria: intake of $\geq$ 40 ml/day of olive oil, > 6 times/week of olive oil, > 3 servings/week of nuts, > 12 servings/week of whole fruits, > 2 servings/week of juice.

[3] The MDS considers the intake of beneficial components (vegetables, legumes, fruits and nuts, cereal, and fish) and detrimental components (meat and meat products, dairy products), the alcohol intake, and the ratio of monounsaturated lipids to saturated lipids. The MDS ranges from 0 (minimal MD adherence) to 9 (maximal adherence). (Trichopoulou et al., 2003)

[4] The rMED is based on the score by Trichopoulou et al. In addition, tertiles of adherence to the single components are calculated, so that a maximum of two points per component can be reached. This results in a range from 0 to 18 points. (Buckland et al., 2009)

[5] The MEDAS is a short screener that collects information on the intake of olive oil, fruit, vegetables, legumes, fish, wine, meat, bread and rice, nuts, carbonated and/or sugar-sweetened beverages, and dishes with a sauce of tomato, garlic, onion, or leeks sautéed in olive oil. Additionally, it considers food intake habits. (Schröder et al., 2011)

[6] In contrast to the score by Psaltopoulou et al, the simplified questionnaire allows no adjustment of food consumption to energy intake. (Garcia-Marcos et al., 2007)

[7] Psaltopoulou et al used the same parameters as Trichopoulou et al. (Psaltopoulou et al., 2004)

[8] ESTEEM Q is a validated short questionnaire for the measurement of MD adherence.

[9] The score considers the consumption of fruit and vegetables every day, fish more than twice a week, meat up to twice a week, maximum of two cups of coffee a day.

[10] The Mediterranean diet score for adolescents (MDS-A) uses the same components as the score by Trichopoulou et al, but dairy products are considered as beneficial and alcohol consumption as a negative component.

[11] Panagiotakos et al use 11 main components (non-refined cereals, fruits, vegetables, potatoes, legumes, olive oil, fish, red meat, poultry, full fat dairy products and alcohol). Scores from 0 to 5 points are given for each component which results in a range from 0 to 55 points. (Panagiotakos et al., 2006)

[12] KIDMED score modified to make it more appropriate for an American population.

[13] In addition to the common MDS, the MDS-P evaluates the intake of micronutrients required in optimal amounts during pregnancy, such as iron, folic acid and calcium. (Mariscal-Arcas et al., 2009)

[14] MD in case of affirmative answers to the following questions: "Olive oil and white or blue fish $\geq$ 3 times/week? Fruit or fruit juice $\geq$ 3 times/week? Fresh or cooked vegetables or salad $\geq$ 3 times/week? Legumes or cereals or pasta $\geq$ 3 times/week? Eggs $\geq$ 2 times/week? Milk or yoghurt $\geq$ 3 times/week?"

[15] For the measurement of MD adherence in pregnant women, the score by Trichopoulou et al was modified to exclude alcohol intake.

[16] Food-frequency-based MDS that does not consider the quantity of intakes.

[17] The Krece Plus food questionnaire collects data on children's food habits and intakes. The score ranges from -5 to 11 points.

[18] The food propensity questionnaire collects data on children's intake of 24 different foods.

[19] Children's Eating Habits Questionnaire collects data on children's intake of 43 different foods.

Appendix 19: Dietary assessment of studies investigating vegetarian diet forms

Table 28: Dietary assessment of studies investigating vegetarian diet forms

Author & year	Type of diet	Measurement of dietary intake
Abriha 2014	low meat ($\leq$ once per week)	FFQ
Akre 2008	vegetarian	questionnaire
Alizadeh 2015	vegetarian	FFQ
Ambroszkiewicz 2018	vegetarian	10-day food diary
Baig-Ansari 2008	low meat (red meat < twice per week)	FFQ + 24-hour-recall
Carmichael 2012a	vegetarian	FFQ
Dagnelie 1989	macrobiotic diet	3-day dietary record
Fikree 1994	vegetarian	not reported
George 2000	vegetarian	interview
Goswmai 2015	vegetarian	not reported
Grant 2008	vegetarian	nutrition survey
Grieger 2014	vegetarian	FFQ
Haddad 2003	vegetarian	interviewer-administered 24-h recall on 2 non-consecutive days
Ibanez 2019	low meat (1st quintile of meat consumption)	FFQ
Jali 2011	vegetarian	not reported
Kaur 2013	vegetarian	not reported
Koirala 2015	vegetarian	interview question: vegetarian/non-vegetarian
Krajcovicova 1997	vegetarian	FFQ
Krasavec 2017	vegan	24-hour-recall
Krebs 2012	multimicronutrient-fortified cereal intervention	counting empty food packets and mothers' reports on weekly basis
Larsson 2002	low meat (eating meat “seldom or never”)	FFQ
Leung 2001	vegetarian	7-day dietary record
Mak 2018	plant-based pattern (3rd tertile)	FFQ
Mari-Sanchis 2018	low meat (1st quartile of meat consumption)	FFQ
Melaku 2018	plant-based pattern (3rd tertile)	FFQ

Misra 2015	vegetarian	FFQ
North 2000	vegetarian	questionnaire
O’Connell 1989	vegetarian/vegan	FFQ
Persky 1992	vegetarian	3-day dietary record
Rona 1987	vegetarian	question: vegetarian/non-vegetarian
Santos Vaz 2013	vegetarian	FFQ
Sharma 2003	vegetarian	FFQ
Sheng 2019	fortified cereal intervention	not reported
Shull 1977	vegetarian	questions about dietary habits
Stuebe 2009	vegetarian	FFQ
Weder 2019	vegetarian/vegan	3-day weighed dietary record
Yang 2019	vegetarian	FFQ
Yen 2008	vegetarian	3-day dietary record
Zulyniak 2017	plant-based pattern (per 1-unit-increase)	FFQ

FFQ = food frequency questionnaire

Appendix 20: Supplementary data on included studies

Table 29: Supplementary data on included studies

Author & year	Total n (% male)	Objective; inclusion/exclusion criteria
Abriha 2014	619 (0)	**objective**: prevalence of anemia and associated factors among pregnant women attending antenatal care; **inclusion**: pregnant women; **exclusion**: serious illness during the data collection period, pregnant women with repeated visits, severe anemia
Akre 2008	719 (100)	**objective**: relationships between hypospadias risk and maternal diet, exposure to exogenous hormones, and exposures thought to reflect placental function; **inclusion**: hypospadias diagnosis confirmed by a pediatric urologist; **exclusion**: concomitant malformations or chromosomal abnormalities
Alizadeh 2015	244 (0)	**objective**: identification of major dietary patterns related to central obesity in Iranian young females to explain different patterns of obesity; **inclusion**: studying at Talaat Intelligent Guidance School, Tabriz, Iran; **exclusion**: any chronic disease or special diet in the year prior to the study
Ambroszkiewicz 2018	130 (NR)	**objective**: evaluation of serum levels of bone metabolism markers in prepubertal children on vegetarian and omnivorous diets, analysis of the relationships between biochemical markers and bone mineral density in subjects following different kind of diets; **inclusion**: LOV diet from birth, prepubertal period, generally healthy (without development and nutrition disorders, BMI z-score between -1 and +1), more than 2 hours/week of physical exercise; **exclusion**: not in the prepubertal period, history of low birth weight, gastrointestinal diseases accompanied by malabsorption, history of chronic renal failure, chronic infection, chronic drug consumption or drug use that negatively affected bone metabolism
Antonogeorgos 2013	1125 (NR)	**objective**: effect of parental education and MD adherence on the obesity status of Greek schoolchildren; **inclusion**: girls had to be premenstrual

Archero 2018	669 (48.8)	**objective**: differences in MD and its components among primary and secondary school children and adolescents, associations of MD adherence and its components with the weight status; **inclusion**: ability to write and read fluently Italian; **exclusion**: schools with specific structured education program on MD in the year of recruitment
Assaf-Balut 2019	874 (0)	**objective**: effect of a late first-trimester degree of MD adherence on materno-fetal complications; **inclusion**: $\geq$18 years old, single gestation; **exclusion**: gestational age at entry >14 GW, intolerance to nuts or extra virgin olive oil, medical conditions or pharmacological therapy that could compromise the effect of the intervention and/or the follow-up program
Bacopoulou 2017	1032 (41.7)	**objective**: effects of a multilevel-multicomponent school-based intervention, in accordance with the principles of MD and healthy lifestyle, on the dietary habits and abdominal obesity of a representative adolescent sample; **inclusion**: consent form, complete KIDMED questionnaire
Baig-Ansari 2008	1366 (0)	**objective**: prevalence of anemia and the dietary and socioeconomic factors associated with anemia in pregnant women living in an urban community setting in Hyderabad, Pakistan; **inclusion**: at 20-26 GW, permanent residents of the study area, consenting to the study
Botto 2016	19353 (NR)	**objective**: association between diet quality in mothers and risk for major non-syndromic CHDs in their children; **inclusion**: depending on study site (seven sites included cases among live births, stillbirths (fetal deaths at > 20 GW) and elective pregnancy terminations, two included live births and stillbirth, and one live birth only); **exclusion**: mothers reporting pregestational diabetes, average daily energy intake < 500 or > 5000 kcal, missing data on two or more food items

Carmichael 2012a	4368 (100)	**objective**: association between the mother having low or no intake of animal products, higher iron intake, lower intake of nutrients that favor less estrogenic metabolites, or worse diet quality and the risk of hypospadias; **inclusion**: second and third degree hypospadias, complete data on covariates; **exclusion**: chordee alone, mild hypospadias, hypospadias not otherwise specified, epispadias, having ambiguous genitalia without further description, single gene disorders or chromosomal abnormalities, average daily energy intake < 500 or > 5000 kcal and missing data on two or more food items
Carmichael 2012b	7083 (NR)	**objective**: association between maternal diet quality and risk of neural tube defects or orofacial clefts; **inclusion**: depending on study site (seven states included liveborn, stillborn (fetal deaths > 20 weeks gestation), and prenatally diagnosed and electively terminated cases, one included only liveborn and stillborn cases, one included only liveborn cases, and one included liveborn cases from 1997–1999 and added stillborn cases in 2000); **exclusion**: mothers reporting pre-gestational diabetes, average daily energy intake < 500 or > 5000 kcal, missing data on two or more food items
Carmichael 2013	5738 (0)	**objective**: association of dietary intake of a broad spectrum of nutrients and general diet quality with risk of preterm delivery; **inclusion**: estimated due dates from September 1998 through December 2005, singleton pregnancies; **exclusion**: type 1 or 2 diabetes, incomplete data
Castro-Rodriguez 2008	1757 (51.5)	**objective**: MD as a protective factor for current wheezing in preschoolers; **inclusion/exclusion**: NR
Castro-Rodriguez 2016	1000 (54.7)	**objective**: influence of MD adherence by the mother during pregnancy and by the child on asthma, rhinitis or dermatitis in the offspring during preschool age; **inclusion**: Spanish origin; **exclusion**: blank answers to the questions related to wheezing, rhinitis or dermatitis

Chacon-Ruberos 2018	1059 (49.4)	**objective**: relationship between different dietary patterns and the practice of PA in a sample of adolescents, associations between the level of MD adherence, practice of PA, motivation and learning strategies in adolescents; **inclusion**: students who studied in the third and fourth years of high school, regularly attend to high school, do not repeat course, do not suffer from important pathologies
Chatzi 2008	460 (49.6)	**objective**: impact of MD adherence during pregnancy and children's MD adherence on asthma symptoms and atopy in childhood; **inclusion/exclusion**: NR
Chatzi 2012	1074 (51.4)	**objective**: association between MD adherence during pregnancy and fetal growth; **inclusion**: $\geq$ 16 years old, singleton pregnancy, not following any program of assisted reproduction, completed FFQ; **exclusion**: implausible values for total energy intake
Chatzi 2013	2516 (51.9)	**objective**: association between MD adherence in pregnancy and the risk of wheeze and eczema in the first year of life; **inclusion**: completed FFQ in the first trimester, infants with available data on respiratory outcomes, singleton pregnancies; **exclusion**: implausible values for total energy intake, incomplete information on reproductive outcomes, spontaneous or induced abortions, stillborn infants
Chatzi 2017	997 (49.2); 569 (54.1)	**objective**: associations of maternal MD adherence during early pregnancy with offspring obesity and cardiometabolic risk; **inclusion**: Project Viva: live singleton births, information on first trimester diet, in-person mid-childhood visit at 6–10 years, blood sample; Rhea: live singleton births, participation at the 4 year follow up visit; **exclusion**: implausible values of energy intake
Dagnelie 1989	110 (52.8)	**objective**: assessment of adequacy of growth and psychomotor development in macrobiotic children; **inclusion**: macrobiotic diet from birth on, born at term; **exclusion**: congenital or neonatal disease
de Batlle 2008	1476 (NR)	**objective**: association between both children's diet in last 12 months and their mother's diet during pregnancy, and asthma and allergic rhinitis prevalence in children; **inclusion**: available dietary data sufficient to compute the MDS and/or the score of the mothers, age 6-7

Donazar-Ezcurra 2017	1466 (0)	**objective**: effect of the pre-pregnancy MD level on the odds of GDM development; **inclusion**: Spanish women, $\geq$ 18 years old, low risk pregnancy; **exclusion**: type 1 or 2 diabetes, or carbohydrate intolerance prior to pregnancy, high risk pregnancies, women that needed to modify their diet or physical activity level in the previous year or during the first half of gestation for a medical reason
Esfahani 2016	840 (50.0)	**objective**: relation of dietary patterns identified by factor analysis of obesity among adolescents, design of a strategy for a balanced diet to avoid obesity; **inclusion**: age 15-17, healthy, resident of Esfahan city; **exclusion**: under medical treatment and receiving medications, physically disabled or receiving hormone therapy, suffering from diseases such as cardiovascular disease and diabetes, remaining > 7 products clear on the FFQ, overall total everyday energy intake outside the range of 800-4200 kcal
Farajian 2011	4786 (49.3)	**objective**: current national data on overweight and obesity prevalence in preadolescent Greek schoolchildren, association between MD adherence and obesity rates; **inclusion/exclusion**: NR
Fernandez-Barres 2016	1827 (51.5)	**objective**: associations between MD adherence during pregnancy and childhood overweight and abdominal obesity risk at 4 years of age; **inclusion**: $\geq$ 16 years old, intention to deliver at the reference hospital, ability to communicate in Spanish or regional languages, singleton pregnancy, no assisted conception; **exclusion**: missing data on total energy intake, missing data on BMI at 4 years, preterm birth
Fernandez-Barres 2019	2195 (51.8)	**objective**: association between maternal MD adherence during pregnancy and offspring's longitudinal BMI trajectories and cardiometabolic risk in early childhood; **inclusion**: $\geq$ 16 years old, intention to deliver at the reference hospital, ability to communicate in Spanish or regional languages, singleton pregnancy, no assisted conception
Fikree 1994	755 (NR)	**objective**: incidence and risk factors for IUGR in a prospective community-based study conducted in four low socioeconomic squatter settlements of Karachi; **inclusion**: singleton infants, information on both birth weight and gestational age; **exclusion**: missing data

Galan-Lopez 2018	387 (54)	**objective**: associations between health-related physical fitness components, body composition, and MD adherence of adolescents from Reykjavik; **inclusion**: 13-16 years old, signed informed consent by parents/guardians, ability to participate regularly in the subject of Physical Education, no type of cognitive or physical/motor limitations
García de la Torre 2019	932 (0)	**objective**: easy, universal nutritional intervention in pregnant women based on MD rich in extra virgin olive oil and nuts, applied in the usual clinical setting as early as possible, with a motivational interview instead of an educational group session, is not different from the results obtained from a previous clinical trial; **inclusion**: women, > 18 years old, normal FBG in the 1st gestational assessment (8–12 GW), signed informed consent; **exclusion**: FBG $\geq$ 92 mg/dL in the 1st gestational assessment, multiple pregnancy, nut allergy, medical condition, ongoing medication or significant disability that would prevent the participant complying with trial consent, treatment and follow-up procedures or potentially jeopardize medical care
Garcia-Marcos 2007	17145 (NR)	**objective**: association between asthma and rhinoconjunctivitis and the individual intake of several foods and of a MD, controlling for obesity and exercise; **inclusion**: 6-7 years old, born in Spain, available data on weight, height, food consumption
George 2000	3633 (51.6)	**objective**: hemoglobin status (anemia), weight for age status and dietary habits of pre-school children living in the rural areas of Kerala State; **inclusion**: willing to donate blood sample; **exclusion**: severe symptoms of fever, bronchitis, and other illnesses
Gomez Roig 2017	127 (NR)	**objective**: differences in lifestyle and dietary habits between pregnant women with SGA fetuses and AGA fetuses; **exclusion**: refusal to participate in the study, use of drugs that might interfere with fetal growth, genetic alterations affecting growth potential, GDM, multiple pregnancy, hypertension or preeclampsia, pregnancy not controlled at the hospital or delivery not attended at the hospital
Goni 2018	619 (51.4)	**objective**: associations of the adherence to the MD and cardiorespiratory fitness with BMI and waist circumference in a sample of Spanish preschool children; **inclusion/exclusion**: NR

Gonzalez Barcala 2010	7354 (50.7)	**objective**: relationship of the MD with the prevalence of asthma symptoms in the child population in the Mediterranean region; **inclusion**: 6-7 years old; **exclusion**: missing data in the food questionnaire
Goswmai 2015	40885 (53.0)	**objective**: evaluation of socioeconomic and demographic determinants of anemia among Indian children aged 6-59 months; **inclusion**: 6-59 months old, being tested for hemoglobin levels from 2005 to 2006
Grant 2008	213 (40.4)	**objective**: relationships between nutrition and lifestyle behavious and selected markers of health in 14-15 year old children attending five Seventh-day Adventist high schools; **inclusion**: generally in good health, at least 14-15 years old; **exclusion**: missing data
Grieger 2014	309 (48)	**objective**: associations between maternal dietary patterns in the 12 months before conception and fetal growth and preterm delivery;**inclusion**: first antenatal visit, > 18 years old; **exclusion**: miscarriage, voluntary termination of the pregnancy
Grigoropoulou 2011	1125 (47.0)	**objective**: interaction of living environment and adherence to the traditional MD on asthma symptoms in children aged 10–12 years from an urban area and two rural areas in Greece; **inclusion**: girls had to be premenstrual
Haapala 2017	161 (48.1)	**objective**: relationships of diet quality in Grade 1, assessed by the MDS, BSDS, and FCHEI, to academic achievement in Grades 1–3 among Finnish primary school children; **inclusion**: 6-8 years old, grade 1; **exclusion**: incomplete data
Haddad 2003	1991 (NR)	**objective**: comparison of nutrient and food consumption patterns of self-defined vegetarians and non-vegetarians in a representative sample of the US population; **inclusion/exclusion**: NR
H Al Wattar 2019	974 (0)	**objective**: effects of a MD (supplemented with mixed nuts and extra virgin olive oil), with individualized dietary advice on maternal and offspring outcomes in pregnant women with metabolic risk factors, compared with routine antenatal care; **inclusion**: $\geq$ 16 years of age, less than 18 GW with a singleton pregnancy, able to consume nuts and olive oil, proficient in written and spoken English, metabolic risk factors such as obesity, raised serum triglycerides or chronic hypertension; **exclusion**: history of preexisting diabetes, GDM, chronic renal disease, or autoimmune disease, or taking lipid-altering drugs such as statins at the time of booking

Haugen 2008	26563 (0)	**objective**: pregnant women in the Norwegian Mother and Child Cohort Study following a MD during the first 17-24 GW and reduced risk of preterm birth; **inclusion**: non-smoking, BMI 19-32, 21-38 years old when giving birth, singleton birth, energy intake between 4200 and 16700 kJ; **exclusion**: > 3 spontaneous abortions prior to this pregnancy
Henriksson 2017	384 (43.0)	**objective**: associations of dietary patterns and macronutrient composition with attention capacity in European adolescents; **inclusion**: adolescents that performed attention capacity assessment, complete dietary data, data for basic confounders
House 2018	325 (53.5)	**objective**: associations between MD and child behavioral outcomes assessed early in life, role of differentially methylated regions regulating genomically imprinted genes in these associations; **inclusion**: $\geq$ 18 years old, speak English or Spanish; **exclusion**: established HIV infection, intention to relinquish custody of offspring, obstetrics care at hospitals other than Duke Obstetrics or Durham Regional Hospitals
Ibanez 2019	1036 (NR)	**objective**: association between maternal dietary intake of meat and meat products during pregnancy and the risk of having a SGA newborn in a Spanish population; **inclusion**: birth weight smaller than the tenth percentile for the infant's gestational age when compared with that expected for the same gestational age and sex, residence in the referral area of the hospital; **exclusion**: congenital malformations
Izadi 2016	459 (0)	**objective**: association between the DASH, MD and the prevalence of GDM; **inclusion**: pregnant women with abnormal fasting glucose for the first time in pregnancy; **exclusion**: multiple pregnancy, abnormal energy intake, type 1 or 2 diabetes, cancer, and cardiovascular diseases, incomplete daily food records and health information
Jali 2011	325 (0)	**objective**: prevalence of GDM among Indian pregnant women; **inclusion**: pregnant women; **exclusion**: history of diabetes
Jennings 2011	1700 (43.8)	**objective**: development of modified dietary indexes for use in children, determine whether these modified diet quality indexes were associated with indicators of weight status and dietary intake in children; **inclusion**: weight status measurements taken, completed 4-day diet diaries, valid physical activity data

