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Abstract

Effects of maternal diet during pregnancy on birth weight of the infant

In Western countries the diet of the mother during pregnancy has little impact on the birth weight of the child. In this part of the World, in general, no real nutritional deficiencies exist. Therefore, there is no reason as yet to adapt dietary guidelines for pregnant women. This is concluded from a literature review of the results from research on the relation between diet and birth weight in humans and animals. This review has been carried out by RIVM and was commissioned by the Ministry of VWS.

Small effects on birth weight are seen in relation to the intake of protein, folate, excessive alcohol and caffeine during pregnancy. Both high and low protein intake lower birth weight. Excessive intake of alcohol (more than two to three glasses per day) and caffeine (more than three cups of coffee per day) also lower birth weight. The higher the folate intake, the higher the birth weight. The differences in birth weight vary between 50 and 200 grams.

Birth weight is an important predictor for body weight at later ages. Both a low ('under 2500 grams') and a high (above 4000 grams) birth weight increase the risk of overweight. Thus already during pregnancy the mother may contribute to the prevention of overweight in her offspring.

Diet during pregnancy may have effects on the health of the child that become apparent later in life. Little is known on this subject. Therefore more research is needed, investigating the relation of the diet of the mother during pregnancy with overweight and chronic diseases later in the child's life.

Key words:

birth weight, pregnancy, maternal diet, programming, obesity

Rapport in het kort

Het effect van de voeding van zwangere vrouwen op het geboortegewicht van hun kinderen

In het westen heeft de voeding van de moeder tijdens de zwangerschap weinig effect op het geboortegewicht van het kind. In dit deel van de wereld bestaan namelijk over het algemeen geen echte tekorten aan voedingsstoffen. Er is daarom vooralsnog geen reden de voedingsrichtlijnen voor zwangere vrouwen aan te passen. Dit blijkt uit een literatuuronderzoek van het RIVM in opdracht van het ministerie van VWS. Hierin zijn de resultaten van onderzoek naar de relatie tussen voeding en geboortegewicht bij mensen en dieren op een rij gezet.

Geringe effecten zijn te zien bij de inname van eiwit, foliumzuur, overmatig alcohol en cafeïne tijdens de zwangerschap. Zowel te veel als te weinig eiwit verlaagt het geboortegewicht. Overmatig gebruik van alcohol (meer dan twee tot drie glazen per dag) en cafeïne (meer dan drie kopjes koffie per dag) verlagen ook het geboortegewicht. Voor foliumzuur geldt: hoe hoger de inname, hoe hoger het geboortegewicht. De verschillen in geboortegewicht variëren tussen 50 en 200 gram.

Geboortegewicht is een belangrijke voorspeller van het gewicht op latere leeftijd. Zowel een laag (onder 2500 gram) als een hoog geboortegewicht (boven 4000 gram) verhoogt het risico op overgewicht. Al tijdens de zwangerschap kan de moeder er dus aan bijdragen dat overgewicht bij haar kinderen wordt voorkomen.

De voeding tijdens de zwangerschap heeft mogelijk effecten op de gezondheid van het kind die pas later in het leven zichtbaar worden. Hierover is nog weinig bekend. Daarom is meer onderzoek nodig naar de relatie tussen voeding van de moeder tijdens de zwangerschap en overgewicht en chronische ziekten in het latere leven van het kind.

Trefwoorden:

geboortegewicht, zwangerschap, voeding, programmering, obesitas

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Summary

According to the thrifty phenotype hypothesis (also known as the Barker hypothesis), exposure to either excess or poor nutrition *in utero* can lead to an adaptation of foetal metabolism and can program susceptibility of the foetus to development of obesity, cardiovascular disease, hypertension, diabetes and cancer later in life. Part of this association might be through effects on birth weight. There are indications that maternal nutritional habits during pregnancy influence birth weight, whereas a large number of epidemiological studies has demonstrated a direct relationship between birth weight and adult adiposity. Overweight and obesity are major health problems. It has been demonstrated that overweight and obese individuals have an increased risk to develop medical problems and chronic diseases.