Julian 2018	179 (49.7)	**objective**: associations between the MDS-A and a DQI-A with the bone mineral content; **inclusion**: two 24-h dietary recalls, dual-energy X-ray absorptiometry bone measurements
Karamanos 2014	1076 (0)	**objective**: association of MD adherence with the incidence of GDM in Mediterranean countries; **inclusion**: pregnant women, OGTT; **exclusion**: history of diabetes in the non-pregnant state, incomplete data
Kaur 2013	747 (0)	**objective**: role of genetic thrombophilia in the causation of various pregnancy complications like pregnancy-induced hypertension, recurrent abortions, IUGR and intrauterine death IUD; **inclusion**: cases: women with early onset of pregnancy-induced hypertension, < 28 weeks showing, significant proteinuria, controls: women with two or more consecutive normal deliveries; **exclusion**: cases: women with chronic hypertension, autoimmune disorders, congenital uterine abnormalities, controls: women with any previous/present pregnancy complications
Koirala 2015	255 (60)	**objective**: assessment of the proportion of LBW and identification of associated factors for LBW in a live born infants among the women in Morang, Nepal; **inclusion**: delivered mother, live birth at the Koshi Zonal Hospital, willingness to participate in the study
Kontogianni 2008	751 (51.0)	**objective**: MD adherence in a representative sample of Greek children and adolescents; **exclusion**: no children in the household, mismatching with age, sex, and geographical distribution
Koutelidakis 2018	1432 (0)	**objective**: MD during the period before pregnancy may affect maternal GWG inside or outside Institute of Medicine recommendations; **exclusion**: high-risk pregnancy, history of arterial hypertension, heart disease, diabetes mellitus, high cholesterol and viral infection
Krajcovicova 1997	58 (43.1)	**objective**: evaluation of health and nutritional status of children with two different nutritional habits; **inclusion**: 11-14 years old, vegetarian diet (one group)

Krasavec 2017	74548 (50.8)	**objective**: risk of stunting in young children with higher dietary diversity and animal source food consumption; **inclusion**: available dataset on the Demographic and Health Surveys website that allowed for generation of the seven food groups used in the dietary diversity measure, child length measurements part of the survey, all controlling variables available, minimum of one national level survey per country; **exclusion**: data missing or biologically implausible
Krebs 2012	1062 (49)	**objective**: testing of hypothesis that daily intake of 30-45 g meat from 6-18 months of age would result in greater linear growth velocity and improved micronutrient status in comparison with an equicaloric multimicronutrient-fortified cereal; **inclusion**: aged 3–4 months, primarily or exclusively breastfed, mothers intended to continue breastfeeding through at least the first year of life; **exclusion**: use of free or subsidized fortified complementary foods or infant formula, multiple births, known congenital anomaly, neurologic deficit
Lange 2010	1376 (51.0)	**objective**: association between maternal dietary pattern during pregnancy and recurrent wheeze in children; **inclusion**: singleton pregnancy, first prenatal visit before 22 GW, plan to continue care at obstetric office, ability to answer questionnaires in English
Larsson 2002	2005 (50.7)	**objective**: comparison of lifestyle-related characteristics of low-meat consumer and omnivore adolescents in Sweden and Norway; **inclusion**: completed questionnaire
Lazarou 2010	823 (NR)	**objective**: association between MD adherence and obesity status in a nationwide, free-living sample of children living in Cyprus; **inclusion/exclusion**: NR
Leung 2001	51 (47.1)	**objective**: investigation of the nutritional status of Chinese LOV children aged 4-14 years; **inclusion**: 4-14 years old, vegetarian diet for at least 1 year
Leventakou 2016	804 (51.2)	**objective**: impact of children's dietary patterns on cognitive and psychomotor development at preschool age; **inclusion**: mothers $\geq$ 16 years old, no communication handicap, pregnant during 2007–2008; **exclusion**: children with specific diet for health purposes, neurodevelopmental disorder diagnosis or other diagnosed medical conditions (plagiocephalus, microcephalus, hydrocephalus, brain tumor), incomplete examination, twins

Mak 2018	1337 (0)	**objective**: association between dietary patterns during early pregnancy and the risk of GDM in Western China, potential effect modification of pre-pregnancy BMI and other confounding factors; **inclusion**: 18-40 years old, singleton pregnancy, signed consent form; **exclusion**: severe chronic or infectious disease, infertility treatment such as in vitro fertilization and intrauterine insemination
Mari-Sanchis 2018	3298 (0)	**objective**: association of total meat, processed, and unprocessed red meat and iron intake with the risk of developing GDM in pregnant women; **inclusion**: female participants, sufficient time to answer at least the first follow-up questionnaire; **exclusion**: diagnoses of GDM at recruitment, reported caloric intake below the 1st percentile or above the 99th, previous diagnosis of diabetes
Martin-Calvo 2016	3942 (45.0)	**objective**: association between MD adherence and BMI change among adolescents; **inclusion/exclusion**: NR
Martinez-Galiano 2018	1036 (NR)	**objective**: effect of the maternal MD and consumption of olive oil on the risk of having a SGA infant; **inclusion**: maternal residence in the hospital coverage area, birth of a single live newborn, absence of congenital malformations, SGA diagnosed according to the tables developed for the Spanish population
Melaku 2018	3788 (48.8)	**objective**: association between household, maternal and child dietary patterns and childhood stunting in Ethiopia; **inclusion**: < 60 months old
Mikkelsen 2008	35657 (0)	**objective**: association between maternal MD and reduced risk of preterm birth; **exclusion**: smoking, < 21 and > 38 years old, BMI < 19 and > 32, a history of more than 3 abortions, twin pregnancies, and chronic hypertension, energy intake < 4200 and > 16700 kJ/d
Misra 2015	123 (NR)	**objective**: impact of maternal factors like knowledge, BMI, GWG, anemia and dietary habits with risk of low birth weight in a tertiary care hospital; **inclusion**: singleton pregnancy; **exclusion**: diabetes, hypertension, twin pregnancy, congenital malformation or any other chronic diseases
Mistretta 2017	1643 (53.9)	**objective**: association between MD adherence and cardio-metabolic parameters among adolescents living in Sicily; **inclusion/exclusion**: NR

Monjardino 2014	1264 (46.8)	**objective**: short- and long-term associations between dietary patterns and bone mineral density during adolescence; **inclusion**: complete information on forearm bone mineral density, anthropometric variables, parental educational level, age at menarche, FFQ
Monteagudo 2016	320 (NR)	**objective**: relationship of maternal diet and in utero exposure to organochlorine pesticides with newborn weight; **inclusion**: delivery at the hospital, written consent to participate in the study, completed questionnaire; **exclusion**: chronic disease (diabetes, hypertension, thyroid pathology), development of pregnancy complications that could affect fetal growth or development, non-residence in the area served by the hospital
Muros 2017a	515 (50.5)	**objective**: description of MD adherence within a sample of children Santiago, Chile, relationship between MD adherence, body composition, physical fitness, self-esteem, and other lifestyle habits; **inclusion**: completion of all elements of testing
Muros 2017b	456 (48.5)	**objective**: association between BMI, physical activity, MD adherence, and health-related quality of life in a sample of Spanish adolescents; **inclusion**: 11-14 years old; **exclusion**: failure to complete some element of testing, failure to attend class on testing day
North 2000	6296 (100)	**objective**: role of maternal nutrition in the origin of hypospadias; **inclusion**: pregnant women, resident in the health districts of Avon, estimated date of delivery between April 1991 and December 1992
O'Connell 1989	404 (NR)	**objective**: effect of a vegetarian diet on child growth in a collective community in Tennessee compared with a US growth reference; **exclusion**: ethnicity, dietary reasons, chronic illness that affects growth (criteria not specified)
Olmedo-Requena 2019	1466 (0)	**objective**: effect of the pre-pregnancy MD level on the odds of GDM development; **inclusion**: Spanish, > 18 years old, low risk pregnancy; **exclusion**: type 1 or 2 diabetes, carbohydrate intolerance prior to pregnancy, high risk pregnancies and women that needed to modify their diet or physical activity level in the previous year or during the first half of gestation for a medical reason

Pellegrini-Belinchon 2016	1164 (51.8)	**objective**: identification of risk factors that may be acted upon in order to modify the evolution of recurrent wheezing in the first months of life; **inclusion/exclusion**: NR
Peraita-Costa 2018	492 (NR)	**objective**: role of MD adherence during pregnancy in the anthropometric development of the newborn; **inclusion**: delivery to the Obstetrics Ward of La Fe Hospital in Valencia, belonging to the health coverage area of this hospital, complete outcome data; **exclusion**: non-available data corresponding to the characteristics of the newborn, inconsistent or incomplete responses by the mother
Persky 1992	75 (0)	**objective**: hormonal differences among teenage girls whose nutritional intakes indicate varying risk of breast cancer, specifically girls who ingest vegetarian or non-vegetarian diets; **exclusion**: girls who had not yet menstruated, pregnancy, taking birth control pills
Poon 2013	1032 (NR)	**objective**: association of overall maternal dietary patterns (AHEI-P and alternate MD) with birthweight, SGA, LGA, and early infant growth by 4–6 months of life; **inclusion**: healthy singleton, delivered after ≥ 35 GW, weight of at least 5 pounds; **exclusion**: intensive care unit for more than 3 days, medical condition that affects infant feeding, caloric intake in the top 2% or bottom 1% of energy intake
Renault 2015	342 (0)	**objective**: improvements and relevance of different dietary factors targeted with respect to GWG in a 3-arm RCT among obese pregnant women; **inclusion**: pre-pregnancy BMI $\geq$, gestational age < 16 weeks, > 18 years old, no disease limiting physical activity, singleton pregnancy; **exclusion**: linguistic problems
Rona 1987	369 (53.1)	**objective**: relation between vegetarian status and growth in terms of height, weight-for-height, and triceps skinfold of children; **inclusion**: Urdu, Gujarati or Punjabi origin
Rosi 2017	690 (48)	**objective**: relationship among BMI, MD adherence, physical activity level, and sleep duration in school-aged children; **inclusion**: written consent from parents, verbal consent from pupils

Santos Vaz 2013	9530 (0)	**objective**: associations between dietary patterns and n-3 PUFA intake from seafood and high levels of anxiety during pregnancy; **inclusion**: pregnant women, resident in the health districts of Avon, estimated date of delivery between April 1991 and December 1992; **exclusion**: missing data on confounding variables
Saunders 2014	728 (50.8)	**objective**: impact of MD adherence during pregnancy on FGR and preterm delivery; **inclusion**: living in Guadeloupe for at least 3 years, liveborn singleton pregnancy; **exclusion**: major congenital malformations, incomplete data, implausible values for total energy intake
Schoenaker 2015	3853 (0)	**objective**: associations between pre-pregnancy dietary patterns and the risk of GDM in a population-based study of women of reproductive age; **exclusion**: pregnant at the time of measurement of dietary intake, no live birth at consecutive surveys, missing data on diet or GDM, implausible energy intake, history of type 1 or type 2 diabetes or GDM, missing covariate data
Schoenaker 2015	3582 (0)	**objective**: associations between pre-pregnancy dietary patterns and risk of developing hypertensive disorders during pregnancy in a population-based study of reproductive-aged Australian women; **exclusion**: pregnant at the time of measurement of dietary intake, no live birth at consecutive surveys, missing data on diet or hypertensive disorders of pregnancy, implausible energy intake, history of history of chronic hypertension, missing covariate data
Sharma 2003	1150 (0)	**objective**: effect of various dietary habits, such as a vegetarian diet or various types of meat, on the prevalence of anemia in pregnant women; **inclusion**: singleton pregnancy, patient sure of dates, willingness to participate in the study; **exclusion**: multiple pregnancy, any medical disorder except anemia, any obstetric complication like bleeding or pregnancy induced hypertension
Sheng 2019	180 (50.6)	**objective**: vitamin B12 status of toddlers living in high-poverty areas of China and to observe the effects of different complementary foods on the vitamin B12 status and cognitive level of these toddlers; **inclusion**: term delivery without serious neonatal complications, absence of acute or chronic illness, healthy singleton status with birth weight > 2000 g, no metabolic or physical problems and being exclusively breastfed

Shull 1977	106 (45.8)	**objective**: effects of a vegetarian diet on growth; **inclusion**: healthy, white, vegetarian, < 5 years old
Silva-del Valle 2013	170 (0)	**objective**: impact of the MD on weight gain and obesity in pregnant women in Gran Canaria; **exclusion**: history of arterial hypertension, heart disease, diabetes mellitus, high cholesterol, concomitant use of folic acid supplements or viral infection, high-risk pregnancies, women who gave birth to children with any pathology
Smith 2015	1890 (0)	**objective**: associations between lifestyle factors and late and moderate preterm birth; **exclusion**: missing data
Stuebe 2009	1388 (0)	**objective**: identification of modifiable risk factors for excessive GWG; **inclusion**: fluent in English, < 22 GW at study entry, singleton pregnancy, data on first- and second-trimester diet and on mid-pregnancy physical activity; **exclusion**: missing information on pre-pregnancy BMI and GWG, delivery before 34 GW, missing data on covariates associated with excessive GWG, including maternal age, race, first trimester nausea, household income, and smoking status
Timmermans 2011	3187 (0)	**objective**: associations of dietary patterns with biomarker concentrations of endothelial function and maternal blood pressure patterns during pregnancy, occurrence of gestational hypertension and preeclampsia; **inclusion**: prenatally enrolled Dutch women with a live-born singleton; **exclusion**: medical history of chronic hypertension, diabetes mellitus, hypercholesterolemia, heart disorders, systemic lupus erythematosus
Timmermans 2012	3207 (NR)	**objective**: associations of maternal diet with utero-placental vascular resistance, placental weight, fetal size and birth weight; **inclusion**: spontaneously conceived, live-born, singleton pregnancy, Spanish ethnicity; **exclusion**: incompleteness of FFQ, fertility treatment, twin pregnancy, termination of pregnancy, intrauterine fetal death
Tambalis 2018	336014 (51)	**objective**: prevalence of total and central obesity groups among 4- to 17-year-old children and adolescents as a basis for effective prevention strategies, association between several anthropometric and lifestyle factors and total/central obesity; **inclusion/exclusion**: NR

Tobias 2012	15254 (0)	**objective**: association between usual pre-pregnancy adherence to dietary patterns, including alternate MD, DASH, and aHEI and associated the risk of GDM; **inclusion**: singleton live births; **exclusion**: GDM in a previous pregnancy, diagnosis of type 2 diabetes or cancer, or a cardiovascular disease event before an otherwise eligible pregnancy, > 70 FFQ items left blank, implausible total energy intake
Tognon 2014	13256 (50.9)	**objective**: cross-sectional and prospective association between high MD adherence and overweight or obesity indicators; **inclusion**: completed questionnaire, weight and height measurements
Vassiloudis 2014	528 (48.5)	**objective**: links between MD adherence, excess body weight, energy balance behaviors, and academic performance in Greek primary schoolchildren; **exclusion**: incomplete data, learning disabilities and attention problems
Voltas 2016	241 (39.0)	**objective**: identification of psychopathological, anthropometric and sociodemographic factors that may influence the risk of low MD adherence; **inclusion/exclusion**: NR
Vujkovic 2009	131 (43.5)	**objective**: identification of dietary patterns in case and control mothers and to examine whether associations exist between these dietary patterns and the risk of spina bifida risk in the offspring; **inclusion**: cases: Dutch Caucasian mothers and their child with a non-syndromic meningo(myelo)cele diagnosed by a neuro-pediatrician at birth, controls: Dutch Caucasian mothers of children without congenital abnormalities of the same age as the cases; **exclusion**: pregnancy at the study moment, consanguinity, a familial relationship between the case and the control families, maternal diabetes mellitus
Weder 2019	430 (48.1)	**objective**: comparison of energy intake, macronutrients, and fiber, as well as birth weight and height, of vegan, vegetarian, and omnivorous; **inclusion**: 1-3 years old, living in Germany; **exclusion**: diagnosed diseases that could affect the studied variables (enteropathy, pancreatic diseases, and metabolic disorders such as phenylketonuria or fructose malabsorption), special diets other than vegan or vegetarian diets,

Wolters 2018	298 (52.7)	**objective**: identification and description of dietary patterns at the beginning of primary school period and patterns of dietary changes during the course of primary school in two German pediatric cohort studies; **inclusion**: dietary data at the beginning of primary school and at least two years later, complete anthropometric measurements at baseline and follow-up, data on potential covariates
Yang 2019	1422 (50.6)	**objective**: associations between dietary patterns and CHD risk in Shaanxi, China; **inclusion**: cases: diagnosed with isolated CHD, controls: no CHD; **exclusion**: gene disorders or chromosomal abnormalities, GDM or multiple gestations
Zulyniak 2017	3997 (51.8)	**objective**: association between maternal diet and birth weight in a multiethnic cohort; **inclusion**: comprehensive clinical and dietary data, birth data; **exclusion**: implausible energy intake, non-singleton pregnancies, preterm delivery (< 36 weeks), not knowing ethnic origin

AGA = appropriate for gestational age; aHEI = alternate Healthy Eating Index; AHEI-P = Alternative Healthy Eating Index for Pregnancy; BMI = body mass index; BSDS = Baltic Sea Diet Score; CHD = congenital heart defect; DASH = Dietary Approaches to Stop Hypertension; DQI-A = Diet Quality Index for Adolescents; FBG = fasting blood glucose; FCHEI = Finnish Children Healthy Eating Index; FFQ = food frequency questionnaire; FGR = fetal growth restriction; GDM = gestational diabetes mellitus; GW = weeks of gestation; GWG = gestational weight gain; IUGR = intrauterine growth retardation; LBW = low birth weight; LGA = large for gestational age; LOV = lacto-ovo-vegetarian; MDS = Mediterranean diet score; MDS-A = Mediterranean Diet Score for Adolescents; NR = not reported; OGTT = oral glucose tolerance test; PA = physical activity; PUFA = polyunsaturated fatty acid ; RCT = randomized controlled trial; SGA = small for gestational age

7 Bibliography

1. Abriha A, Yesuf ME, Wassie MM (2014). Prevalence and associated factors of anemia among pregnant women of Mekelle town: a cross sectional study. BMC research notes 7:1–6.
2. Ackman R (1989). Nutritional composition of fats in seafoods. Progress in food & nutrition science 13:161–289.
3. Agrawal S, Nathani S (2009). Neuro-regression in vitamin B12 deficiency. BMJ Case Rep 2009.
4. Akre O, Boyd HA, Ahlgren M, Wilbrand K, Westergaard T, Hjalgrim H, Nordenskjöld A, Ekbom A, Melbye M (2008). Maternal and gestational risk factors for hypospadias. Environmental health perspectives 116:1071–1076.
5. Alizadeh M, Didarloo A, Esmaillzadeh A (2015). Dietary patterns of young females and their association with waist circumference as a health index in northwest of Iran, 2007. Iranian Red Crescent Medical Journal 17.
6. Amati F, Hassounah S, Swaka A (2019). The impact of mediterranean dietary patterns during pregnancy on maternal and offspring health. Nutrients 11:1098.
7. Ambroszkiewicz J, Chełchowska M, Szamotulska K, Rowicka G, Klemarczyk W, Strucińska M, Gajewska J (2018). The Assessment of bone regulatory pathways, bone turnover, and bone mineral density in vegetarian and omnivorous children. Nutrients 10:183.
8. Amoroso S, Scarpa MG, Poropat F, Giorgi R, Murru FM, Barbi E (2018). Acute small bowel obstruction in a child with a strict raw vegan diet. Archives of disease in childhood:archdischild–2018.
9. Antonogeorgos G, Panagiotakos D, Grigoropoulou D (2013). The mediating effect of parents' educational status on the association between adherence to the Mediterranean diet and childhood obesity: the PANACEA study. Int J Public Health 58:401–408.
10. Appleby PN, Key TJ (2016). The long-term health of vegetarians and vegans. Proceedings of the Nutrition Society 75:287–293.
11. Archero F, Ricotti R, Solito A, Carrera D, Civello F, Di Bella R, Bellone S, Prodam F (2018). Adherence to the Mediterranean diet among school children and adolescents living in northern Italy and unhealthy food behaviors associated to overweight. Nutrients 10:1322.

12. Arnold F, Parasuraman S, Arokiasamy P, Kothari M (2009). Nutrition in India. National Family Health Survey. NFHS 3.

13. Assaf-Balut C, Garcia de la Torre N, Fuentes M, Duran A, Bordiu E, Del Valle L, Valerio J, Jimenez I, Herraiz MA, Izquierdo N, et al. (2019). A high adherence to six food targets of the Mediterranean diet in the late first trimester is associated with a reduction in the risk of materno-foetal outcomes: The St. Carlos Gestational Diabetes Mellitus Prevention Study. Nutrients 11:66.

14. Bacopoulou F, Landis G, Rentoumis A, Tsitsika A, Efthymiou V (2017). Mediterranean diet decreases adolescent waist circumference. European journal of clinical investigation 47:447–455.

15. Baig-Ansari N, Badruddin SH, Karmaliani R, Harris H, Jehan I, Pasha O, Moss N, McClure EM, Goldenberg RL (2008). Anemia prevalence and risk factors in pregnant women in an urban area of Pakistan. Food and nutrition bulletin 29:132–139.