If indeed maternal diet during pregnancy influences birth weight and the risk of future diseases of the child, prevention of obesity and associated health problems can already be started during pregnancy. In the Netherlands, the Ministry of Health, Welfare and Sports has developed an interactive educational programme about a healthy lifestyle for pregnant women and young parents. The programme is called 'Hello World' and aims at increasing awareness among (future) parents about the importance of a healthy lifestyle, for example by informing them about a healthy diet. This will enable them to make healthy choices for their children. However, the impact of this programme might be larger if maternal diet during pregnancy indeed influences birth weight and weight development of the offspring. To get more insight into the first part of this association, i.e. the effect of maternal nutrition during pregnancy on birth weight, we reviewed the literature on the effect of nutrients on birth weight of offspring in relatively well-nourished women. Both epidemiological studies and animal studies (published studies as well as unpublished studies performed at National Institute for Public Health and the Environment (RIVM)) were included in this review.

This literature review showed a clear reduction in birth weight of the offspring in the Dutch famine study, where pregnant women were involuntary exposed to a reduction in energy intake in their third trimester of pregnancy due to the absence of sufficient food supplies. Experimental research in animals also showed that offspring of dams exposed to caloric restriction during pregnancy are generally born with low birth weight. In contrast, several observational studies among humans with energy intake within the normal range observed no association between energy intake during pregnancy and birth weight. Apparently, only more extreme deviations from the normal range adversely affect birth weight. Of the macronutrients, alcohol and protein intake are most likely to influence birth weight. High alcohol consumption during pregnancy, i.e. above 2-3 consumptions a day, reduces birth weight. Human data and data from experimental research with animals show that both a low and a high protein intake as compared to normal protein intake during pregnancy result in reduced birth weight. The associations potentially depend on the stage of pregnancy, but the results on this issue are highly contradictory. There seems to be no association between quantitative carbohydrate and fat intake during pregnancy and birth weight, however, the type of carbohydrates and fatty acids might be associated with birth weight. Namely, animal experiments at RIVM showed that perinatal exposure to high-fat diets based on n-3 fatty acids resulted in heavier pups later in life as compared to exposure to n-6 fatty acids. In compliance, several observational studies in humans showed that birth weight might be increased when mothers have a high intake of n-3 fatty acids, fish or fish oil. Several large epidemiological studies, however, showed no or even an inverse association, so definite conclusions can not be drawn yet.

Several studies found no association between birth weight and the maternal intake or blood concentrations of several micronutrients (vitamins A, B1, B2, B3, B6, B12 and D). Some studies showed a positive association between vitamin C or vitamin E intake and birth weight, but this association could not be confirmed by others. Moreover, an animal experiment performed at RIVM showed the opposite association. More consistent are the results on folate intake during pregnancy and birth weight. Although not observed in all studies, many observational studies on folate intake or folate levels during pregnancy suggest a positive association between folate status and birth weight.

Of the dietary minerals, especially iron and zinc have been associated with birth weight. Iron deficiency anemia may result in low birth weight in both humans and experimental animals. Iron supplementation may therefore improve pregnancy outcome when the mother is iron deficient. However, no association has been observed between dietary iron intake and birth weight in human observational studies, neither in one of the RIVM studies. Similar findings are reported for zinc. For other minerals results are not consistent (copper, magnesium) or no associations have been reported (calcium, phosphorus, sodium, potassium, selenium).

Also the intake of caffeine has been related to birth weight, but it seems unlikely that caffeine intakes less than 300 mg/day (3 cups of coffee) adversely affect foetal growth.

A high intake of fruit and vegetables was associated with increased birth weight in a Danish study involving well-nourished women. In the same study, women with a Western diet, characterized by a high consumption of red and processed meat and high-fat dairy, gave birth to somewhat lighter babies than women with a health conscious diet. Before definite conclusions can be drawn, these associations need to be confirmed by other studies.

The results of this literature review show that the effects of maternal diet on birth weight in industrialised countries are small. The differences in weight of the child between women with a high and low intake of a certain nutrient lie around 50-200 grams, while on average the birth weight of the babies is within the normal range. This does not necessarily imply that prenatal nutrition has no impact on birth weight and body weight later in life. Firstly, in several human observational studies and animal experiments the effect of nutrient intake on birth weight depended on the period of gestation. Although a large part of the research has been carried out in mid or late pregnancy, it has been suggested that the nutrient supply in early pregnancy, or even preconception nutrition might have a greater influence on birth weight. Secondly, we cannot rule out the possibility that some nutrients, although not deficient, may have an effect that becomes more prominent in later life. The results from some of the RIVM animal studies indeed support this hypothesis, but little is known on this topic in humans to date.

Based on this literature review there is no evidence to date that the dietary guidelines for pregnant women should be specified in the light of the prevention of unfavorable birth weights. Fetal undernutrition as well as excessive energy supply should be avoided, but under normal circumstances, maternal diet during pregnancy, at least in industrialised populations, seems to have only a small effect on birth weight. Still though, the impact of maternal diet during pregnancy and the development of overweight and chronic diseases later in life needs further study in both humans and experimental animals.

1 Introduction

Overweight and obesity are major health problems. It has been demonstrated that overweight and obese individuals have an increased risk to develop medical problems and chronic diseases, including high blood pressure, coronary heart disease, type 2 diabetes, diseases of the gall bladder and some types of cancer. The number of people being overweight or obese continues to expand worldwide. In 2005 about 1.6 billion adults and at least 20 million children (under age 5) were overweight and about 400 million adults were obese (Body Mass Index (BMI) > 25kg/m²)¹. Also in the Netherlands, overweight and obesity are a major problem. Especially the percentage of children with obesity is alarming². Already 12% of boys and 15% of girls, age four to fifteen, is overweight and this number is markedly increasing, expected to lead to more and more serious health problems in the future.

Research findings suggest that the risk of becoming an obese adult is at least partly determined early in life. Obese children have a higher relative risk of becoming an obese adult than children with healthy weight³⁻⁵. According to the thrifty phenotype hypothesis (also known as the Barker hypothesis), exposure to either excess or poor nutrition *in utero* can lead to an adaptation of foetal glucose-insulin metabolism and can program susceptibility of the foetus to development of obesity, cardiovascular disease, hypertension, diabetes and cancer later in life⁶⁻⁹. Results from the Dutch Famine Cohort showed that infants of mothers who were exposed to famine in the first or second trimester of their pregnancy, had a lower birth weight and about 50% higher risk of obesity later in life than infants not exposed to the famine^{9,10}. Among the low-birth weight babies, especially male babies who caught up fast in height (i.e. relatively achieved more height by the age of 7 years) are most vulnerable to develop obesity^{8,11}. A large number of epidemiological studies has demonstrated a direct relationship between birth weight and adult adiposity^{8,12}. A higher birth weight is associated with higher attained Body Mass Index (BMI). Some studies, however, found a 'J'- shaped or 'U'- shaped association, with a higher prevalence of obesity occurring at both low and high birth weights. It seems that individuals who were small at birth have more abdominal obesity, despite their lower BMI^{8,12}.