16. Bailey R, Froggatt A, Wellesley L (2014). Livestock–climate change's forgotten sector. Chatham House.

17. Bao W, Bowers K, Tobias DK, Hu FB, Zhang C (2013). Prepregnancy dietary protein intake, major dietary protein sources, and the risk of gestational diabetes mellitus: a prospective cohort study. Diabetes care 36:2001–2008.

18. Baroni L, Cenci L, Tettamanti M, Berati M (2007). Evaluating the environmental impact of various dietary patterns combined with different food production systems. European journal of clinical nutrition 61:279–286.

19. Benton D (2004). Role of parents in the determination of the food preferences of children and the development of obesity. International journal of obesity 28:858–869.

20. Bergen N, Jaddoe V, Timmermans S, Hofman A, Lindemans J, Russcher H, Raat H, Steegers-Theunissen R, Steegers E (2012). Homocysteine and folate concentrations in early pregnancy and the risk of adverse pregnancy outcomes: the Generation R Study. BJOG: An International Journal of Obstetrics & Gynaecology 119:739–751.

21. Berkow SE, Barnard ND (2005). Blood pressure regulation and vegetarian diets. Nutr. Rev. 63:1–8.

22. Berry RJ, Li Z, Erickson JD, Li S, Moore CA, Wang H, Mulinare J, Zhao P, Wong LYC, Gindler J, et al. (1999). Prevention of neural-tube defects with folic acid in China. New England journal of medicine 341:1485–1490.

23. Biagi C, Di Nunzio M, Bordoni A, Gori D, Lanari M (2019). Effect of adherence to Mediterranean diet during pregnancy on children's health: a systematic review. Nutrients 11:997.

24. Biesalski HK (2016). The 1,000-day window and cognitive development. Hidden Hunger 115:1–15.

25. Bo S, Menato G, Lezo A, Signorile A, Bardelli C, De Michieli F, Massobrio M, Pagano G (2001). Dietary fat and gestational hyperglycaemia. Diabetologia 44:972–978.
26. Bothwell TH (2000). Iron requirements in pregnancy and strategies to meet them. The American journal of clinical nutrition 72:257S–264S.
27. Botto LD, Krikov S, Carmichael SL, Munger RG, Shaw GM, Feldkamp ML (2016). Lower rate of selected congenital heart defects with better maternal diet quality: a population-based study. Archives of Disease in Childhood-Fetal and Neonatal Edition 101:43–49.
28. Bousselamti A, El Hasbaoui B, Echahdi H, Krouile Y (2018). Psychomotor regression due to vitamin B12 deficiency. Pan Afr Med J 30:152.
29. Bowers K, Tobias DK, Yeung E, Hu FB, Zhang C (2012). A prospective study of prepregnancy dietary fat intake and risk of gestational diabetes. The American journal of clinical nutrition 95:446–453.
30. Brenna JT, Carlson SE (2014). Docosahexaenoic acid and human brain development: evidence that a dietary supply is needed for optimal development. Journal of human evolution 77:99–106.
31. Breymann C (2015). *Iron deficiency anemia in pregnancy. Seminars in hematology*. Vol. 52. Elsevier:339–347.
32. Buckland G, Bach A, Serra-Majem L (2008). Obesity and the Mediterranean diet: a systematic review of observational and intervention studies. Obesity reviews 9:582–593.
33. Buckland G, Gonzalez CA, Agudo A, Vilardell M, Berenguer A, Amiano P, Ardanaz E, Arriola L, Barricarte A, Basterretxea M, et al. (2009). Adherence to the Mediterranean diet and risk of coronary heart disease in the Spanish EPIC Cohort Study. American journal of epidemiology 170:1518–1529.
34. Carlson SE, Colombo J, Gajewski BJ, Gustafson KM, Mundy D, Yeast J, Georgieff MK, Markley LA, Kerling EH, Shaddy DJ (2013). DHA supplementation and pregnancy outcomes. The American journal of clinical nutrition 97:808–815.
35. Carmichael SL, Ma C, Feldkamp ML, Munger RG, Olney RS, Botto LD, Shaw GM, Correa A (2012a). Nutritional factors and hypospadias risks. Paediatric and perinatal epidemiology 26:353–360.
36. Carmichael SL, Yang W, Feldkamp M, Munger R, Siega-Riz A, Botto LD, Shaw GM, et al. (2012b). Higher diet quality reduces risks of neural tube defects and orofacial clefts. Archives of pediatrics & adolescent medicine 166:121.
37. Carmichael SL, Yang W, Shaw GM, Study TNBDP (2013). Maternal dietary nutrient intake and risk of preterm delivery. American journal of perinatology 30:579.
38. Casanueva E, Ripoll C, Tolentino M, Morales RM, Pfeffer F, Vilchis P, Vadillo-Ortega F (2005). Vitamin C supplementation to prevent premature rupture of the chorioamniotic membranes: a randomized trial. The American journal of clinical nutrition 81:859–863.

39. Casella EB, Valente M, Navarro JM de, Kok F (2005). Vitamin B12 deficiency in infancy as a cause of developmental regression. Brain and Development 27:592–594.
40. Cassidy ES, West PC, Gerber JS, Foley JA (2013). Redefining agricultural yields: from tonnes to people nourished per hectare. Environmental Research Letters 8:034015.
41. Castro-Rodriguez J, Ramirez-Hernandez M, Padilla O, Pacheco-Gonzalez R, Perez-Fernandez V, Garcia-Marcos L (2016). Effect of foods and Mediterranean diet during pregnancy and first years of life on wheezing, rhinitis and dermatitis in preschoolers. Allergologia et immunopathologia 44:400–409.
42. Castro-Rodriguez JA, Garcia-Marcos L, Rojas JDA, Valverde-Molina J, Sanchez-Solis M (2008). Mediterranean diet as a protective factor for wheezing in preschool children. The Journal of pediatrics 152:823–828.
43. Cetin I, Berti C, Calabrese S (2010). Role of micronutrients in the periconceptional period. Human reproduction update 16:80–95.
44. Chacon-Cuberos R, Zurita-Ortega F, Martinez-Martinez A, Olmedo-Moreno EM, Castro-Sanchez M (2018). Adherence to the Mediterranean diet is related to healthy habits, learning processes, and academic achievement in adolescents: a cross-sectional study. Nutrients 10:1566.
45. Chatzi L, Garcia R, Roumeliotaki T, Basterrechea M, Begiristain H, Iniguez C, Vioque J, Kogevinas M, Sunyer J (2013). Mediterranean diet adherence during pregnancy and risk of wheeze and eczema in the first year of life: INMA (Spain) and RHEA (Greece) mother–child cohort studies. British journal of nutrition 110:2058–2068.
46. Chatzi L, Mendez M, Garcia R, Roumeliotaki T, Ibarluzea J, Tardon A, Amiano P, Lertxundi A, Iniguez C, Vioque J, et al. (2012). Mediterranean diet adherence during pregnancy and fetal growth: INMA (Spain) and RHEA (Greece) mother–child cohort studies. British Journal of Nutrition 107:135–145.
47. Chatzi L, Rifas-Shiman SL, Georgiou V, Joung KE, Koinaki S, Chalkiadaki G, Margioris A, Sarri K, Vassilaki M, Vafeiadi M, et al. (2017). Adherence to the Mediterranean diet during pregnancy and offspring adiposity and cardiometabolic traits in childhood. Pediatric obesity 12:47–56.
48. Chatzi L, Torrent M, Romieu I, Garcia-Esteban R, Ferrer C, Vioque J, Kogevinas M, Sunyer J (2008). Mediterranean diet in pregnancy is protective for wheeze and atopy in childhood. Thorax 63:507–513.
49. Chia AR, Chen LW, Lai JS, Wong CH, Neelakantan N, Dam RM van, Chong MFF (2019). Maternal dietary patterns and birth outcomes: a systematic review and meta-analysis. Advances in Nutrition 10:685–695.

50. Chiu YH, Williams PL, Gillman MW, Gaskins AJ, Minguez-Alarcon L, Souter I, Toth TL, Ford JB, Hauser R, Chavarro JE (2018). Association Between Pesticide Residue Intake From Consumption of Fruits and Vegetables and Pregnancy Outcomes Among Women Undergoing Infertility Treatment With Assisted Reproductive Technology. JAMA Intern Med 178:17–26.

51. Ciani F, Poggi G, Pasquini E, Donati M, Zammarchi E (2000). Prolonged exclusive breast-feeding from vegan mother causing an acute onset of isolated methylmalonic aciduria due to a mild mutase deficiency. Clinical Nutrition 19:137–139.

52. Council NR (2010). Weight gain during pregnancy: reexamining the guidelines.

53. Craig WJ, Mangels AR (2009). Position of the American Dietetic Association: vegetarian diets. Journal of the American dietetic association 109:1266.

54. Cundiff DK, Harris W (2006). Case report of 5 siblings: malnutrition? Rickets? DiGeorge syndrome? Developmental delay? Nutrition journal 5:1–8.

55. Curtis JA, Kooh S, Fraser D, Greenberg M (1983). Nutritional rickets in vegetarian children. Canadian Medical Association Journal 128:150.

56. Dagnelie P, Van Staveren W, Verschuren S, Hautvast J (1989). Nutritional status of infants aged 4 to 18 months on macrobiotic diets and matched omnivorous control infants: a population-based mixed-longitudinal study. I. Weaning pattern, energy and nutrient intake. European journal of clinical nutrition 43:311–323.

57. Dagnelie PC, Staveren WA van (1994). Macrobiotic nutrition and child health: results of a population-based, mixed-longitudinal cohort study in The Netherlands. The American journal of clinical nutrition 59:1187–1196.

58. Davey GK, Spencer EA, Appleby PN, Allen NE, Knox KH, Key TJ (2003). EPIC–Oxford: lifestyle characteristics and nutrient intakes in a cohort of 33 883 meat-eaters and 31 546 non meat-eaters in the UK. Public health nutrition 6:259–268.

59. De Batlle J, Garcia-Aymerich J, Barraza-Villarreal A, Anto J, Romieu I (2008). Mediterranean diet is associated with reduced asthma and rhinitis in Mexican children. Allergy 63:1310–1316.

60. Deriemaeker P, Alewaeters K, Hebbelinck M, Lefevre J, Philippaerts R, Clarys P (2010). Nutritional status of Flemish vegetarians compared with non-vegetarians: a matched samples study. Nutrients 2:770–780.

61. DGE (2013). Referenzwerte Folat. Cited on 20.02.2021. URL: `https://www.dge.de/wissenschaft/referenzwerte/folat/`.

62. Donazar-Ezcurra M, Lopez-del Burgo C, Martinez-Gonzalez MA, Basterra-Gortari FJ, Irala J de, Bes-Rastrollo M (2017). Pre-pregnancy adherences to empirically derived dietary patterns and gestational diabetes risk in a Mediterranean cohort: the Seguimiento Universidad de Navarra (SUN) project. British Journal of Nutrition 118:715–721.

63. Doyle J, Langevin A, Zipursky A (1989). Nutritional vitamin B12 deficiency in infancy: three case reports and a review of the literature. Pediatric hematology and oncology 6:161–172.

64. Dror DK, Allen LH (2018). Iodine in human milk: a systematic review. Advances in Nutrition 9:347S–357S.

65. Duval S, Tweedie R (2000). Trim and fill: A simple funnel-plot-based method of testing and adjusting for publication bias in meta-analysis. Biometrics 56 2:455–63.

66. Dyett PA, Sabaté J, Haddad E, Rajaram S, Shavlik D (2013). Vegan lifestyle behaviors. An exploration of congruence with health-related beliefs and assessed health indices. Appetite 67:119–124.

67. Eaton JC, Rothpletz-Puglia P, Dreker MR, Iannotti L, Lutter C, Kaganda J, Rayco-Solon P (2019). Effectiveness of provision of animal-source foods for supporting optimal growth and development in children 6 to 59 months of age. Cochrane database of systematic reviews.

68. Eilander A, Hundscheid D, Osendarp S, Transler C, Zock P (2007). Effects of n-3 long chain polyunsaturated fatty acid supplementation on visual and cognitive development throughout childhood: a review of human studies. Prostaglandins, Leukotrienes and Essential Fatty Acids 76:189–203.

69. Elmadfa I, Leitzmann C (2019). *Ernährung des Menschen*. utb GmbH.

70. Elorinne AL, Alfthan G, Erlund I, Kivimäki H, Paju A, Salminen I, Turpeinen U, Voutilainen S, Laakso J (2016). Food and nutrient intake and nutritional status of Finnish vegans and non-vegetarians. PloS one 11:e0148235.

71. Erdeve O, Arsan S, Atasay B, Ileri T, Uysal Z (2009). A breast-fed newborn with megaloblastic anemia-treated with the vitamin B12 supplementation of the mother. Journal of pediatric hematology/oncology 31:763–765.

72. Esfahani NB, Dashti NG, Dashti MG, Noorv MI, Koon PB, Abd Talib R, Lubis SH (2016). Dietary predictors of overweight and obesity in Iranian adolescents. Iranian Red Crescent Medical Journal 18.

73. Esposito K, Kastorini CM, Panagiotakos DB, Giugliano D (2013). Mediterranean diet and metabolic syndrome: an updated systematic review. Reviews in Endocrine and Metabolic Disorders 14:255–263.

74. Farajian P, Risvas G, Karasouli K, Pounis GD, Kastorini CM, Panagiotakos DB, Zampelas A (2011). Very high childhood obesity prevalence and low adherence rates to the Mediterranean diet in Greek children: the GRECO study. Atherosclerosis 217:525–530.

75. Fernandez-Barres S, Romaguera D, Valvi D, Martinez D, Vioque J, Navarrete-Munoz E, Amiano P, Gonzalez-Palacios S, Guxens M, Pereda E, et al. (2016). Mediterranean dietary pattern in pregnant women and offspring risk of overweight and abdominal obesity in early childhood: the INMA birth cohort study. Pediatric obesity 11:491–499.

76. Fernandez-Barres S, Vrijheid M, Manzano-Salgado CB, Valvi D, Martinez D, Iniguez C, Jimenez-Zabala A, Riano-Galan I, Navarrete-Munoz EM, Santa-Marina L, et al. (2019). The association of mediterranean diet during pregnancy with longitudinal body mass index trajectories and cardiometabolic risk in early childhood. The Journal of pediatrics 206:119–127.

77. Fikree FF, Berendes HW, Midhet F, D'Souza R, Hussain R (1994). Risk factors for intrauterine growth retardation: results of a community-based study from Karachi. Journal of Pakistan Medical Association 44:30.

78. Finkelstein JL, Layden AJ, Stover PJ (2015). Vitamin B-12 and Perinatal Health. Adv Nutr 6:552–563.

79. Fox N, Ward K (2008). Health, ethics and environment: A qualitative study of vegetarian motivations. Appetite 50:422–429.

80. Fraser GE (1999). Associations between diet and cancer, ischemic heart disease, and all-cause mortality in non-Hispanic white California Seventh-day Adventists. Am. J. Clin. Nutr. 70:532–538.

81. Fritz T (2011). Brot oder Trog-Futtermittel, Flächenkonkurrenz und Ernährungssicherheit, Diakonisches Werk der EKD e. V., Stuttgart Dezember.

82. Gaillard R, Durmus B, Hofman A, Mackenbach JP, Steegers EA, Jaddoe VW (2013). Risk factors and outcomes of maternal obesity and excessive weight gain during pregnancy. Obesity 21:1046–1055.

83. Galan-Lopez P, Ries F, Gisladottir T, Dominguez R, Sanchez-Oliver AJ (2018). Healthy lifestyle: Relationship between Mediterranean diet, body composition and physical fitness in 13 to 16-years old Icelandic students. International journal of environmental research and public health 15:2632.

84. Gambon R, Lentze M, Rossi E (1986). Megaloblastic anaemia in one of monozygous twins breast fed by their vegetarian mother. European journal of pediatrics 145:570–571.

85. Gao J, Xiao H, Li J, Guo X, Cai W, Li D (2019). N-3 polyunsaturated fatty acids decrease long-term diabetic risk of offspring of gestational diabetes rats by postponing shortening of hepatic telomeres and modulating liver metabolism. Nutrients 11:1699.

86. Garcia de la Torre N, Assaf-Balut C, Jimenez Varas I, Del Valle L, Duran A, Fuentes M, Del Prado N, Bordiu E, Valerio JJ, Herraiz MA, et al. (2019). Effectiveness of following Mediterranean diet recommendations in the real world in the incidence of gestational diabetes mellitus (GDM) and adverse Maternal-Foetal outcomes: a prospective, universal, interventional study with a single group. The ST Carlos study. Nutrients 11:1210.

87. Garcia-Marcos L, Canflanca IM, Garrido JB, Varela ALS, Garcia-Hernandez G, Grima FG, Gonzalez-Diaz C, Carvajal-Uruena I, Arnedo-Pena A, Busquets-Monge RM, et al. (2007). Relationship of asthma and rhinoconjunctivitis with obesity, exercise and Mediterranean diet in Spanish schoolchildren. Thorax 62:503–508.

88. Gaskins A, Nassan F, Chiu YH (2019). Dietary patterns and outcomes of assisted reproduction. Am J Obstet Gynecol 220:1–18.
89. Gebauer SK, Psota TL, Harris WS, Kris-Etherton PM (2006). n- 3 fatty acid dietary recommendations and food sources to achieve essentiality and cardiovascular benefits. The American journal of clinical nutrition 83:1526S–1535S.
90. George K, Kumar NS, Lal JJ, Sreedevi R (2000). Anemia and nutritional status of pre-school children in Kerala. The Indian Journal of Pediatrics 67:575–578.
91. Gilsing AM, Crowe FL, Lloyd-Wright Z, Sanders TA, Appleby PN, Allen NE, Key TJ (2010). Serum concentrations of vitamin B12 and folate in British male omnivores, vegetarians and vegans: results from a cross-sectional analysis of the EPIC-Oxford cohort study. European journal of clinical nutrition 64:933–939.
92. Gómez Roig MD, Mazarico E, Ferrero S, Montejo R, Ibáñez L, Grima F, Vela A (2017). Differences in dietary and lifestyle habits between pregnant women with small fetuses and appropriate-for-gestational-age fetuses. Journal of Obstetrics and Gynaecology Research 43:1145–1151.
93. Goni IL, Arenaza L, Medrano M, Garcia N, Cadenas-Sanchez C, Ortega FB (2018). Associations between the adherence to the Mediterranean diet and cardiorespiratory fitness with total and central obesity in preschool children: the PREFIT project. European journal of nutrition 57:2975–2983.
94. Gonzalez Barcala F, Pertega S, Bamonde L, Garnelo L, Perez Castro T, Sampedro M, Sanchez Lastres J, San Jose Gonzalez M, Lopez Silvarrey A (2010). Mediterranean diet and asthma in Spanish schoolchildren. Pediatric allergy and immunology 21:1021–1027.
95. Goswmai S, Das KK (2015). Socio-economic and demographic determinants of childhood anemia. Jornal de Pediatria (Versao em Portugues) 91:471–477.
96. Gowda VK, Kolli V, Benakappa A, Srinivasan VM, Shivappa SK, Benakappa N (2018). Case Series of Infantile Tremor Syndrome in Tertiary Care Paediatric Centre from Southern India. J. Trop. Pediatr. 64:284–288.
97. Grant R, Bilgin A, Zeuschner C, Guy T, Pearce R, Hokin B, Ashton J (2008). The relative impact of a vegetable-rich diet on key markers of health in a cohort of Australian adolescents. Clinical Nutrition 17:107–115.
98. Grattan-Smith P, Wilcken B, Procopis P, Wise G (1997). The neurological syndrome of infantile cobalamin deficiency: developmental regression and involuntary movements. Movement disorders: official journal of the Movement Disorder Society 12:39–46.
99. Grieger JA, Grzeskowiak LE, Clifton VL (2014). Preconception dietary patterns in human pregnancies are associated with preterm delivery. The Journal of nutrition 144:1075–1080.

100. Grigoropoulou D, Priftis KN, Yannakoulia M, Papadimitriou A, Anthracopoulos MB, Yfanti K, Panagiotakos DB (2011). Urban environment adherence to the Mediterranean diet and prevalence of asthma symptoms among 10-to 12-year-old children: The Physical Activity, Nutrition, and Allergies in Children Examined in Athens study. 32:351.

101. Grosso G, Mistretta A, Frigiola A, Gruttadauria S, Biondi A, Basile F, Vitaglione P, D'Orazio N, Galvano F (2014). Mediterranean diet and cardiovascular risk factors: a systematic review. Critical reviews in food science and nutrition 54:593–610.

102. Guez S, Chiarelli G, Menni F, Salera S, Principi N, Esposito S (2012). Severe vitamin B12 deficiency in an exclusively breastfed 5-month-old Italian infant born to a mother receiving multivitamin supplementation during pregnancy. BMC pediatrics 12:1–5.

103. H. Al Wattar B, Dodds J, Placzek A, Beresford L, Spyreli E, Moore A, Gonzalez Carreras FJ, Austin F, Murugesu N, Roseboom TJ, et al. (2019). Mediterranean-style diet in pregnant women with metabolic risk factors (ESTEEM): A pragmatic multicentre randomised trial. PLoS medicine 16:e1002857.