There are indications that birth weight might be influenced by maternal nutritional habits during pregnancy. If indeed maternal diet during pregnancy influences birth weight and the risk of future diseases of the child, prevention of obesity and associated health problems can already be started during pregnancy. This requires attention from a public health policy point of view. In the Netherlands, the Ministry of Health, Welfare and Sports has developed an interactive educational programme about healthy lifestyle for pregnant women and young parents. The programme is called 'Hello World' (Hallo Wereld in Dutch) and aims at increasing awareness among (future) parents about the importance of a healthy lifestyle, for example by informing them about a healthy diet. This will enable them to make healthy choices for their children. However, the impact of this programme might be larger if maternal diet during pregnancy indeed influences birth weight and weight development of the offspring directly. By adopting a healthy diet during pregnancy they may also influence the future risks for chronic diseases in their children. Education about a healthy life-style already during pregnancy might therefore be even more effective in the prevention of obesity.

To get more insight into the first part of this association, i.e. the effect of maternal nutrition during pregnancy on birth weight of the offspring, we reviewed the literature on the effect of nutrients on birth weight in relatively well-nourished women. Both data obtained from epidemiological studies and animal studies (both published studies as well as animal studies performed at RIVM) will be discussed and interrelated. Chapter 2 describes the approach that was used to obtain information from the literature and animal studies. The results are presented in chapter 3 (macronutrients) and chapter 4

(micronutrients and other food components). The results will be discussed in chapter 5, while in chapter 6 the conclusions are reported.

2 Approach

2.1 Literature search for human epidemiological studies

A systematic computerized literature search of internationally published studies was performed. For this purpose Pubmed was searched with a combination of the following defined Mesh terms: Birth weight, Fatty Acids, Fetal development, Fetal Growth Retardation, Maternal Nutrition Physiology, Nutritional Status, Prenatal nutrition physiology, Pregnant women, Term Birth. All titles and abstracts of the resulting papers were scanned and all papers describing the effect of maternal nutrition on birth weight were selected. We searched for additional relevant papers in the reference lists of selected papers. We only searched for human studies. Furthermore, we focused our literature study on the intake of nutrients within the normal range, and not on deficiencies. Hence, studies that were based in developing countries were excluded. We did this because low birth weight, i.e. below 2500 grams according to WHO criteria¹³, secondary to maternal undernutrition, has become rare in industrialized countries. A very low birth weight, is more often linked to vascular placental failure or to exposure to toxins such as alcohol, than to maternal undernutrition¹⁴. Moreover, we focus on normal pregnancies, and exclude publications that involve particular populations with increased risk of complications. For example, adolescent pregnancies are at particularly high risk for fetal growth retardation. A large part of this problem results from the fact that many adolescent girls are still growing themselves¹⁵. Women with (gestational) diabetes are also at an increased risk for complications¹⁶.

2.2 Literature search for animal studies

To review animal studies that focus on the effect of maternal nutrition during pregnancy on birth weight, a systematic computerized search was performed on internationally published literature. For this purpose Pubmed was used to search for all available articles with the keywords: prenatal, food, diet, weight, animal, monkey, rat, guinea pig, pig, sheep, rat and/or mice. All titles and abstracts of the resulting papers were scanned and publications describing effects of prenatal exposure to food components on birth weight were selected. Of these, all studies which did not clearly state nutrient content in control and/or experimental diet were excluded. The results of this search are shown in Appendix A.

2.3 Animal studies performed at RIVM

At the RIVM, a number of animal studies have been performed, in which mice or rats were exposed to modified diets during gestation and/or early in life. Most of these studies were designed to examine other endpoints than body weight, but data were re-analyzed in those cases where information about birth weight was available. All studies describing experiments performed with food components were selected from the DPA database containing all RIVM animal studies. An example of the composition of experimental diets used in these studies is shown in Appendix B. Subsequently, birth weight and body weight data of these studies were re-evaluated and summarized. Statistical analyses were performed by using a nonlinear mixed effects model or One-Way ANOVA. The level of statistical significance was taken as $P \leq 0.05$. Some of these studies have not been published yet, but details of

these studies are summarized in Appendix A. All animal studies were approved and performed in accordance with the appropriate institutional and federal regulations.