104. Haapala EA, Eloranta AM, Venalainen T, Jalkanen H, Poikkeus AM, Ahonen T, Lindi V, Lakka TA (2017). Diet quality and academic achievement: a prospective study among primary school children. European journal of nutrition 56:2299–2308.

105. Haddad EH, Tanzman JS (2003). What do vegetarians in the United States eat? The American journal of clinical nutrition 78:626S–632S.

106. Haldimann M, Alt A, Blanc A, Blondeau K (2005). Iodine content of food groups. Journal of food Composition and Analysis 18:461–471.

107. Hamilton-Reeves JM, Vazquez G, Duval SJ, Phipps WR, Kurzer MS, Messina MJ (2010). Clinical studies show no effects of soy protein or isoflavones on reproductive hormones in men: results of a meta-analysis. Fertility and sterility 94:997–1007.

108. Hans KB, Jana T (2018). Micronutrients in the life cycle: Requirements and sufficient supply. NFS journal 11:1–11.

109. Haugen M, Margrete Meltzer H, Lise Brantsæter A, Mikkelsen T, Louise Østerdal M, Alexander J, Olsen SF, Bakketeig L (2008). Mediterranean-type diet and risk of preterm birth among women in the Norwegian Mother and Child Cohort Study (MoBa): a prospective cohort study. Acta obstetricia et gynecologica Scandinavica 87:319–324.

110. Henriksson P, Cuenca-Garcia M, Labayen I, Esteban-Cornejo I, Henrikson H, Kersting M, Vanhelst J, Widhalm K, Gottrand F, Moreno LA, et al. (2017). Diet quality and attention capacity in European adolescents: The Healthy Lifestyle in Europe by Nutrition in Adolescence (HELENA) study. British Journal of Nutrition 117:1587–1595.

111. Higginbottom MC, Sweetman L, Nyhan WL (1978). A syndrome of methylmalonic aciduria, homocystinuria, megaloblastic anemia and neurologic abnormalities in a vitamin B12-deficient breast-fed infant of a strict vegetarian. New England Journal of Medicine 299:317–323.

112. Hoffman SR, Stallings SF, Bessinger RC, Brooks GT (2013). Differences between health and ethical vegetarians. Strength of conviction, nutrition knowledge, dietary restriction, and duration of adherence. Appetite 65:139–144.

113. House JS, Mendez M, Maguire RL, Gonzalez-Nahm S, Huang Z, Daniels J, Murphy SK, Fuemmeler BF, Wright FA, Hoyo C (2018). Periconceptional maternal mediterranean diet is associated with favorable offspring behaviors and altered CpG methylation of imprinted genes. Frontiers in cell and developmental biology 6:107.

114. Ibanez NC, Galiano JMM, Prieto CA, Requena RO, Cavanillas AB, Rodriguez MD (2019). Meat and meat products intake in pregnancy and risk of small for gestational age infants. A case-control study. Nutricion hospitalaria: Organo oficial de la Sociedad espanola de nutricion parenteral y enteral 36:405–411.

115. Idelson PI, Scalfi L, Valerio G (2017). Adherence to the Mediterranean Diet in children and adolescents: A systematic review. Nutrition, Metabolism and Cardiovascular Diseases 27:283–299.

116. Idris N, Arsyad A (2012). Vitamin B12 deficiency presenting as pancytopenia in pregnancy: a case report. Malaysian family physician: the official journal of the Academy of Family Physicians of Malaysia 7:46.

117. Imamura F, Micha R, Wu JH, Oliveira Otto MC de, Otite FO, Abioye AI, Mozaffarian D (2016). Effects of saturated fat, polyunsaturated fat, monounsaturated fat, and carbohydrate on glucose-insulin homeostasis: a systematic review and meta-analysis of randomised controlled feeding trials. PLoS medicine 13:e1002087.

118. Izadi V, Tehrani H, Haghighatdoost F, Dehghan A, Surkan PJ, Azadbakht L (2016). Adherence to the DASH and Mediterranean diets is associated with decreased risk for gestational diabetes mellitus. Nutrition 32:1092–1096.

119. Jali M, Desai B, Gowda S, Kambar S, Jali SM (2011). A hospital based study of prevalence of gestational diabetes mellitus in an urban population of India. RGUHS Journal of Medical Sciences 1:22–26.

120. Jayanthi V (2001). Vegetarianism in India. Perit Dial Int 21 Suppl 3:322–325.

121. Jennings A, Welch A, Sluijs EM van, Griffin SJ, Cassidy A (2011). Diet quality is independently associated with weight status in children aged 9–10 years. The Journal of nutrition 141:453–459.

122. Jong RB de, Bekhof J, Roorda R, Zwart P (2005). Severe nutritional vitamin deficiency in a breast-fed infant of a vegan mother. European journal of pediatrics 164:259.

123. Julian C, Huybrechts I, Gracia-Marco L, Gonzalez-Gil E, Gutierrez A, Gonzalez-Gross M, Marcos A, Widhalm K, Kafatos A, Vicente-Rodriguez G, et al. (2018). Mediterranean diet, diet quality, and bone mineral content in adolescents: The HELENA study. Osteoporosis International 29:1329–1340.

124. Kalfa N, Sultan C, Baskin LS (2010). Hypospadias: etiology and current research. Urologic Clinics 37:159–166.

125. Kanra G, Cetin M, Unal S, Haliloglu G, Akça T, Akalan N, Kara A (2005). Answer to hypotonia: a simple hemogram. Journal of child neurology 20:930–931.

126. Karamanos B, Thanopoulou A, Anastasiou E, Assaad-Khalil S, Albache N, Bachaoui M, Slama CB, El Ghomari H, Jotic A, Lalic N, et al. (2014). Relation of the Mediterranean diet with the incidence of gestational diabetes. European Journal of Clinical Nutrition 68:8–13.

127. Karayiannis D, Kontogianni MD, Mendorou C, Mastrominas M, Yiannakouris N (2018). Adherence to the Mediterranean diet and IVF success rate among non-obese women attempting fertility. Hum. Reprod. 33:494–502.

128. Kastorini CM, Milionis HJ, Esposito K, Giugliano D, Goudevenos JA, Panagiotakos DB (2011). The effect of Mediterranean diet on metabolic syndrome and its components: a meta-analysis of 50 studies and 534,906 individuals. J. Am. Coll. Cardiol. 57:1299–1313.

129. Kaur L, Puri M, Kaushik S, Sachdeva MP, Trivedi SS, Saraswathy KN (2013). Genetic thromobophilia in pregnancy: a case–control study among North Indian women. Journal of thrombosis and thrombolysis 35:250–256.

130. Keller M, Müller S (2016). Vegetarische und vegane Ernährung bei Kindern-Stand der Forschung und Forschungsbedarf. Complementary Medicine Research 23:81–88.

131. Key TJ, Fraser GE, Thorogood M, Appleby PN, Beral V, Reeves G, Burr ML, Chang-Claude J, Frentzel-Beyme R, Kuzma JW, et al. (1999). Mortality in vegetarians and nonvegetarians: detailed findings from a collaborative analysis of 5 prospective studies. The American journal of clinical nutrition 70:516s–524s.

132. Kocaoglu C, Akin F, Caksen H, Böke SB, Arslan S, Aygün S (2014). Cerebral atrophy in a vitamin B12-deficient infant of a vegetarian mother. J Health Popul Nutr 32:367–371.

133. Koebnick C, Heins UA, Hoffmann I, Dagnelie PC, Leitzmann C (2001). Folate status during pregnancy in women is improved by long-term high vegetable intake compared with the average western diet. The Journal of nutrition 131:733–739.

134. Koirala AK, Bhatta DN (2015). Low-birth-weight babies among hospital deliveries in Nepal: a hospital-based study. International journal of women's health 7:581.

135. Kontogianni MD, Vidra N, Farmaki AE, Koinaki S, Belogianni K, Sofrona S, Magkanari F, Yannakoulia M (2008). Adherence rates to the Mediterranean diet are low in a representative sample of Greek children and adolescents. The Journal of nutrition 138:1951–1956.

136. Koutelidakis AE, Alexatou O, Kousaiti S, Gkretsi E, Vasios G, Sampani A, Tolia M, Kiortsis DN, Giaginis C (2018). Higher adherence to Mediterranean diet prior to pregnancy is associated with decreased risk for deviation from the maternal recommended gestational weight gain. International journal of food sciences and nutrition 69:84–92.

137. Krajcovicova-Kudlaakova M, Simoncic R, Bederova A, Grancicova E, Magalova T (1997). Influence of vegetarian and mixed nutrition on selected haematological and biochemical parameters in children. Food/Nahrung 41:311–314.

138. Krajčovičová-Kudláčková M, Bučková K, Klimeš I, Šeboková E (2003). Iodine deficiency in vegetarians and vegans. Annals of Nutrition and Metabolism 47:183–185.

139. Krasevec J, An X, Kumapley R, Begin F, Frongillo EA (2017). Diet quality and risk of stunting among infants and young children in low-and middle-income countries. Maternal & child nutrition 13:e12430.

140. Krebs NF, Mazariegos M, Chomba E, Sami N, Pasha O, Tshefu A, Carlo WA, Goldenberg RL, Bose CL, Wright LL, et al. (2012). Randomized controlled trial of meat compared with multimicronutrient-fortified cereal in infants and toddlers with high stunting rates in diverse settings. The American journal of clinical nutrition 96:840–847.

141. Kristensen NB, Madsen ML, Hansen TH, Allin KH, Hoppe C, Fagt S, Lausten MS, Gøbel RJ, Vestergaard H, Hansen T, et al. (2015). Intake of macro-and micronutrients in Danish vegans. Nutrition journal 14:1–10.

142. Kühne T, Bubl R, Baumgartner R (1991). Maternal vegan diet causing a serious infantile neurological disorder due to vitamin B 12 deficiency. European journal of pediatrics 150:205–208.

143. Lampkin BC, Saunders E, et al. (1969). Nutritional vitamin B12 deficiency in an infant. Journal of Pediatrics 75:1053–1055.

144. Lange NE, Rifas-Shiman SL, Camargo Jr CA, Gold DR, Gillman MW, Litonjua AA (2010). Maternal dietary pattern during pregnancy is not associated with recurrent wheeze in children. Journal of Allergy and Clinical Immunology 126:250–255.

145. Larsen PS, Nybo Andersen AM, Uldall P, Bech BH, Olsen J, Hansen AV, Strandberg-Larsen K (2014). Maternal vegetarianism and neurodevelopment of children enrolled in The Danish National Birth Cohort. Acta Paediatrica 103:507–509.

146. Larsson CL, Johansson GK (2002). Dietary intake and nutritional status of young vegans and omnivores in Sweden. The American journal of clinical nutrition 76:100–106.

147. Lazarou C, Panagiotakos DB, Matalas AL (2010). Physical activity mediates the protective effect of the Mediterranean diet on children's obesity status: The CYKIDS study. Nutrition 26:61–67.

148. Leahy E, Lyons S, Tol R (2010). An Estimate of the Number of Vegetarians in the World.

149. Lee HY, Woo J, Chen ZY, Leung SF, Peng XH (2000). Serum fatty acid, lipid profile and dietary intake of Hong Kong Chinese omnivores and vegetarians. Eur J Clin Nutr 54:768–773.

150. Leitzmann C, Keller M (2020). Vegetarische und vegane Ernährung.

151. Leung S, Lee R, Sung R, Luo H, Kam C, Yuen M, Hjelm M, Lee S (2001). Growth and nutrition of Chinese vegetarian children in Hong Kong. Journal of paediatrics and child health 37:247–253.

152. Leventakou V, Roumeliotaki T, Sarri K, Koutra K, Kampouri M, Kyriklaki A, Vassilaki M, Kogevinas M, Chatzi L (2016). Dietary patterns in early childhood and child cognitive and psychomotor development: the Rhea mother–child cohort study in Crete. British Journal of Nutrition 115:1431–1437.

153. Lövblad KO, Ramelli G, Remonda L, Nirkko AC, Ozdoba C, Schroth G (1997). Retardation of myelination due to dietary vitamin B 12 deficiency: cranial MRI findings. Pediatric radiology 27:155–158.

154. Mak JK, Pham NM, Lee AH, Tang L, Pan XF, Binns CW, Sun X (2018). Dietary patterns during pregnancy and risk of gestational diabetes: a prospective cohort study in Western China. Nutrition journal 17:1–11.

155. Mari-Sanchis A, Diaz-Jurado G, Basterra-Gortari FJ, Fuente-Arrillaga C de la, Martinez-Gonzalez MA, Bes-Rastrollo M (2018). Association between pre-pregnancy consumption of meat, iron intake, and the risk of gestational diabetes: the SUN project. European Journal of Nutrition 57:939–949.

156. Mariscal-Arcas M, Rivas A, Monteagudo C, Granada A, Cerrillo I, Olea-Serrano F (2009). Proposal of a Mediterranean diet index for pregnant women. British journal of nutrition 102:744–749.

157. Martin-Calvo N, Chavarro JE, Falbe J, Hu FB, Field AE (2016). Adherence to the Mediterranean dietary pattern and BMI change among US adolescents. International journal of obesity 40:1103–1108.

158. Martinez-Galiano JM, Olmedo-Requena R, Barrios-Rodriguez R, Amezcua-Prieto C, Bueno-Cavanillas A, Salcedo-Bellido I, Jimenez-Moleon JJ, Delgado-Rodriguez M (2018). Effect of adherence to a Mediterranean diet and olive oil intake during pregnancy on risk of small for gestational age infants. Nutrients 10:1234.

159. McLeod A et al. (2011). *World livestock 2011-livestock in food security.* Food and Agriculture Organization of the United Nations (FAO).

160. Melaku YA, Gill TK, Taylor AW, Adams R, Shi Z, Worku A (2018). Associations of childhood, maternal and household dietary patterns with childhood stunting in Ethiopia: proposing an alternative and plausible dietary analysis method to dietary diversity scores. Nutrition journal 17:1–15.

161. Melina V, Craig W, Levin S (2016). Position of the academy of nutrition and dietetics: vegetarian diets. Journal of the Academy of Nutrition and Dietetics 116:1970–1980.

162. Mensink G, Barbosa CL, Brettschneider AK (2016). *Verbreitung der vegetarischen Ernährungsweise in Deutschland. Journal of Health Monitoring*. Robert Koch-Institut, Epidemiologie und Gesundheitsberichterstattung.

163. Michaud J, Lemieux B, Ogier H, Lambert M (1992). Nutritional vitamin B 12 deficiency: two cases detected by routine newborn urinary screening. European journal of pediatrics 151:218–220.

164. Mignini LE, Latthe PM, Villar J, Kilby MD, Carroli G, Khan KS (2005). Mapping the theories of preeclampsia: the role of homocysteine. Obstetrics & Gynecology 105:411–425.

165. Mijatovic-Vukas J, Capling L, Cheng S, Stamatakis E, Louie J, Cheung NW, Markovic T, Ross G, Senior A, Brand-Miller JC, Flood VM (2018). Associations of Diet and Physical Activity with Risk for Gestational Diabetes Mellitus: A Systematic Review and Meta-Analysis. Nutrients 10.

166. Mikkelsen TB, Louise Osterdal M, Knudsen VK, Haugen M, Meltzer HM, Bakketeig L, Olsen SF (2008). Association between a Mediterranean-type diet and risk of preterm birth among Danish women: a prospective cohort study. Acta obstetricia et gynecologica Scandinavica 87:325–330.

167. Misra A, Ray S, Patrikar S (2015). A longitudinal study to determine association of various maternal factors with neonatal birth weight at a tertiary care hospital. medical journal armed forces india 71:270–273.

168. Mistretta A, Marventano S, Antoci M, Cagnetti A, Giogianni G, Nolfo F, Rametta S, Pecora G, Marranzano M (2017). Mediterranean diet adherence and body composition among Southern Italian adolescents. Obesity research & clinical practice 11:215–226.

169. Monjardino T, Lucas R, Ramos E, Barros H (2014). Associations between a priori-defined dietary patterns and longitudinal changes in bone mineral density in adolescents. Public health nutrition 17:195–205.

170. Monteagudo C, Mariscal-Arcas M, Heras-Gonzalez L, Ibanez-Peinado D, Rivas A, Olea-Serrano F (2016). Effects of maternal diet and environmental exposure to organochlorine pesticides on newborn weight in Southern Spain. Chemosphere 156:135–142.

171. Morrison A, Polisena J, Husereau D, Moulton K, Clark M, Fiander M, Mierzwinski-Urban M, Clifford T, Hutton B, Rabb D (2012). The effect of English-language restriction on systematic review-based meta-analyses: a systematic review of empirical studies. International journal of technology assessment in health care 28:138.

172. Muhammad R, Fernhoff P, Rasmussen S, Bowman B (2003). Neurologic impairment in children associated with maternal dietary deficiency of cobalamin-Georgia, 2001. JAMA 289:979–979.

173. Muros JJ, Cofre-Bolados C, Arriscado D, Zurita F, Knox E (2017a). Mediterranean diet adherence is associated with lifestyle, physical fitness, and mental wellness among 10-y-olds in Chile. Nutrition 35:87–92.

174. Muros JJ, Perez FS, Ortega FZ, Sanchez VMG, Knox E (2017b). The association between healthy lifestyle behaviors and health-related quality of life among adolescents. Jornal de Pediatria (Versao em Portugues) 93:406–412.

175. NHLBI (Cited on 03.06.2020). Quality Assessment of Systematic Reviews and Meta-Analyses. Cited on 03.06.2020. URL: `https://www.nhlbi.nih.gov/health-topics/study-quality-assessment-tools`.

176. North K, Golding J, Team AS (2000). A maternal vegetarian diet in pregnancy is associated with hypospadias. BJU international 85:107–113.

177. O'Connell JM, Dibley MJ, Sierra J, Wallace B, Marks JS, Yip R (1989). Growth of vegetarian children: the Farm Study. Pediatrics 84:475–481.

178. Obeid R, Pannenbäcker A (2020). Sicherheit der pflanzenbasierten Ernährungsformen in der Schwangerschaft für Mutter und Kind. Ernährung & Medizin 35:55–60.

179. Olmedo-Requena R, Gomez-Fernandez J, Amezcua-Prieto C, Mozas-Moreno J, Khan KS, Jimenez-Moleon JJ (2019). Pre-pregnancy adherence to the Mediterranean diet and gestational diabetes mellitus: a case-control study. Nutrients 11:1003.

180. Orlich MJ, Singh PN, Sabaté J, Jaceldo-Siegl K, Fan J, Knutsen S, Beeson WL, Fraser GE (2013). Vegetarian dietary patterns and mortality in Adventist Health Study 2. JAMA internal medicine 173:1230–1238.

181. Panagiotakos DB, Pitsavos C, Stefanadis C (2006). Dietary patterns: a Mediterranean diet score and its relation to clinical and biological markers of cardiovascular disease risk. Nutrition, Metabolism and Cardiovascular Diseases 16:559–568.

182. Park S, Kim M, Baik SH, Woo J, Kwon Y, Daily J, Park Y, Yang J, Kim S (2013). Gestational diabetes is associated with high energy and saturated fat intakes and with low plasma visfatin and adiponectin levels independent of prepregnancy BMI. European journal of clinical nutrition 67:196–201.

183. Pavlova T, Petrukhin V, Zhiliaeva O, Nadezhdin S (2007). Placental morphology in pregnancy complicated with iron-deficiency anemia. Arkhiv patologii 69:31–32.

184. Pawlak R, Lester SE, Babatunde T (2014). The prevalence of cobalamin deficiency among vegetarians assessed by serum vitamin B12: a review of literature. Eur J Clin Nutr 68:541–548.

185. Pawlak R, Parrott SJ, Raj S, Cullum-Dugan D, Lucus D (2013). How prevalent is vitamin B12 deficiency among vegetarians? Nutrition reviews 71:110–117.

186. Pellegrini-Belinchon J, Lorente-Toledano F, Galindo-Villardon P, Gonzalez-Carvajal I, Martin-Martin J, Mallol J, Garcia-Marcos L (2016). Factors associated to recurrent wheezing in infants under one year of age in the province of Salamanca, Spain: Is intervention possible? A predictive model. Allergologia et immunopathologia 44:393–399.

187. Peraita-Costa I, Llopis-Gonzalez A, Perales-Marin A, Sanz F, Llopis-Morales A, Morales-Suarez-Varela M (2018). A retrospective cross-sectional population-based study on prenatal levels of adherence to the Mediterranean diet: Maternal profile and effects on the newborn. International journal of environmental research and public health 15:1530.

188. Persky VW, Chatterton RT, Van Horn LV, Grant MD, Langenberg P, Marvin J (1992). Hormone levels in vegetarian and nonvegetarian teenage girls: potential implications for breast cancer risk. Cancer research 52:578–583.

189. Piccoli GB, Clari R, Vigotti FN, Leone F, Attini R, Cabiddu G, Mauro G, Castelluccia N, Colombi N, Capizzi I, Pani A, Todros T, Avagnina P (2015). Vegan-vegetarian diets in pregnancy: danger or panacea? A systematic narrative review. BJOG 122:623–633.

190. Poon AK, Yeung E, Boghossian N, Albert PS, Zhang C (2013). Maternal dietary patterns during third trimester in association with birthweight characteristics and early infant growth. Scientifica 2013.

191. Psaltopoulou T, Naska A, Orfanos P, Trichopoulos D, Mountokalakis T, Trichopoulou A (2004). Olive oil, the Mediterranean diet, and arterial blood pressure: the Greek European Prospective Investigation into Cancer and Nutrition (EPIC) study. The American journal of clinical nutrition 80:1012–1018.

192. Rachmel A, Steinberg T, Ashkenazi S, Sela BA (2003). Cobalamin deficiency in a breast-fed infant of a vegetarian mother. IMAJ-RAMAT GAN- 5:534–535.

193. Radnitz C, Beezhold B, DiMatteo J (2015). Investigation of lifestyle choices of individuals following a vegan diet for health and ethical reasons. Appetite 90:31–36.

194. Reghu A, Hosdurga S, Sandhu B, Spray C (2005). Vitamin B12 deficiency presenting as oedema in infants of vegetarian mothers. European journal of pediatrics 164:257–258.

195. Renault F, Verstichel P, Ploussard JP, Costil J (1999). Neuropathy in two cobalamin-deficient breast-fed infants of vegetarian mothers. Muscle & Nerve: Official Journal of the American Association of Electrodiagnostic Medicine 22:252–254.

196. Renault KM, Carlsen EM, Norgaard K, Nilas L, Pryds O, Secher NJ, Olsen SF, Halldorsson TI (2015). Intake of sweets, snacks and soft drinks predicts weight gain in obese pregnant women: detailed analysis of the results of a randomised controlled trial. PloS one 10:e0133041.

197. Rendle-Short J, Tiernan J, Hawgood S (1979). Vegan mothers with vitamin B12 deficiency. The Medical journal of Australia 2:483.

198. Reveiz L, Gyte GM, Cuervo LG, Casasbuenas A (2011). Treatments for iron-deficiency anaemia in pregnancy. Cochrane Database of Systematic Reviews.

199. Richter M, Boeing H, Grünewald-Funk D, Heseker H, Kroke A, Leschik-Bonnet E, Oberritter H, Strohm D, Watzl B (2016). Vegane Ernährung. stil 1:2.

200. Rinaldo P, Stanley CA, Hsu BY, Sanchez LA, Stern HJ, et al. (1997). Sudden neonatal death in carnitine transporter deficiency. The Journal of pediatrics 131:304–305.

201. Ritchie H (2017). How much of the world's land would we need in order to feed the global population with the average diet of a given country? Our World in Data 3.

202. Rizzo NS, Jaceldo-Siegl K, Sabate J, Fraser GE (2013). Nutrient profiles of vegetarian and nonvegetarian dietary patterns. Journal of the Academy of Nutrition and Dietetics 113:1610–1619.

203. Roberts JM, Pearson G, Cutler J, Lindheimer M (2003). Summary of the NHLBI working group on research on hypertension during pregnancy. Hypertension 41:437–445.

204. Rodrigues V, Dias A, Brito MJ, Galvão I, Ferreira GC (2011). Severe megaloblastic anaemia in an infant. Case Reports 2011:bcr0220113835.

205. Romero R, Chaiworapongsa T, Espinoza J (2003). Micronutrients and intrauterine infection, preterm birth and the fetal inflammatory response syndrome. The Journal of nutrition 133:1668S–1673S.

206. Rona R, Chinn S, Duggal S, Driver A (1987). Vegetarianism and growth in Urdu, Gujarati, and Punjabi children in Britain. Journal of Epidemiology & Community Health 41:233–236.

207. Rosell M, Appleby P, Spencer E, Key T (2006). Weight gain over 5 years in 21,966 meat-eating, fish-eating, vegetarian, and vegan men and women in EPIC-Oxford. Int J Obes (Lond) 30:1389–1396.

208. Rosell MS, Lloyd-Wright Z, Appleby PN, Sanders TA, Allen NE, Key TJ (2005). Long-chain n-3 polyunsaturated fatty acids in plasma in British meat-eating, vegetarian, and vegan men. Am. J. Clin. Nutr. 82:327–334.

209. Rosi A, Calestani MV, Parrino L, Milioli G, Palla L, Volta E, Brighenti F, Scazzina F (2017). Weight status is related with gender and sleep duration but not with dietary habits and physical activity in primary school Italian children. Nutrients 9:579.

210. Rudolf M, Arulanantham K, Greenstein RM (1980). Unsuspected nutritional rickets. Pediatrics 66:72–76.

211. Sabaté J (2003). The contribution of vegetarian diets to health and disease: a paradigm shift? The American Journal of Clinical Nutrition 78:502S–507S. URL: `https://doi.org/10.1093/ajcn/78.3.502S`.

212. Sanders TA (2009). DHA status of vegetarians. Prostaglandins, leukotrienes and essential fatty acids 81:137–141.

213. Santos Vaz J dos, Kac G, Emmett P, Davis JM, Golding J, Hibbeln JR (2013). Dietary patterns, n-3 fatty acids intake from seafood and high levels of anxiety symptoms during pregnancy: findings from the Avon Longitudinal Study of Parents and Children. PLoS One 8:e67671.

214. Saunders L, Guldner L, Costet N, Kadhel P, Rouget F, Monfort C, Thome JP, Multigner L, Cordier S (2014). Effect of a M editerranean Diet during Pregnancy on Fetal Growth and Preterm Delivery: Results From a F rench Caribbean Mother–Child Cohort Study (TIMOUN). Paediatric and perinatal epidemiology 28:235–244.

215. Scarborough P, Appleby PN, Mizdrak A, Briggs AD, Travis RC, Bradbury KE, Key TJ (2014). Dietary greenhouse gas emissions of meat-eaters, fish-eaters, vegetarians and vegans in the UK. Climatic change 125:179–192.

216. Schoenaker DA, Soedamah-Muthu SS, Callaway LK, Mishra GD (2015a). Prepregnancy dietary patterns and risk of developing hypertensive disorders of pregnancy: results from the Australian Longitudinal Study on Women's Health. Am. J. Clin. Nutr. 102:94–101.

217. Schoenaker DA, Soedamah-Muthu SS, Mishra GD (2016). Quantifying the mediating effect of body mass index on the relation between a Mediterranean diet and development of maternal pregnancy complications: the Australian Longitudinal Study on Women's Health. Am. J. Clin. Nutr. 104:638–645.

218. Schoenaker DA, Soedamah-Muthu SS, Callaway LK, Mishra GD (2015b). Pre-pregnancy dietary patterns and risk of gestational diabetes mellitus: results from an Australian population-based prospective cohort study. Diabetologia 58:2726–2735.

219. Scholl TO, Reilly T (2000). Anemia, iron and pregnancy outcome. The Journal of nutrition 130:443S–447S.

220. Schröder H, Fitó M, Estruch R, Martinez-González MA, Corella D, Salas-Salvado J, Lamuela-Raventós R, Ros E, Salaverria I, Fiol M, et al. (2011). A short screener is valid for assessing Mediterranean diet adherence among older Spanish men and women. The Journal of nutrition 141:1140–1145.

221. Schüpbach R, Wegmüller R, Berguerand C, Bui M, Herter-Aeberli I (2017). Micronutrient status and intake in omnivores, vegetarians and vegans in Switzerland. European journal of nutrition 56:283–293.

222. Schürmann S, Kersting M, Alexy U (2017). Vegetarian diets in children: a systematic review. European journal of nutrition 56:1797–1817.

223. Schwingshackl L, Hoffmann G (2014). Mediterranean dietary pattern, inflammation and endothelial function: a systematic review and meta-analysis of intervention trials. Nutrition, Metabolism and Cardiovascular Diseases 24:929–939.

224. Serra-Majem L, Ribas L, Ngo J, Ortega RM, Garcia A, Perez-Rodrigo C, Aranceta J (2004). Food, youth and the Mediterranean diet in Spain. Development of KIDMED, Mediterranean Diet Quality Index in children and adolescents. Public health nutrition 7:931–935.

225. Shaikh M, Anderson J, Hall S, Jackson M (2003). Transient neonatal hypothyroidism due to a maternal vegan diet. Journal of pediatric endocrinology & metabolism: JPEM 16:111–113.

226. Sharma JB, Soni D, Murthy NS, Malhotra M (2003). Effect of dietary habits on prevalence of anemia in pregnant women of Delhi. Journal of obstetrics and gynaecology research 29:73–78.

227. Sheng X, Wang J, Li F, Ouyang F, Ma J (2019). Effects of dietary intervention on vitamin B 12 status and cognitive level of 18-month-old toddlers in high-poverty areas: a cluster-randomized controlled trial. BMC pediatrics 19:1–9.

228. Shinwell ED, Gorodischer R (1982). Totally vegetarian diets and infant nutrition. Pediatrics 70:582–586.

229. Shull MW, Reed RB, Valadian I, Palombo R, Thorne H, Dwyer JT (1977). Velocities of growth in vegetarian preschool children. Pediatrics 60:410–417.

230. Silva-del Valle MA, Sánchez-Villegas A, Serra-Majem L (2013). Association between the adherence to the Mediterranean diet and overweight and obesity in pregnant women in Gran Canaria. Nutricion hospitalaria 28:654–659.

231. Sklar R (1986). Nutritional vitamin B12 deficiency in a breast-fed infant of a vegan-diet mother. Clinical pediatrics 25:219–221.

232. SKOPOS (2008). 1,3 Millionen Deutsche leben vegan. Cited on 23.05.2020. URL: `https://www.skopos-group.de/news/13-millionen-deutsche-leben-vegan.html`.

233. Smith LK, Draper ES, Evans TA, Field DJ, Johnson SJ, Manktelow BN, Seaton SE, Marlow N, Petrou S, Boyle EM (2015). Associations between late and moderately preterm birth and smoking, alcohol, drug use and diet: a population-based case–cohort study. Archives of Disease in Childhood-Fetal and Neonatal Edition 100:F486–F491.

234. Sobiecki JG, Appleby PN, Bradbury KE, Key TJ (2016). High compliance with dietary recommendations in a cohort of meat eaters, fish eaters, vegetarians, and vegans: results from the European Prospective Investigation into Cancer and Nutrition–Oxford study. Nutrition Research 36:464–477.

235. Steinfeld H, Gerber P, Wassenaar T, Castel V, Rosales M, Rosales M, Haan C de (2006). *Livestock's long shadow: environmental issues and options*. Food & Agriculture Org.

236. Stollhoff K, Schulte F (1987). Vitamin B 12 and brain development. European journal of pediatrics 146:201–205.

237. Story M, Neumark-Sztainer D, French S (2002). Individual and environmental influences on adolescent eating behaviors. Journal of the American Dietetic association 102:S40–S51.

238. Stuebe AM, Oken E, Gillman MW (2009). Associations of diet and physical activity during pregnancy with risk for excessive gestational weight gain. American journal of obstetrics and gynecology 201:58–e1.

239. Tambalis KD, Panagiotakos D, Psarra G, Sidossis LS (2018). Current data in Greek children indicate decreasing trends of obesity in the transition from childhood to adolescence; results from the National Action for Children's Health (EYZHN) program. Journal of preventive medicine and hygiene 59:E36.

240. Tan C, Zhao Y, Wang S (2019). Is a vegetarian diet safe to follow during pregnancy? A systematic review and meta-analysis of observational studies. Crit Rev Food Sci Nutr 59:2586–2596.

241. Timmermans S, Steegers-Theunissen RP, Vujkovic M, Breeijen H den, Russcher H, Lindemans J, Mackenbach J, Hofman A, Lesaffre EE, Jaddoe VV, et al. (2012). The Mediterranean diet and fetal size parameters: the Generation R Study. British Journal of Nutrition 108:1399–1409.

242. Timmermans S, Steegers-Theunissen RP, Vujkovic M, Bakker R, Breeijen H den, Raat H, Russcher H, Lindemans J, Hofman A, Jaddoe VW, et al. (2011). Major dietary patterns and blood pressure patterns during pregnancy: the Generation R Study. American journal of obstetrics and gynecology 205:337–e1.

243. Tobias DK, Zhang C, Chavarro J, Bowers K, Rich-Edwards J, Rosner B, Mozaffarian D, Hu FB (2012). Prepregnancy adherence to dietary patterns and lower risk of gestational diabetes mellitus. The American journal of clinical nutrition 96:289–295.

244. Tognon G, Hebestreit A, Lanfer A, Moreno L, Pala V, Siani A, Tornaritis M, De Henauw S, Veidebaum T, Molnar D, et al. (2014). Mediterranean diet, overweight and body composition in children from eight European countries: cross-sectional and prospective results from the IDEFICS study. Nutrition, Metabolism and Cardiovascular Diseases 24:205–213.

245. Tonstad S, Stewart K, Oda K, Batech M, Herring R, Fraser G (2013). Vegetarian diets and incidence of diabetes in the Adventist Health Study-2. Nutrition, metabolism and cardiovascular diseases 23:292–299.

246. Torloni M, Betran A, Horta B, Nakamura M, Atallah A, Moron A, Valente O (2009). Prepregnancy BMI and the risk of gestational diabetes: a systematic review of the literature with meta-analysis. Obesity reviews 10:194–203.

247. Trichopoulou A, Costacou T, Bamia C, Trichopoulos D (2003). Adherence to a Mediterranean diet and survival in a Greek population. N. Engl. J. Med. 348:2599–2608.

248. Troiano RP, Flegal KM (1998). Overweight children and adolescents: description, epidemiology, and demographics. Pediatrics 101:497–504.

249. Tucker KL (2014). Vegetarian diets and bone status. Am. J. Clin. Nutr. 100 Suppl 1:329–35.

250. Van Der Put NM, Van Straaten HW, Trijbels FJ, Blom HJ (2001). Folate, homocysteine and neural tube defects: an overview. Experimental Biology and Medicine 226:243–270.

251. Vassiloudis I, Yiannakouris N, Panagiotakos DB, Apostolopoulos K, Costarelli V (2014). Academic performance in relation to adherence to the Mediterranean diet and energy balance behaviors in Greek primary schoolchildren. Journal of nutrition education and behavior 46:164–170.

252. VEBU (2015). Anzahl der Veganer und Vegetarier in Deutschland. Cited on 10.04.2021. URL: `vebu.de/veggie-fakten/entwicklung-in-zahlen/anzahl-veganer-und-vegetarier-in-deutschland/`.

253. Vegetarian Resource Group (2016). How many adults in the U.S are vegetarian and vegan? Cited on 23.05.2020. URL: `https://www.skopos-group.de/news/13-millionen-deutsche-leben-vegan.html`.

254. Vergeer L, Vanderlee L, White CM, Rynard VL, Hammond D (2020). Vegetarianism and other eating practices among youth and young adults in major Canadian cities. Public Health Nutr 23:609–619.

255. Verkleij-Hagoort AC, Vries JH de, Ursem NT, Jonge R de, Hop WC, Steegers-Theunissen RP (2006). Dietary intake of B-vitamins in mothers born a child with a congenital heart defect. European journal of nutrition 45:478–486.

256. Vitamin B12 Deficiency in the Breast-Fed Infant of a Strict Vegetarian (1979). Nutrition Reviews 37:142–144.

257. Voltas N, Arija V, Aparicio E, Canals J (2016). Longitudinal study of psychopathological, anthropometric and sociodemographic factors related to the level of Mediterranean diet adherence in a community sample of Spanish adolescents. Public health nutrition 19:1812–1822.

258. Vujkovic M, Steegers EA, Looman CW, Ocke MC, Spek PJ van der, Steegers-Theunissen RP (2009). The maternal Mediterranean dietary pattern is associated with a reduced risk of spina bifida in the offspring. BJOG: An International Journal of Obstetrics & Gynaecology 116:408–415.

259. Waldmann A, Koschizke J, Leitzmann C, Hahn A (2003). Dietary intakes and lifestyle factors of a vegan population in Germany: results from the German Vegan Study. European journal of clinical nutrition 57:947–955.

260. Wang F, Zheng J, Yang B, Jiang J, Fu Y, Li D (2015). Effects of Vegetarian Diets on Blood Lipids: A Systematic Review and Meta-Analysis of Randomized Controlled Trials. J Am Heart Assoc 4.

261. Watanabe F (2007). Vitamin B12 sources and bioavailability. Experimental biology and medicine 232:1266–1274.

262. Weder S, Hoffmann M, Becker K, Alexy U, Keller M (2019). Energy, Macronutrient Intake, and Anthropometrics of Vegetarian, Vegan, and Omnivorous Children (1-3 Years) in Germany (VeChi Diet Study). Nutrients 11.

263. Wolters M, Joslowski G, Plachta-Danielzik S, Standl M, Muller MJ, Ahrens W, Buyken AE (2018). Dietary patterns in primary school are of prospective relevance for the development of body composition in two German pediatric populations. Nutrients 10:1442.

264. Yang J, Kang Y, Cheng Y, Zeng L, Yan H, Dang S (2019). Maternal dietary patterns during pregnancy and congenital heart defects: a case-control study. International journal of environmental research and public health 16:2957.

265. Yen CE, Yen CH, Huang MC, Cheng CH, Huang YC (2008). Dietary intake and nutritional status of vegetarian and omnivorous preschool children and their parents in Taiwan. Nutrition research 28:430–436.

266. Ying H, Wang DF (2006). Effects of dietary fat on onset of gestational diabetes mellitus. Zhonghua fu chan ke za zhi 41:729–731.

267. Yoganathan S, Varman M, Oommen SP, Thomas M (2017). A tale of treatable infantile neuroregression and diagnostic dilemma with glutaric aciduria type I. Journal of pediatric neurosciences 12:356.

268. Yougov (2019). Wie veggie ist Deutschland? Cited on 23.05.2020. URL: `https://yougov.de/news/2019/06/27/wie-veggie-ist-deutschland`.

269. Zhang C, Tobias DK, Chavarro JE, Bao W, Wang D, Ley SH, Hu FB (2014). Adherence to healthy lifestyle and risk of gestational diabetes mellitus: prospective cohort study. BMJ 349:g5450.

270. Zhang Y, Lin J, Fu W, Liu S, Gong C, Dai J (2019). Mediterranean diet during pregnancy and childhood for asthma in children: A systematic review and meta-analysis of observational studies. Pediatr. Pulmonol. 54:949–961.

271. Zimmermann MB (2012). The effects of iodine deficiency in pregnancy and infancy. Paediatric and perinatal epidemiology 26:108–117.

272. Zulyniak MA, Souza RJ de, Shaikh M, Desai D, Lefebvre DL, Gupta M, Wilson J, Wahi G, Subbarao P, Becker AB, et al. (2017). Does the impact of a plant-based diet during pregnancy on birth weight differ by ethnicity? A dietary pattern analysis from a prospective Canadian birth cohort alliance. BMJ open 7.

8 Study registration

Rima Obeid, Arved Pannenbäcker. The association between a plant-based diet and maternal and child health: a systematic review. PROSPERO 2020; CRD42020211102

9 Publications

Pannenbäcker A, Obeid R (2020). Mediterrane Diät vor und während der Schwangerschaft. Ernährung & Medizin 2020; 35(02): 61-67.

Obeid R, Pannenbäcker A (2020). Sicherheit der pflanzenbasierten Ernährungsformen in der Schwangerschaft für Mutter und Kind. Ernährung & Medizin 2020; 35(02): 55-60.

10 Acknowledgements

Throughout the writing of this dissertation I have received a great deal of support and assistance.

First of all, I would like to thank Prof. Dr. rer. med. Rima Obeid for consigning the topic of my choice to me. Your excellent supervision, constructive feedback and the possibility to ask you for advice at any time made this dissertation possible.

I would like to thank Prof. Dr. med. Jürgen Geisel for the opportunity to work in his Department of Clinical Chemistry and Laboratory Medicine.

Moreover, I would like to thank Mr. Johannes Stein for his availability for queries and sharing his experience with systematic reviews and meta-analyses with me.

I would also like to thank my friends, Lisa and Khang, for introducing me to the software LaTeX and being patient with my programming skills. A big thank you also goes to my friend Anja for the lively exchange about the current progress of the dissertation and the mutual motivation to follow through.

In addition, I would like to thank my parents for their wise counsel and sympathetic ear. You are always there for me. I dedicate this work to my dad.

Mediterrane Diät vor und während der Schwangerschaft

Arved Pannenbäcker, Rima Obeid

Im Vergleich zu veganen und vegetarischen Ernährungsformen ist die mediterrane Diät (MD) vielfältiger, ausgewogener in Bezug auf Makro- und Mikronährstoffe und mithilfe von Score-Systemen in der Literatur besser definiert. Studien weisen darauf hin, dass die MD vor und während der Schwangerschaft protektive Effekte auf die Gesundheit von Mutter und Kind haben kann, so z. B. gegenüber Gestationsdiabetes, Präeklampsie, einem niedrigen Geburtsgewicht oder Frühgeburtlichkeit.

Gute Daten: Mediterrane Kost sollte Frauen mit Kinderwunsch und Schwangeren empfohlen werden. Quelle: Kirsten Oborny, Thieme Gruppe

Einleitung

Es liegen hinreichende Beweise dafür vor, dass eine mediterrane Diät (MD) während der Schwangerschaft einem negativen Schwangerschaftsausgang wie beispielsweise Gestationsdiabetes, Präeklampsie und Frühgeburtlichkeit entgegenwirkt. Klinische Studien im Bereich der Reproduktionsmedizin zeigen einen Zusammenhang zwischen einem höheren Score bei der MD und der Erfolgsrate einer künstlichen Befruchtung bei Frauen mit Infertilitätsproblemen. Die Vorteile der MD könnten in der Diversität und der Ausgewogenheit der Makro- und Mikronährstoffe der MD im Vergleich mit der vegetarischen Ernährung begründet sein.

Merke

Der gesundheitliche Nutzen der MD ist ausgeprägter als derjenige der veganen oder vegetarischen Ernährungsformen.

Des Weiteren haben epidemiologische Studien eine klare Definition der Zusammensetzung der MD mithilfe von Diät-Scores gezeigt, die die systematische Abgrenzung zwischen Subgruppen mit unterschiedlich strenger Diäteinhaltung ermöglichen könnten [1]. Außerdem könnten die in der MD vermehrt vorkommenden Nahrungsbestandteile, die in veganen oder vegetarischen Ernährungsformen vernachlässigt werden, wie beispielsweise Fisch, Milchprodukte und Ei, einen unabhängigen gesundheitlichen Nutzen aufweisen. Obwohl es sich größtenteils um Observationsstudien (und nicht Interventionsstudien) handelt, existieren auch einige randomisierte kontrollierte Studien, die Bestandteile oder das gesamte Konzept der MD betrachteten und deren gesundheitlichen Nutzen untersuchten.

Die mediterrane Diät als perikonzeptionelle Ernährungsform

Zahlreiche Studien stützen die These, dass eine Einhaltung der MD, ein hoher Score bei der Diät oder der Verzehr bestimmter Bestandteile der Diät (Fisch, Milchprodukte etc.) zu einer Verbesserung der Raten für klinische Schwangerschaften und Lebendgeburten nach In-vitro-Fertilisation (IVF) führen [2][3]. Jedoch ist die Generalisierbarkeit einzelner Studien auf alle Frauen mit Fertilitätsproblemen nicht möglich. Eine strengere Einhaltung der MD war mit einem besseren IVF-Ausgang assoziiert, aber es wurde keine dosisabhängige Beziehung festgestellt [2].

In einer weiteren Untersuchung zeigte eine Pro-Fertilitätsdiät als Vorbehandlung mit höherer Zufuhr von Folsäure, Vitamin B_{12}, Vitamin D, Obst und Gemüse ohne Pestizidrückstände, Vollkornprodukten, Milchprodukten, Soja, Meeresfrüchten und wenig Fleisch noch bessere IVF-Ergebnisse als die MD [2]. Die Ergebnisse sollten aufgrund des beobachtenden Studiencharakters (keine randomisierte kontrollierte Studie) mit Vorsicht betrachtet werden.

Zudem existieren Studien, die einen negativen Einfluss bei perikonzeptionellem Verzehr von Lebensmitteln mit Pestizidrückständen auf eine erfolgreiche Schwangerschaft bei Frauen mit Fertilitätsproblemen implizieren. Dieser Faktor könnte den gesundheitsfördernden Effekt von Obst und Gemüse aufheben. Andererseits ist der Konsum von Bio-Obst und -Gemüse (frei von Pestizidrückständen) oft mit höherem Sozialstatus assoziiert, was wiederum die Aussage erschwert, ob die MD der Hauptakteur bei der erfolgreichen Schwangerschaft ist.

Merke

Viel Gemüse und Obst allein haben noch keinen ausreichend protektiven Einfluss; es kommt auch auf die Qualität der Nahrung und ggf. auf damit abhängige sozioökonomische Faktoren an.

Eine Studie aus Rotterdam zeigte eine Assoziation zwischen einer perikonzeptionellen Ernährungsform (reich an Fisch und Olivenöl, wenig Fleisch) und fetalem Wachstum in den ersten 90 Schwangerschaftstagen bei Frauen, die spontan schwanger wurden [4]. Die Einhaltung einer Ernährungsform reich an Milchprodukten war mit einem höheren pränatalen Wachstum des Kleinhirns assoziiert [5]. Dazu wurde der transzerebelläre Durchmesser in Schwangerschaftswoche 9 (+ 6,8 % höher), 11 (+ 6 % höher) und 32 (+ 2,8 % höher) per Ultraschall bestimmt und mit Frauen, die weniger Milchprodukte konsumierten, verglichen [6]. Der Effekt einer strengen Einhaltung der mütterlichen Ernährung reich an Milchprodukten war im 1. Trimester stärker ausgeprägt als im 3. Trimester, was darauf hindeutet, dass weitere Faktoren zumindest teilweise die Auswirkungen der mütterlichen Ernährung auf das Hirnwachstum verbessern oder kompensieren können [6]. Im Gegensatz dazu konnte die niederländische Studie keine Assoziation zwischen fetalem zerebellären Wachstum und einer perikonzeptionellen mütterlichen MD, einer westlichen Ernährungsform oder einer Ernährung reich an Eiern während der Schwangerschaft feststellen [6]. Die Ergebnisse legen nahe, dass in der Frühschwangerschaft spezifische Effekte der Ernährung auf fetales Wachstum vorliegen. Ebenfalls deuten die Ergebnisse darauf hin, dass verschiedene Faktoren den Einfluss der gesunden mütterlichen Ernährung auf das Wachstum des Kindes abmildern oder gar aufheben können. Beispiele für diese Faktoren könnten sein:

- der mütterliche Body-Mass-Index (BMI) vor der Schwangerschaft und
- die tägliche Aufnahme von Fetten, Fleisch und der Gesamtkalorienzahl.

Merke

Die Studienlage zum Fischverzehr als Teil der mediterranen Diät während der Schwangerschaft in Bezug auf Übergewicht des Kindes ist uneinheitlich.

Kombinierte Analysen der Daten von 26184 schwangeren Frauen und deren Kindern aus 11 europäischen Ländern untersuchten die Assoziation von Fischzufuhr während der Schwangerschaft und dem BMI des Kindes zwischen 3 Monaten nach Geburt bis zum Alter von 6 Jahren [7]. Frauen, die während der Schwangerschaft häufiger als 3-mal pro Woche Fisch aßen, gebaren Kinder mit höheren BMI-Werten im Säuglings- bis mittleren Kindesalter im Vergleich zu Frauen mit geringerem Fischkonsum (≤ 3-mal/Woche) [7]. Ein hoher Fischkonsum während der Schwangerschaft war verglichen mit einem geringeren Fischkonsum mit einem erhöhten Risiko für Übergewicht/Adipositas bei Nachkommen insbesondere bei Mädchen assoziiert [7]. Die Konsequenz wäre theoretisch eine Warnung gegen Fischkonsum während der Schwangerschaft. Dennoch wurden landesspezifische Variationen im Fischkonsum und weitere, möglicherweise mit dem Fischkonsum assoziierte Faktoren festgestellt, die in der Analyse keine Beachtung fanden.

Eine US-amerikanische Studie zeigte, dass ein höherer Score der mütterlichen MD mit einer niedrigeren Wahrscheinlichkeit (Odds Ratio, OR) für Depressionen, Angstzustände, Anpassungsstörungen und Autismus bei Kindern im Alter von 12–24 Monaten (Durchschnitt 13,9 Monaten) assoziiert ist [8]. Die DNA-Methylierung mehrerer Gene (z. B. IGF2) im Nabelschnurblut der Neugeborenen war mit der Einhaltung der MD bei der Mutter assoziiert und der Zusammenhang variierte zwischen weiblichen und männlichen Neugeborenen [8].

STUDIENFAZIT

Zusammengefasst ist die perikonzeptionelle mütterliche Diät mit hohem MD-Score, einem hohen Anteil von Fisch und Milchprodukten und wenig Fleisch mit einer größeren Wahrscheinlichkeit einer erfolgreichen Schwangerschaft bei Fertilitätsproblemen und positiven gesundheitlichen Effekten auf das Kind assoziiert.

MD in der Schwangerschaft

Gestationsdiabetes

Kinder von Frauen mit Gestationsdiabetes haben oft ein höheres Risiko für übermäßiges oder vermindertes Wachstum und die Entwicklung von Adipositas im späteren Lebensverlauf. Die MD ist assoziiert mit einem um 18–46 % verringerten Risiko für Gestationsdiabetes – abhängig vom Scoring-System und der Strenge der Diäteinhaltung [9] [10]. Wenn zusätzliche Faktoren wie körperliche Aktivität, Nichtrauchen und normaler BMI beachtet wurden, erhöht sich die mit der MD assoziierte Risikoreduktion auf 83 % [11]. Schätzungen zufolge sind die folgenden 4 Risikofaktoren für 47,5 % (95 % Konfidenzintervall KI: 35,6–56,6 %) aller Fälle von Gestationsdiabetes verantwortlich [11]:

- Rauchen
- körperliche Inaktivität
- Übergewicht
- schlechte Ernährung.

Merke

Der vorschwangerschaftliche BMI ist ein erwiesener Risikofaktor für Gestationsdiabetes.

Dabei ist die wichtigste Frage, ob eine frühe Intervention in Form der MD Gestationsdiabetes vorbeugen, Blutzuckerspiegel normalisieren oder negative Folgen nach der Diagnose Gestationsdiabetes verhindern kann.

Studien mit Ernährungstherapie

In einer spanischen Kohortenstudie mit 874 Schwangeren wurden 177 Frauen mit Gestationsdiabetes (24–28 Schwangerschaftswochen) diagnostiziert und 697 wiesen normale Werte beim oralen Glucosetoleranztest auf [12]. Die Frauen mit Gestationsdiabetes erhielten eine medizinische Ernährungstherapie in Form einer MD (nicht-kontrollierte Intervention) und 27 % bekamen bei nicht ausreichender Wirkung der Diät zusätzlich eine Insulinbehandlung [12]. Durch die Intervention konnte näherungsweise Normoglykämie erreicht werden mit ähnlichen HbA_{1c}-Werten wie bei Frauen ohne Gestationsdiabetes nach 36–38 Schwangerschaftswochen [12]. Die Raten für unzureichende Gewichtszunahme und Neugeborene, die „zu klein für das Gestationsalter“ (small for gestational age, SGA) waren, blieben signifikant höher bei Frauen mit Gestationsdiabetes [12].

In einer weiteren Studie erhielten mehr als 800 Schwangere entweder eine MD (angereichert mit nativem Olivenöl und Nüssen) oder eine Kontrolldiät mit Beginn der 8.–12. Schwangerschaftswoche (randomisierte kontrollierte Studie) [7]. Die Inzidenz von Gestationsdiabetes nach 24–28 Schwangerschaftswochen, mütterliche Gewichtszunahme und andere Schwangerschaftskomplikationen wurden dokumentiert [7]. Die Wahrscheinlichkeit einen Gestationsdiabetes zu entwickeln, war in der Interventionsgruppe niedriger als in der Kontrollgruppe [Adjustierte OR 0,75 (95 % KI: 0,57–0,98); $p = 0{,}039$]. Die Intervention mit der MD verringerte die Raten von insulinbehandeltem Diabetes, Frühgeburtlichkeit, mütterlicher Gewichtszunahme und zu kleiner und zu großer Neugeborener (alle $p < 0{,}05$) [7].

In einer Subgruppe von 697 Frauen, die während der Schwangerschaft normoglykämisch blieben, wirkte die MD protektiv auf zahlreiche mütterlich-fetale Schwangerschaftsausgänge [13]. Außerdem zeigte die MD eine Assoziation mit einem erniedrigten Risiko für das metabolische Syndrom oder dessen Komponenten bei 12–14 Wochen postpartum untersuchten Frauen [relatives Risiko (RR) = 0,74 (95 % KI, 0,60–0,90)]. Die Rate von Frauen mit Insulinresistenz postpartum (HOMA-IR ≤ 3,5) wies keine Unterschiede zwischen beiden Interventionsgruppen auf [14]. Somit gibt diese Studie Anhalt dafür, dass die MD (in der Studie zusätzlich angereichert mit nativem Olivenöl und Nüssen) universell für Hoch- und Niedrigrisikoschwangerschaften empfohlen werden könnte.

Eine Metaanalyse schätzte die Risikoreduktion für Gestationsdiabetes durch eine gesunde mütterliche Ernährung (beinhaltet eine MD) auf 15–38 %, während körperliche Aktivität vor und im frühen Stadium der Schwangerschaft mit einer Risikoreduktion von jeweils 30 % beziehungsweise 21 % assoziiert war [15].

Merke

Eine Kombination von gesunder Ernährung und körperlicher Aktivität, im Optimalfall mit Beginn vor der Schwangerschaft, stellt die vielversprechendste Strategie zur Vorbeugung von Gestationsdiabetes dar.

Es existieren zahlreiche nichtdiätetische Modifikatoren dieser Assoziation. Lindsay et al. fanden beispielsweise keine Assoziation zwischen MD und Insulinresistenz, aber sie berichteten von einer Kombination psychologischer Faktoren wie Ängstlichkeit, Trauer, Wut und Stress als möglichem abmildernden Faktor der Assoziation zwischen mütterlicher MD und Insulinresistenz (HOMA-IR) [16].

Der BMI ist zusätzlich mit unterschiedlichen Verhältnissen der Fettsäurenzusammensetzung der Muttermilch assoziiert, was wiederum die Gewichtszunahme des Säuglings in den ersten Lebensmonaten beeinflussen könnte [17].

Eine prospektive Studie mit 1337 Chinesinnen untersuchte die Assoziation zwischen Ernährung und dem Risiko für Gestationsdiabetes, indem der Diabetes mithilfe des oralen Glucosetoleranztests zwischen der 24. und 28. Schwangerschaftswoche diagnostiziert wurde [18]. Drei Ernährungsformen wurden unterschieden:

- pflanzenbasiert,
- fleischbasiert und
- eine proteinreiche und kohlenhydratarme Ernährungsform.

199 Frauen (14,9 %) entwickelten einen Gestationsdiabetes im Laufe der Schwangerschaft [18]. Nur bei Frauen mit erhöhtem vorschwangerschaftlichem BMI ≥ 24 kg/m^2 und in der Gruppe mit der proteinreichen und kohlenhydratarmen Ernährungsform zeigte sich ein Zusammenhang mit einer geringeren Wahrscheinlichkeit für mütterlichen Diabetes [die OR für das höchste versus das niedrigste Tertil des Diät-Scores = 0,29 (0,09–0,94)] [18]. Das obere Tertil der Ernährungsform war reich an Obst, Fleisch, Fisch, Nüssen, Samen, Milch, Eiern und arm an Getreide (Reis, Nudeln, Brot und Mais).

PRAXISTIPP

Frauen, die eine Schwangerschaft planen und einen hohen BMI haben, sind eine leicht zu identifizierende Risikogruppe und könnten von einer Risikoreduktion für Gestationsdiabetes durch eine mediterrane Diät profitieren.

Studien mit Ernährungsberatung

In einer Studie mit 5384 Frauen, erhielten 46,9 % der Teilnehmerinnen eine Ernährungsberatung, wenn sie vor ihrer pränatalen Untersuchung als Risikogruppe für Gestationsdiabetes identifiziert wurden [19]. Nur 6 % der Frauen, die im Laufe der Schwangerschaft die Diagnose Gestationsdiabetes entwickelten, erhielten eine Ernährungsberatung vor der Schwangerschaft [19]. Des Weiteren wird die mütterliche MD vor der Schwangerschaft mit einem geringeren Risiko für Gestationsdiabetes verbunden [20]. Frauen mit Gestationsdiabetes schienen signifikante Ernährungsumstellungen während der Schwangerschaft vorzunehmen, was vermutlich ein Resultat der erhaltenen Ernährungsberatung war [17].

Damit bleibt die wichtigste Frage offen, ob eine Intervention in Form von „Ernährungsberatung“ vor der Schwangerschaft das Risiko von Gestationsdiabetes reduzieren kann. Ergebnisse von 5 Studien zeigten eine mögliche Reduktion des Risikos für Gestationsdiabetes bei Frauen, die eine Ernährungsberatung erhielten. Vier Studien wiesen auf keinen deutlichen Unterschied zwischen Frauen mit wenig und Frauen mit mittlerer bis hoher Beratungsintensität [21]. Es wurde eine mögliche Reduktion des schwangerschaftsinduzierten Bluthochdrucks bei Frauen mit Ernährungsberatung beobachtet [21].

Es gibt inzwischen eine gute Evidenzlage zum protektiven Effekt einer „Ernährungsberatung in Form von MD“ für alle Frauen, die eine Schwangerschaft planen, oder solche, die zu einer Risikogruppe gehören (z. B. hoher BMI, früherer Gestationsdiabetes, Fertilitätsprobleme). Allerdings verfügen viele der Studien über Limitationen, die wiederum die Generalisierbarkeit der Ergebnisse einschränken. Dies kann sich mit der Zeit ändern, wenn besser konzipierte Studien verfügbar sind und Metaanalysen durchgeführt werden können. Allerdings beansprucht die Ernährungsumstellung viel Zeit und die Ernährungsberatung könnte für Frauen, die die Schwangerschaft nicht geplant haben, zu spät sein.

AUSBLICK

Aus Sicht der Bevölkerungsgesundheit lohnt es sich, in die Prävention zu investieren, insbesondere bei Risikogruppen. Für die Inanspruchnahme von Ernährungsberatung fehlen allerdings oft die Ressourcen, das Bewusstsein der Frauen und die Fähigkeit zur Umsetzung der Empfehlungen.

Geburtsgröße, Wachstum des Kindes, Übergewicht und kardiovaskuläre Risikofaktoren

Laut einer Studie hatten Frauen, die eine MD befolgten, ein niedrigeres Risiko, Kinder mit intrauteriner Wachstumsretardierung zu gebären [22]. Kürzlich wurde in einem systematischen Review die Assoziation zwischen mütterlicher MD und kindlicher Gesundheit untersucht [23]. Die Autoren identifizierten bei insgesamt 29 Studien 8 Studien zum Risiko von niedriger Geburtsgröße, 7 Studien zu Asthma und Allergien und 6 Studien zum Risiko für Frühgeburtlichkeit. Mit Ausnahme einer Studie [7] handelte es sich ausschließlich um Observationsstudien (keine Interventionsstudien) [23].

Zahlreiche Publikationen zeigten, dass eine Intervention mit einer MD mit einem besseren Schwangerschaftsausgang für Neugeborene von Müttern mit Risiko für Gestationsdiabetes und von Müttern ohne Gestationsdiabetes assoziiert war (St. Carlos GMD Prevention Study) [7].

In einer kürzlich erschienenen Studie wurden 1257 amerikanische Schwangere und ihre Kinder bis zum Alter von

4 Jahren untersucht. Die Entwicklung des kindlichen BMI wurde unter dem Gesichtspunkt zweier mütterlicher Ernährungsformen betrachtet: Fastfood und verarbeitete Lebensmittel [24]. Der Anteil von Kindern mit hohem BMI-Verlauf war im höchsten Quartil der mütterlichen Fastfood-Ernährungsform (z. B. höherer Verzehr von frittiertem Hähnchen und Fisch, Fruchtsäften, Mayonnaise und gezuckerten Getränken) höher im Vergleich zum niedrigsten Quartil (14,9 % vs. 8,6 %; p = 0,02). Der Prozentsatz bei Kindern mit Adipositas/Übergewicht lag bei 34,5 % beziehungsweise 25,4 % (p = 0,01) [24]. Die mütterliche Ernährungsform mit verarbeiteten Lebensmitteln (höhere Zufuhr von Milchprodukten, Salatdressing, verarbeitetem Fleisch, Cornflakes und Müsli) war weder mit höheren BMI-Verläufen noch mit Übergewicht/Adipositas beim Kind assoziiert.

Eine niederländische Studie untersuchte die Assoziation von mütterlicher Ernährung mit der Körperzusammensetzung der Kinder im Alter von 6 Jahren mithilfe der Doppelröntgen-Absorptiometrie [25]. Der Zusammenhang wurde durch Anpassung für Lebensstil- und soziodemografische Faktoren abgeschwächt, was darauf hindeutet, dass die Assoziationen nicht unabhängig voneinander waren [25].

Eine amerikanische Mutter-Kind-Kohortenstudie berichtete von einer Beziehung zwischen der Qualität mütterlicher Diät während des 3. Schwangerschaftstrimesters und dem Kindeswachstum 1 und 3 Monate postpartum sowie der Körperfettverteilung im Alter von 6 Monaten [26]. Eine höhere Qualität der mütterlichen Diät während der Schwangerschaft bis 3 Monate postpartum war mit niedrigeren kindlichen Werten für den Gewicht-für-Größe-Z-Score (standardisiertes Maß für Kindeswachstum) in den ersten 6 Lebensmonaten und einem geringeren Körperfettanteil im Alter von 6 Monaten assoziiert. Eine höhere Qualität der mütterlichen Diät in den ersten 3 Monaten nach der Geburt war ebenfalls mit einer geringeren kindlichen Fettmasse nach 6 Monaten assoziiert.

MESSGRÖSSE NAHRUNGSQUALITÄT

Die Qualität der mütterlichen Diät während der Schwangerschaft wurde mithilfe eines Score-Systems bemessen. Der Gesamtscore bildet sich aus der Summe von 13 untergeordneten Scores, der Adäquanz (Obst, Gemüse, Bohnen, Vollkornprodukte, Milchprodukte, Gesamtprotein, Meeresfrüchte, pflanzliches Protein und das Verhältnis von ungesättigten zu gesättigten Fettsäuren) und der Mäßigung (raffiniertes Getreide, Natrium, Zusatz von Zucker und gesättigten Fettsäuren).

Die Assoziation mütterlicher MD mit kindlichem BMI (2195 Mutter-Kind-Paare) und kardiometabolischen Risikofaktoren im Alter von 4 Jahren (697 Mutter-Kind-Paare) wurde bei einer spanischen Kohorte untersucht [27]. Ein höherer Score bei der MD war mit niedrigerem Risiko für hohe Geburtsgröße und darauffolgend beschleunigter Zunahme des BMI assoziiert (verglichen mit Kindern mit durchschnittlicher Geburtsgröße und langsamer Zunahme des BMI) [27]. Es lagen keine Assoziationen vor zwischen mütterlichem Score bei der MD und kardiometabolischen Risikofaktoren im Alter von 4 Jahren wie Blutdruck, Triglyzeride, HDL, Leptin, C-Peptid, Adiponektin und Entzündungsmarkern wie CRP und IL-6 (nach Anpassung für mütterliches Rauchen, Alter, Geschlecht, Energiezufuhr etc.). Dennoch wurden andere Variablen nicht analysiert, die das Risiko für Adipositas und kardiometabolische Risikofaktoren beim Kind beeinflussen könnten, wie z. B. mütterliche Bildung, Ernährung des Kindes und Dauer der Stillzeit [27].

Ähnliche Ergebnisse brachte eine Studie mit 997 US-amerikanischen und 569 griechischen Mutter-Kind-Paaren hervor [28]: Bei jeder Erhöhung des Scores für die MD um 3 Punkte verringerte sich bei dem Kind der BMI-Z-Score um 0,14 Einheiten (95 % KI, −0,15 bis −0,13), der Bauchumfang um 0,39 cm (95 % KI, −0,64 bis −0,14) und die Summe der Hautfaltendicken um 0,63 mm (95 % KI, −0,98 bis −0,28). Auch der kindliche systolische und diastolische Blutdruck war niedriger bei einem höheren mütterlichen Diät-Score [28].

Somit kamen die Studien zu dem einheitlichen Ergebnis, dass die Befolgung einer MD während der Schwangerschaft (möglicherweise begonnen vor oder im Frühstadium der Schwangerschaft) mit weniger Anzeichen für Adipositas im Vorschulalter assoziiert ist.

Merke

Trotz der limitierten Anzahl von Interventionsstudien kann man annehmen, dass eine mediterrane Diät während der Schwangerschaft protektive Effekte auf das Kind haben könnte.

Angeborene Fehlbildungen

Eine kürzlich erschienene Fall-Kontroll-Studie mit Chinesinnen, die zur Entbindung kamen (n = 474 mit angeborenen Herzfehlern und 948 Normalgeburten), zeigte, dass Schwangere im höchsten Tertil der „umsichtigen“ (auf English prudent) Ernährungsform ein niedrigeres Risiko für angeborene Herzfehler im Vergleich zu Schwangeren im niedrigsten Tertil (OR = 0,65, 95 % KI: 0,48–0,89) aufwiesen [29]. Schwangere mit hohen Scores bei der vegetarischen Ernährungsform hatten ein erhöhtes Risiko für angeborene Herzfehler (mittleres versus niedrigstes Tertil: adjustierte OR = 1,50, 95 % KI = 1,03–2,17; höchstes versus niedrigstes Tertil: OR = 1,56, 95 % KI = 1,13–2,15; p = 0,015) [29]. Schwangere mit hohen Scores für eine Ernährungsform reich an Milchprodukten und Eiern hatten ein niedriges Risiko für angeborene Herzfehler (mittleres versus niedrigstes Tertil: OR = 0,66, 95 % KI = 0,49–0,90; höchstes versus niedrigstes Tertil: OR = 0,60, 95 % KI = 0,43–0,82; p = 0,001). Jedoch unterschieden sich Fälle und Kontrollen in der Prävalenz von Folsäuresupplementation und anderen Lebensstilfaktoren [29]. Die gleiche Fragestellung wurde in der National Birth Defects Prevention Study untersucht, einer multizentrischen bevölkerungsbasierten Fall-Kontroll-Studie mit 9885 Müttern von Neugeborenen mit großen angeborenen Herzfehlern und 9468 Müttern von Kontrollkindern [5]. Die Qualität der mütterlichen Ernährung wurde mithilfe des Diet Quality Index for Pregnancy und dem Score für die MD beurteilt. Eine entgegengesetzte Assoziation zwischen höherer Qualität der Ernährung und dem Risiko für ausgewählte konotrunkale Fehlbildungen und Septumdefekte lag vor, wobei die entgegengesetzte Assoziation schwächer für die MD als für den Diet Quality Index for Pregnancy ausgeprägt war [5].

Fazit

Generell sind die Studien zur MD beständiger als die Studien zu vegetarischer oder veganer Ernährung in Bezug auf Richtung und Ausmaß der Zusammenhänge mit den Gesundheitsendpunkten. Die wenigen verfügbaren randomisierten kontrollierten Studien unterstützen die MD als mögliche Ernährungsform der Wahl für alle Frauen während der Schwangerschaft.

KERNAUSSAGEN

- Es liegen viele Hinweise dafür vor, dass die MD vor und während der Schwangerschaft einen positiven Effekt auf die Zeugung eines Kindes bei Frauen mit Infertilitätsproblemen haben könnte.
- Die Einhaltung einer MD wirkt möglicherweise protektiv gegen negative Schwangerschaftsausgänge wie Gestationsdiabetes, Präeklampsie, niedriges Geburtsgewicht und Frühgeburtlichkeit.
- Obwohl es sich bei der Mehrzahl der Studien zur MD um Observationsstudien handelt, sind die Studien einheitlich in Bezug auf Richtung und Ausmaß der Assoziationen.
- Die wenigen verfügbaren randomisierten kontrollierten Studien untermauern, dass die MD die Ernährungsform der Wahl vor und während der Schwangerschaft sein könnte.

Interessenkonflikt

Die Autoren geben an, dass keine Interessenkonflikte bestehen.

Über die Autoren

Arved Pannenbäcker

Arved Pannenbäcker wurde am 23.09.1995 in Malente in Schleswig-Holstein geboren. Nach dem Abitur begann er mit dem Medizinstudium an der Universität des Saarlandes in Homburg. Aktuell beschäftigt er sich im Rahmen seiner Doktorarbeit mit pflanzenbasierten Ernährungsformen und deren Auswirkung auf die Gesundheit der Mutter und des Kindes.

Rima Obeid

Prof. Dr. Rima Obeid studierte Pharmazie und promovierte im Bereich Labormedizin. Nach einem 2,5-jährigen Forschungsaufenthalt an der Universität Aarhus in Dänemark arbeitet und forscht sie seit 2017 am Universitätsklinikum des Saarlandes. Sie beschäftigt sich mit dem Einfluss von Nährstoffen auf den Stoffwechsel und diesbezüglichen Erkrankungen. Schwerpunkte sind Vitamine, Homocystein, epigenetische Veränderungen durch Ernährung, Wertigkeit von Biomarkern sowie deren Interpretation und prognostische Aussagen.

Korrespondenzadresse

Prof. (apl.) Dr. Rima Obeid
Universitätsklinikum des Saarlandes
Klinische Chemie und Laboratoriumsmedizin/Zentrallabor,
Gebäude 57
66421 Homburg/Saar
E-Mail: rima.obeid@uks.eu

Literatur

[1] Amati F, Hassounah S, Swaka A. The impact of Mediterranean dietary patterns during pregnancy on maternal and offspring health. Nutrients 2019; 11 (5): 1098. doi: 10.3390/nu11051098

[2] Gaskins AJ, Nassan FL, Chiu YH et al. Dietary patterns and outcomes of assisted reproduction. Am J Obstet Gynecol 2019; 220: 567

[3] Karayiannis D, Kontogianni MD, Mendorou C et al. Adherence to the Mediterranean diet and IVF success rate among non-obese women attempting fertility. Hum Reprod 2018; 33: 494–502

[4] Parisi F, Rousian M, Huijgen NA et al. Periconceptional maternal ‘high fish and olive oil, low meat’ dietary pattern is associated with increased embryonic growth: The Rotterdam Periconceptional Cohort (Predict) Study. Ultrasound Obstet Gynecol 2017; 50: 709–716

[5] Botto LD, Krikov S, Carmichael SL et al. Lower rate of selected congenital heart defects with better maternal diet quality: a population-based study. Arch Dis Child Fetal Neonatal Ed 2016; 101: F43–F49

[6] Parisi F, Rousian M, Koning IV et al. Periconceptional maternal dairy-rich dietary pattern is associated with prenatal cerebellar growth. PLoS ONE 2018; 13: e0197901

[7] Assaf-Balut C, Garcia dlT, Duran A et al. A Mediterranean diet with additional extra virgin olive oil and pistachios reduces the incidence of gestational diabetes mellitus (GDM): A randomized controlled trial: The St. Carlos GDM prevention study. PLoS ONE 2017; 12: e0185873

[8] House JS, Mendez M, Maguire RL et al. Periconceptional maternal Mediterranean diet is associated with favorable offspring behaviors and altered CpG methylation of imprinted genes. Front Cell Dev Biol 2018; 6: 107

[9] Izadi V, Tehrani H, Haghighatdoost F et al. Adherence to the DASH and Mediterranean diets is associated with decreased risk for gestational diabetes mellitus. Nutrition 2016; 32: 1092–1096

[10] Tobias DK, Zhang C, Chavarro J et al. Prepregnancy adherence to dietary patterns and lower risk of gestational diabetes mellitus. Am J Clin Nutr 2012; 96: 289–295

[11] Zhang C, Tobias DK, Chavarro JE et al. Adherence to healthy lifestyle and risk of gestational diabetes mellitus: prospective cohort study. Br Med J 2014; 349: g5450

[12] Assaf-Balut C, Garcia dlT, Duran A et al. Medical nutrition therapy for gestational diabetes mellitus based on Mediterranean Diet principles: a subanalysis of the St Carlos GDM Prevention Study. BMJ Open Diabetes Res Care 2018; 6: e000550

[13] Assaf-Balut C, Garcia dlT, Duran A et al. A Mediterranean diet with an enhanced consumption of extra virgin olive oil and pistachios improves pregnancy outcomes in women without gestational diabetes mellitus: A sub-analysis of the St. Carlos Gestational Diabetes Mellitus Prevention Study. Ann Nutr Metab 2019; 74: 69–79

[14] Assaf-Balut C, Garcia dlT, Duran A et al. An early, universal Mediterranean diet-based intervention in pregnancy reduces cardiovascular risk factors in the “fourth trimester”. J Clin Med 2019; 8: 1499

[15] Mijatovic-Vukas J, Capling L, Cheng S et al. Associations of diet and physical activity with risk for gestational diabetes mellitus: A systematic review and meta-analysis. Nutrients 2018; 10: 698. doi: 10.3390/nu10060698

[16] Lindsay KL, Buss C, Wadhwa PD, Entringer S. The effect of a maternal Mediterranean diet in pregnancy on insulin resistance is moderated by maternal negative affect. Nutrients 2020; 12: 420

[17] de la Garza PA, Marti AA, Chisaguano AM et al. The effect of maternal obesity on breast milk fatty acids and its association with infant growth and cognition – the PREOBE follow-up. Nutrients 2019; 11: 2154

[18] Mak JKL, Pham NM, Lee AH et al. Dietary patterns during pregnancy and risk of gestational diabetes: a prospective cohort study in Western China. Nutr J 2018; 17: 107

[19] Lawrence RL, Wall CR, Bloomfield FH. Dietary Patterns and Dietary Adaptations in Women with and without Gestational Diabetes: Evidence from the Growing Up in New Zealand Study. Nutrients 2020; 12. doi: 10.3390/nu12010227

[20] Schoenaker DA, Soedamah-Muthu SS, Callaway LK, Mishra GD. Pre-pregnancy dietary patterns and risk of gestational diabetes mellitus: results from an Australian population-based prospective cohort study. Diabetologia 2015; 58: 2726–2735

[21] Tieu J, Shepherd E, Middleton P, Crowther CA. Dietary advice interventions in pregnancy for preventing gestational diabetes mellitus. Cochrane Database Syst Rev 2017; 1: CD006674

[22] Parlapani E, Agakidis C, Karagiozoglou-Lampoudi T et al. The Mediterranean diet adherence by pregnant women delivering prematurely: association with size at birth and complications of prematurity. J Matern Fetal Neonatal Med 2019; 32: 1084–1091

[23] Biagi C, Nunzio MD, Bordoni A et al. Effect of adherence to Mediterranean diet during pregnancy on children’s health: A systematic review. Nutrients 2019; 11: 997. doi: 10.3390/nu11050997

[24] Hu Z, Tylavsky FA, Kocak M et al. Effects of maternal dietary patterns during pregnancy on early childhood growth trajectories and obesity risk: The CANDLE Study. Nutrients 2020; 12: 465

[25] van den Broek M, Leermakers ET, Jaddoe VW et al. Maternal dietary patterns during pregnancy and body composition of the child at age 6 y: the Generation R Study. Am J Clin Nutr 2015; 102: 873–880

[26] Tahir MJ, Haapala JL, Foster LP et al. Higher maternal diet quality during pregnancy and lactation is associated with lower infant weight-for-length, body fat percent, and fat mass in early postnatal life. Nutrients 2019; 11: 632. doi: 10.3390/nu11030632

[27] Buckland G, Gonzalez CA, Agudo A et al. Adherence to the Mediterranean diet and risk of coronary heart disease in the Spanish EPIC Cohort Study. Am J Epidemiol 2009; 170: 1518–1529

[28] Chatzi L, Rifas-Shiman SL, Georgiou V et al. Adherence to the Mediterranean diet during pregnancy and offspring adiposity and cardiometabolic traits in childhood. Pediatr Obes 2017; 12 (Suppl 1): 47–56

[29] Yang J, Kang Y, Cheng Y et al. Maternal dietary patterns during pregnancy and congenital heart defects: A case-control study. Int J Environ Res Public Health 2019; 16: 2957. doi: 10.3390/ijerph16162957

Bibliografie

DOI https://doi.org/10.1055/a-1164-1777
Ernährung & Medizin 2020; 35: 61–67

ISSN 1439-1635

Sicherheit der pflanzenbasierten Ernährungsformen in der Schwangerschaft für Mutter und Kind

Bewertung der aktuellen Evidenzlage

Rima Obeid, Arved Pannenbäcker

Die Sicherheit einer mütterlichen streng veganen Diät während der Schwangerschaft wird oft infrage gestellt, insbesondere in Anbetracht ihres Mangels an essenziellen Nährstoffen wie Eisen und Vitamin B_{12}. Studienergebnisse hierzu sind widersprüchlich – nicht zuletzt aufgrund der Vielfalt an vegetarischen oder veganen Ernährungsformen und der geringen Zahl kontrollierter Studien.

Gesund oder Gefahr für Mangelernährung? Schwangere, die sich vegetarisch oder vegan ernähren, benötigen eine Ernährungsberatung. Quelle: Kirsten Oborny, Thieme Gruppe

Hintergrund

Das Interesse an vegetarischer und veganer Ernährung wächst weltweit, insbesondere bei jungen Menschen [1] [2]. In einer repräsentativen Umfrage der National Health and Nutrition Examination Survey (NHANES) aus den Jahren 1999–2004 gaben 7,5 % der amerikanischen Frauen an, sich vegetarisch zu ernähren [3]. Laut der SKOPOS-Marktforschung leben 1,3 Millionen Deutsche vegan. Der typische Veganer ist demnach weiblich, Ende 20 bzw. Anfang 30 und befindet sich im Übergang vom Studium zum Beruf. Er lebt mit einem Lebenspartner zusammen, der ebenfalls Veganer ist (https://www.skopos-group.de/news/13-millionen-deutsche-leben-vegan.html). Die Zahl der Vegetarier in Deutschland wird auf 6–8 Millionen geschätzt. Die Studie zur Gesundheit Erwachsener in Deutschland (DEGS 1) bei 6933 deutschen Teilnehmern zeigte, dass 6,1 % der Frauen und 2,5 % der Männer im Alter von 18–79 Jahren sich vegetarisch ernähren [1]. Mit zunehmender Bildung ernährt sich ein höherer Anteil von Personen üblicherweise vegetarisch [1]. Gleiches gilt für

▶**Tab. 1** Ernährungsweisen wie üblicherweise in medizinischer Literatur beschrieben.

Ernährungsweise	**Enthaltene Lebensmittel**	**Ausgeschlossene Lebensmittel**
vegan	Gemüse, Obst, Getreide	Fleisch, Fisch, Milchprodukte, Eier, jegliche tierische Produkte
Lacto-Ovo-Vegetarismus (LOV)	Milchprodukte, Eier, jegliche pflanzliche Produkte	Fleisch, Fisch
Lacto-Vegetarismus (LV)	Milchprodukte, jegliche pflanzliche Produkte	Eier, Fleisch, Fisch
Ovo-Vegetarismus (OV)	Eier, jegliche pflanzliche Produkte	Milchprodukte, Fleisch, Fisch
Rohkost („Raw food diet“)	Gemüse, Getreide, Hülsenfrüchte, frisches und getrocknetes Obst, Samen, Milch und Eier, Nahrungsmittel werden roh verzehrt	Unterformen, die auf verschiedene tierische Produkte verzichten
Obst-Diät	lediglich frisches und getrocknetes Obst, Samen und einige Gemüsesorten	
makrobiotische Diät	Getreide, Hülsenfrüchte, Gemüse, Meeresalgen, Sojaprodukte, Fisch	Milchprodukte, Eier einige Gemüsesorten
mediterrane Diät	Olivenöl, wenig Fleisch, viel Obst und Gemüse, Fisch	

Personen, die in Großstädten leben, und für Menschen, die mehr als 4 Stunden pro Woche Sport treiben. Der Anteil an Frauen im Alter von 18–29 Jahren, die sich vegetarisch ernähren, war 73 % (CI 95 %: 57–84 %) höher als in der Altersgruppe 70–79 Jahre [1]. Frauen und Männer, die sich üblicherweise vegetarisch ernähren, konsumieren im Vergleich zu Nicht-Vegetarierinnen und -Vegetariern nicht nur signifikant weniger Fleisch und Wurst, sondern auch weniger kalorienreduzierte Getränke, Bier und Wein sowie mehr Milchprodukte, Tee, Obst und Gemüse [1].

Es existieren zahlreiche pflanzenbasierte Ernährungsformen mit unterschiedlicher Zusammensetzung (▶**Tab. 1**) [4][5]. Die Gründe für den Verzicht auf tierische Produkte sind ethischer, kultureller und religiöser Natur. Während der Vegetarismus unter jungen Menschen in westlichen Ländern mit höherer Bildung assoziiert ist, steht er in den asiatischen Ländern in Verbindung mit einem niedrigeren sozioökonomischen Status, da tierische Produkte teurer sind. Maßgebliche geografische Unterschiede in der Zusammensetzung der vegetarischen Ernährung wurden berichtet. Europäische und nordamerikanische Vegetarier befolgen eher einen Lacto-Ovo-Vegetarismus (LOV) [6], während indische Vegetarier größtenteils Lacto-Vegetarier sind [7]. In China wiederum konsumieren die Vegetarier wenig Milchprodukte [8].

Merke

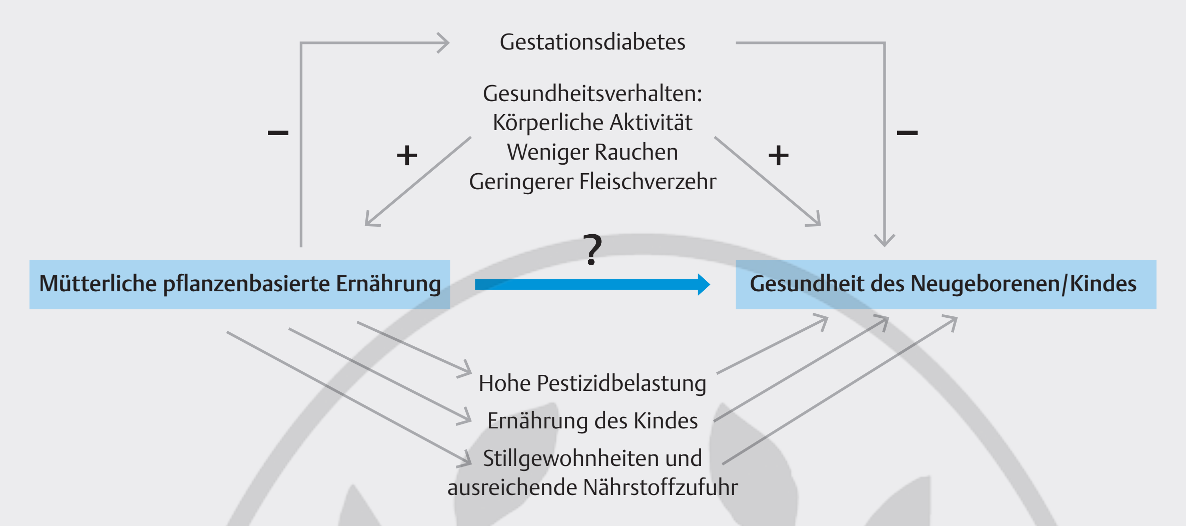
Es gibt zahlreiche Varianten einer fleischlosen Ernährungsform, weshalb Studien bezüglich der Nährstoffe nicht so einfach miteinander verglichen werden können.

Eine vegetarische Ernährung ist mit einer niedrigeren Prävalenz von Risikofaktoren für kardiovaskuläre Erkrankungen wie Hyperlipidämie [9], Bluthochdruck [10] und Adipositas [11] assoziiert. Eine vegetarische Lebensweise könnte im Vergleich mit einer omnivoren Ernährung einen protektiven Effekt gegenüber einigen Krebserkrankungen und Diabetes Typ 2 aufweisen. Das Lebenszeitrisiko für ischämische Herzerkrankungen war bei männlichen Vegetariern verglichen mit Nicht-Vegetariern um 37 % niedriger [12]. Kolon- und Prostatakarzinome lagen signifikant häufiger bei Nicht-Vegetariern vor [Relatives Risiko (RR) von jeweils 1,88 und 1,54]. Dies könnte durch den niedrigeren Verzehr von Fleisch und/oder den höheren Verzehr von Ballaststoffen begründet sein. Es bleibt jedoch offen, ob die Assoziationen zwischen Vegetarismus und niedrigerem Risiko für bestimmte Erkrankungen kausal sind. Möglicherweise erklären andere Lebensstilfaktoren den schützenden Effekt eines vegetarischen Lebensstils.

Merke

Aufgrund möglicher anderer beeinflussender Faktoren ist die Kausalität von Studienergebnissen bezüglich einer vegetarischen Ernährung und niedrigerem Erkrankungsrisiko nicht eindeutig gegeben.

Somit können Einflussfaktoren wie Herkunftsland, Gründe für die Ernährungsform und begleitende Lebensstilfaktoren, die nicht direkt Teil der Ernährung sind, die Interpretationen der epidemiologischen Studien stark beeinflussen. Ein weiterer Einflussfaktor ist die Tatsache, dass pflanzenbasierte Ernährungsformen im Allgemeinen eher von Nichtrauchern und körperlich aktiveren Menschen praktiziert werden und somit mit einem insgesamt gesünderen Lebensstil assoziiert sind. Die Assoziation zwischen Vegetarismus und Gesundheit kann theoretisch durch den geringeren Verzehr von Fleisch, große Mengen an Obst und Gemüse und begleitende Verhaltensweisen erklärt werden. Auf diese Weise kann das mit der vegetarischen Ernährung einhergehende Verhalten eine verzerrte Assoziation zwischen Ernährung und Gesundheit verursachen (▶**Abb. 1**). Einen weiteren Faktor stellen die Rückstände von Pestiziden in Obst und Gemüse dar, da sie die protektive Wirkung von beispielsweise Antioxidanzien abschwächen oder aufheben könnten [13].



▶ **Abb. 1** Konzeptualisierung der Mediatoren und Verzerrfaktoren im Zusammenhang zwischen einer pflanzlichen Ernährung der Mutter und der Gesundheit des Kindes. Die traditionelle Denkweise, dass die mütterliche pflanzenbasierte Ernährung als Modifikator der kindlichen Gesundheit agiert, sollte auch weitere „diätische und nichtdiätische Faktoren" beachten. Die Ernährung des Kindes im Vorschulalter korreliert stark mit der mütterlichen Ernährung (sofern diese im selben Haushalt leben) und ist durch diese vorhersagbar. Somit kann beispielsweise das mütterliche Gesundheitsverhalten eine Assoziation zwischen der pflanzlichen Ernährung der Mutter und der Gesundheit/Krankheitsrisiko des Kindes hervorrufen oder verstärken. Ein geringeres Risiko für Schwangerschaftsdiabetes, Stillen und kindliche Ernährung sind wichtige Mediatoren in dieser Assoziation. Hohe Pestizidanteile in der pflanzenbasierten Ernährung könnten hingegen jeglichen positiven Effekten entgegenwirken.

Merke

Die Quantifizierung des Zusammenhangs zwischen Vegetarismus und gesundheitlichen Gesichtspunkten unterliegt der starken Heterogenität der Essgewohnheiten der Vegetarier.

Pflanzenbasierte Ernährung vor und während der Schwangerschaft

Die Sicherheit einer pflanzenbasierten Ernährung für Frauen im gebärfähigen Alter wurde aufgrund vieler Fallberichte von Neugeborenen und Kindern (insbesondere im 1. Lebensjahr) mit schweren und teilweise irreversiblen neurologischen Störungen aufgrund eines Vitamin-B_{12}-Mangels infrage gestellt [14][15][16]. Einige Wissenschaftler argumentieren, dass eine gut geplante vegane oder vegetarische Ernährung während der Schwangerschaft und Stillzeit als geeignet betrachtet werden kann, falls die Nährstoffmängel durch gezielte Supplementierung vermieden werden können. Jedoch ist die Evidenzlage, die diese Aussage stützt, fraglich aufgrund vieler interferierender (diätischer und nichtdiätischer) Faktoren (▶ **Abb. 1**), die in den vorhandenen Studien nicht berücksichtigt wurden. Einen wichtigen Grund zur Besorgnis stellt die pflanzliche Ernährung über mehrere Generationen dar. Diese könnte zur Depletion essenzieller Nährstoffe beim Fetus führen und das Imprinting von Genen verändern. Die mütterliche Ernährung sollte nicht als alleinstehender Faktor betrachtet werden, der die Gesundheit des Kindes modifizieren kann.

Einige Studien zeigten positive gesundheitliche Auswirkungen für Mutter und Kind, wenn die Mütter Nahrungsmittel wie Obst und Gemüse, die in einer pflanzenbasierten Ernährung vermehrt vorkommen, zu sich nahmen. Das klärt jedoch nicht die Frage der Assoziation zwischen einer rein pflanzlichen Ernährung und Gesundheit. Eine japanische Mutter-Kind-Kohortenstudie kam zu dem Ergebnis, dass eine mütterliche Ernährung, die reich an Gemüse, Obst und Antioxidanzien ist, mit einem niedrigeren Risiko für verschiedene Verhaltensstörungen der Kinder im Alter von 5 Jahren (z. B. Hyperaktivität und emotionale Probleme) assoziiert war [17]. Die Ergebnisse wurden für die Einflussfaktoren wie Alter der Mutter, sozioökonomischer Status, Geburtsgewicht, Geschlecht des Kindes und Stillen korrigiert [17].

Vorsicht

Der positive Einfluss einer vermehrten Zufuhr von Obst und Gemüse auf die Gesundheit darf nicht auf eine rein pflanzliche Ernährung extrapoliert werden.

Die Unbedenklichkeit einer mütterlichen vegetarischen Ernährung während der Schwangerschaft in Bezug auf die Gesundheit von Mutter und Fetus wurde in einem kürzlich erschienenen (2019) systematischen Review und einer Metaanalyse von 19 Studien untersucht [18]. Schwangerschaften von Vegetarierinnen zeigten eine Tendenz zu einer Assoziation mit niedrigem Geburtsgewicht [Odds Ratio (OR) = 1,27 (0,98, 1,65), P = 0,07]. Diese Assoziation war signifikant bei asiatischen Frauen [1,33 (1,01, 1,76), P = 0,04]. Jedoch zeigte die Differenz der Mittelwerte des

▶ **Tab. 2** Mechanismen von Störungen der Entwicklung des Nervensystems bei Kindern mit Vitamin-B_{12}-Mangel.

Veränderungen/Symptome	**Für die Hirnfunktion relevante Mechanismen**
reduziertes Methylierungspotenzial (z. B. S-Adenosylmethionin)	epigenetische Modifikationen (DNA- und Histonmethylierung) Hypomethylierung spezifischer Positionen des Myelins
Hyperhomocysteinämie	Homocystein ist neurotoxisch
erhöhte Zytokine und Wachstumsfaktoren	verursachen Unausgeglichenheit zwischen Tumornekrosefaktor-alpha (TNF-α) und Epidermal Growth Factor. TNF-α wirkt als Neurotoxin bei demyelinisierenden ZNS-Erkrankungen
Akkumulation neurotoxischer Metabolite bei Vitamin-B_{12}-Mangel	Laktat reichert sich im Gehirn an, Störungen des oxidativen Energiestoffwechsels des Gehirns
Veränderungen des Energiestoffwechsels des Gehirns	Reduktion von N-Acetylaspartat, Kreatin, Myo-Inositol, Glutamat und Glutamin in weißer und grauer Substanz des Gehirns
Diarrhö	dadurch Malabsorption weiterer Nährstoffe
Veränderung der Aminosäuren im Plasma	erniedrigtes Methionin
Fütterungsprobleme und wenig Appetit	verursacht verminderte Aufnahme weiterer, für Wachstum und Entwicklung essenzieller Nährstoffe wie Eisen, Folat und anderer Spurenelemente

Geburtsgewichts in 5 Studien keinen Unterschied zwischen Vegetariern und Omnivoren [18]. Aufgrund der Heterogenität der identifizierten Studien war eine Schlussfolgerung bezüglich des Risikos für Hypospadie, intrauterine Wachstumsretardierung, mütterliche Anämie und Gestationsdiabetes nicht möglich [18].

In einem vorherigen systematischen Review (2015) wurden 22 relevante Publikationen identifiziert [18]; 13 davon berichteten von mütterlichen/fetalen Outcomes und 9 berichteten von Nährstoffmängeln in der Ernährung [19]. Bis auf einen Bericht von vermehrtem Auftreten von Hypospadie bei Säuglingen vegetarischer Mütter erwähnte keine der Studien eine erhöhte Anzahl von schwerwiegenden Outcomes oder größeren Fehlbildungen. Fünf Studien berichteten von niedrigerem Geburtsgewicht bei vegetarischen Müttern, während in 2 Studien die Kinder vegetarischer Mütter ein höheres Geburtsgewicht aufwiesen [19].

Merke

Die 9 heterogenen Studien zu Spurenelementen und Vitaminen weisen darauf hin, dass vegane oder vegetarische Frauen einem höheren Risiko für Vitamin-B_{12}- und Eisenmangel ausgesetzt sind [19].

Mechanismen

Mütterliche Mangelernährung könnte das kindliche Wachstum durch die Veränderung des Plazentagewichts und den Nährstofftransport von der Mutter zum Fetus beeinträchtigen. Eine pflanzenbasierte Ernährung (der Mutter oder des Kindes) ist mit einem Mangel an Nährstoffen wie Proteinen, Eisen, Vitamin D, Kalzium, Iod, Omega-3-Fettsäuren, Cholin und Vitamin B_{12} assoziiert [4].

Merke

Mütterlicher Vitamin-B_{12}-Mangel verursacht eine Hyperhomocysteinämie und DNA-Hyper- oder -Hypomethylierungen.

Die DNA-Hyper- oder -Hypomethylierungen können zu einer Veränderung der Zellprogrammierung in utero und somit zu Langzeiteffekten auf die Gesundheit des Kindes führen. Die Hyperhomocysteinämie bei Schwangeren ist ein unabhängiger Risikofaktor für Geburtsfehler [20] und Schwangerschaftskomplikationen wie Präeklampsie. Erhöhte Plasmakonzentrationen von Homocystein und Methylmalonsäure (beide sind bei Vitamin-B_{12}-Mangel erhöht) finden sich häufig bei Veganern und Vegetariern [6][7]. Vitamin-B_{12}-Mangel während der Schwangerschaft kann neurologische Störungen und Störungen der Entwicklung des Nervensystems durch verschiedene Mechanismen (▶ **Tab. 2**) verursachen. Erhöhtes Homocystein und erniedrigtes Vitamin B_{12} im Plasma von schwangeren Frauen zeigten Assoziationen mit einem limitierten fetalen Wachstum in den ersten 11 Schwangerschaftswochen [21]. Weitere Studien berichteten von zahlreichen Komponenten vegetarischer und veganer Ernährung (z. B. Brokkoli, Soja, grüner Tee), Fisch und Ei als Modifikatoren epigenetischer Ereignisse bei pränataler Verabreichung [22].

Eine Hypomethylierungsdiät während der Gravidität kann den Phänotyp der Nachkommen sowie die Anfälligkeit für Krankheiten durch Gen-Silencing oder -aktivierung beeinflussen. Ein gutes Beispiel für diesen Mechanismus sind die gelben Agouti-Mäuse, die eine Genmutation (/Avy/a) tragen. Agouti-Mäuse sind im fortgeschrittenen Alter anfällig für Adipositas und Diabetes. Wird einer weiblichen Maus 2 Wochen vor der Paarung und während Gravidität und Laktation Nahrung angereichert mit Methylgruppendonatoren und Kofaktoren (Folsäure, Vitamin B_{12}, Cholin und

Betain) verabreicht, weisen die Nachkommen eine dunkle Fellfarbe auf und haben eine geringere Neigung zu Adipositas und Diabetes im fortgeschrittenen Alter [23][24]. Die Methylierungsdiät hat bei Verabreichung erst nach der Geburt keinen Effekt auf die Fellfarbe oder das Auftreten von Diabetes bei den Mäusen. Dies impliziert, dass ein Silencing des Agouti-Gens in utero von methylierungsabhängigen epigenetischen Mechanismen erfolgt.

Zusammengefasst lässt sich festhalten, dass sich die Evidenzlage zu möglichem Nutzen einer vegetarischen Ernährung während der Schwangerschaft als schwach darstellt. Ein Hauptfaktor, der die Evidenzlage in diesem Feld limitiert, ist das Fehlen von randomisierten kontrollierten Studien, die den Effekt der Charaktereigenschaften, die die Menschen zu einem bestimmten Lebensstil bewegen, reduziert. Im Gegensatz dazu steht eine Vielzahl von Publikationen über Fallbeispiele von Kindern von Veganern. Sie berichten über neurologische und hämatologische Symptome, die zum Teil langfristige Gesundheitsschäden verursachen können.

KERNAUSSAGEN

- Die mütterliche Ernährung ist eine von vielen Komponenten, die die Gesundheit des Kindes beeinflussen könnte.
- Vegane oder vegetarische Ernährungsformen stehen oft im Zusammenhang mit Lebensgewohnheiten, wie z. B. Rauchen oder körperliche Aktivität, die wiederum selbst Auswirkungen auf die Gesundheit des Kindes haben könnten.
- Es existieren zahlreiche Fallberichte von ausschließlich gestillten Kindern, deren vegane Mütter einen Vitamin-B_{12}-Mangel aufwiesen. Die Kinder entwickelten Anämien oder neurologische Störungen.
- Die Qualität der Studienlage zu möglichen Vor- und Nachteilen einer vegetarischen Ernährung während der Schwangerschaft ist niedrig aufgrund der Heterogenität vegetarischer Ernährungsformen und den geografischen Unterschieden in den Studienpopulationen.
- Die widersprüchlichen Daten von Beobachtungsstudien und der Mangel an randomisierten kontrollierten Studien schwächt die Evidenzlage zur Empfehlung einer vegetarischen Ernährungsform für schwangere Frauen.

Interessenkonflikt

Die Autoren geben an, dass keine Interessenkonflikte bestehen.

Über die Autoren

Prof. Rima Obeid

Prof. Dr. Rima Obeid studierte Pharmazie und promovierte im Bereich Labormedizin. Nach einem 2,5-jährigen Forschungsaufenthalt an der Universität Aarhus in Dänemark arbeitet und forscht sie seit 2017 am Universitätsklinikum des Saarlandes. Sie beschäftigt sich mit dem Einfluss von Nährstoffen auf den Stoffwechsel und diesbezüglichen Erkrankungen. Schwerpunkte sind Vitamine, Homocystein, epigenetische Veränderungen durch Ernährung, Wertigkeit von Biomarkern sowie deren Interpretation und prognostische Aussagen.

Arved Pannenbäcker

Arved Pannenbäcker wurde am 23.09.1995 in Malente in Schleswig-Holstein geboren. Nach dem Abitur begann er mit dem Medizinstudium an der Universität des Saarlandes in Homburg. Aktuell beschäftigt er sich im Rahmen seiner Doktorarbeit mit pflanzenbasierten Ernährungsformen und deren Auswirkung auf die Gesundheit der Mutter und des Kindes.

Korrespondenzadresse

Prof. Dr. Rima Obeid
Universitätsklinikum des Saarlandes
Klinische Chemie und Laboratoriumsmedizin/Zentrallabor,
Gebäude 57
66421 Homburg/Saar
E-Mail: rima.obeid@uks.eu

Literatur

[1] Mensink GB, Lage Barbosa C, Brettschneider A. Verbreitung der vegetarischen Ernährungsweise in Deutschland. J Health Monitoring 2016; 1: 2–15

[2] Vergeer L, Vanderlee L, White CM et al. Vegetarianism and other eating practices among youth and young adults in major Canadian cities. Public Health Nutr 2020; 23: 609–619

[3] Farmer B, Larson BT, Fulgoni VL et al. A vegetarian dietary pattern as a nutrient-dense approach to weight management: an analysis of the national health and nutrition examination survey 1999–2004. J Am Diet Assoc 2011; 111: 819–827

[4] Sebastiani G, Herranz BA, Borras-Novell C et al. The effects of vegetarian and vegan diet during pregnancy on the health of mothers and offspring. Nutrients 2019; 11: 557. doi: 10.3390/nu11030557

[5] Trichopoulou A, Costacou T, Bamia C, Trichopoulos D. Adherence to a Mediterranean diet and survival in a Greek population. N Engl J Med 2003; 348: 2599–2608

[6] Gallego-Narbon A, Zapatera B, Barrios L, Vaquero MP. Vitamin B_{12} and folate status in Spanish lacto-ovo vegetarians and vegans. J Nutr Sci 2019; 8: e7

[7] Herrmann W, Schorr H, Obeid R, Geisel J. Vitamin B_{12} status, particularly holotranscobalamin II and methylmalonic acid concentrations, and hyperhomocysteinemia in vegetarians. Am J Clin Nutr 2003; 78: 131–136

[8] Lee HY, Woo J, Chen ZY et al. Serum fatty acid, lipid profile and dietary intake of Hong Kong Chinese omnivores and vegetarians. Eur J Clin Nutr 2000; 54: 768–773

[9] Wang F, Zheng J, Yang B et al. Effects of vegetarian diets on blood lipids: A systematic review and meta-analysis of randomized controlled trials. J Am Heart Assoc 2015; 4: e002408

[10] Berkow SE, Barnard ND. Blood pressure regulation and vegetarian diets. Nutr Rev 2005; 63: 1–8

[11] Rosell M, Appleby P, Spencer E, Key T. Weight gain over 5 years in 21,966 meat-eating, fish-eating, vegetarian, and vegan men and women in EPIC-Oxford. Int J Obes (Lond) 2006; 30: 1389–1396

[12] Fraser GE. Associations between diet and cancer, ischemic heart disease, and all-cause mortality in non-Hispanic white California Seventh-day Adventists. Am J Clin Nutr 1999; 70: 532S–538S

[13] Miyake Y, Tanaka K, Okubo H et al. Maternal consumption of vegetables, fruit, and antioxidants during pregnancy and risk for childhood behavioral problems. Nutrition 2020; 69: 110572

[14] Codazzi D, Sala F, Parini R, Langer M. Coma and respiratory failure in a child with severe vitamin B(12) deficiency. Pediatr Crit Care Med 2005; 6: 483–485

[15] Kocaoglu C, Akin F, Caksen H et al. Cerebral atrophy in a vitamin B_{12}-deficient infant of a vegetarian mother. J Health Popul Nutr 2014; 32: 367–371

[16] Weiss R, Fogelman Y, Bennett M. Severe vitamin B_{12} deficiency in an infant associated with a maternal deficiency and a strict vegetarian diet. J Pediatr Hematol Oncol 2004; 26: 270–271

[17] Miyake Y, Tanaka K, Okubo H et al. Maternal consumption of vegetables, fruit, and antioxidants during pregnancy and risk for childhood behavioral problems. Nutrition 2020; 69: 110572

[18] Tan C, Zhao Y, Wang S. Is a vegetarian diet safe to follow during pregnancy? A systematic review and meta-analysis of observational studies. Crit Rev Food Sci Nutr 2019; 59: 2586–2596

[19] Piccoli GB, Clari R, Vigotti FN et al. Vegan-vegetarian diets in pregnancy: danger or panacea? A systematic narrative review. Br J Obstet Gynaecol 2015; 122: 623–633

[20] Blom HJ, Smulders Y. Overview of homocysteine and folate metabolism. With special references to cardiovascular disease and neural tube defects. J Inherit Metab Dis 2011; 34: 75–81

[21] Parisi F, Rousian M, Koning AH et al. Periconceptional maternal biomarkers of one-carbon metabolism and embryonic growth trajectories: the Rotterdam Periconceptional Cohort (Predict Study). Fertil Steril 2017; 107: 691–698

[22] Li S, Chen M, Li Y, Tollefsbol TO. Prenatal epigenetics diets play protective roles against environmental pollution. Clin Epigenetics 2019; 11: 82

[23] Warzak DA, Johnson SA, Ellersieck MR et al. Effects of post-weaning diet on metabolic parameters and DNA methylation status of the cryptic promoter in the A(vy) allele of viable yellow mice. J Nutr Biochem 2015; 26: 667–674

[24] Waterland RA, Jirtle RL. Early nutrition, epigenetic changes at transposons and imprinted genes, and enhanced susceptibility to adult chronic diseases. Nutrition 2004; 20: 63–68

Bibliografie

DOI https://doi.org/10.1055/a-1164-1745
Ernährung & Medizin 2020; 35: 55–60

ISSN 1439-1635