3 Maternal energy and macronutrient intake in relation to birth weight

3.1 Maternal energy intake and birth weight

The Dutch famine study found a clear reduction in birth weight of the offspring when pregnant women during the second world war involuntary were exposed to a reduction in energy intake in their third trimester of pregnancy¹⁷. Energy restriction has also been the focus of a large body of experimental work in animals¹⁸⁻²⁷. These experimental interventions ranged from mild (75% of normal food intake) up to severe restriction (30% of normal food intake). Offspring of dams exposed to caloric restriction during pregnancy are generally born with low birth weight. This ranged up to a dramatic 40% reduction in a study performed with guinea pigs which were restricted to 60% of their normal food intake²¹. Interestingly, introduction of food restriction during a specific gestational period can influence the degree of birth weight reduction. Fifty percent caloric restriction during the first 30 days pregnancy in sheep with subsequent realimentation did not reduce lamb birth weight, whereas birth weight was lowered upon caloric restriction during parts of the first and second trimester (gestational day 28 to 78)²²⁻²⁷. Supportive for the observation that late caloric restriction has a greater effect on birth weight than early restriction is a guinea pig study described by Dwyer et al.²¹. They observed a 12% birth weight reduction in pups derived from mothers exposed to 60% of normal food intake during the first trimester (until gestational day 25), whereas a 50% reduction was found in pups derived from mothers with this restriction applied during the last two trimesters (from day 25 until the end of gestation, i.e. day 68). In contrast to the results of the Dutch famine cohort and the animal studies, several observational studies among humans observed no association between energy intake during pregnancy and birth weight²⁸⁻³². This discrepancy can possibly be explained by the fact that in those human observational studies normal intakes have been investigated, while the other studies clearly investigated the effect of relatively large energy restrictions.

3.2 Maternal carbohydrate intake and birth weight

Carbohydrates are one of the macronutrients providing energy to the body. The other macronutrients are fat protein and alcohol. Carbohydrates provide a substantial proportion of the energy in the diet of the Western population (40-70%). Common sources of carbohydrates in the diet are bread, cereals, pasta, rice, potatoes and legumes³³.

Godfrey and co-workers found, in a relatively well-nourished population, that a high carbohydrate intake in *early* pregnancy was associated with a lower birth weight³⁰⁻³⁴. Others, however, could not confirm that finding²⁸⁻³⁵⁻³⁶. There seems to be no association between carbohydrate intake during *late* pregnancy and birth weight²⁸⁻³²⁻³⁵.

No animal studies have been published up to now analyzing the effect of prenatal dietary carbohydrate manipulation on birth weight

Different types of carbohydrates and carbohydrate-rich foods can be ranked by their glycaemic index, based on their effect on blood glucose levels. Carbohydrates with a high glycaemic index are absorbed quickly and can raise blood glucose levels rapidly. Corn flakes, white bread and white rice are

examples of foods with a high glycaemic index. Carbohydrates with a low glycaemic index break down more steadily and give a gradual rise in blood glucose levels. Foods with a low glycaemic index are for example most fruits and vegetables, nuts and whole grain bread³⁷. Because glucose is the main energy source for intrauterine growth and higher levels of maternal plasma glucose are associated with an increased birth weight, it can therefore be hypothesized that the glycaemic index of the diet during pregnancy may influence birth weight. In a small intervention study providing a diet with a high glycaemic index during pregnancy resulted in a larger birth weight and an increase in the number of large-for-gestational-age babies³⁸. In a study among low income pregnant women a diet with a relatively high glycaemic index, however, did not augment the infant's birth weight³⁹. This discrepancy may lay in the fact that the overall quality of the diet was much lower in the latter study. In this study, women with a very low glycaemic index diet during pregnancy delivered infants with a more than hundred grams lower mean birth weight than the other women. Also, the risk of a small-for-gestational-age birth was increased about two times. These results suggest that glycaemic index of the diet might influence birth weight, but more studies are needed before any definite conclusion can be drawn.

3.3 Maternal protein intake and birth weight

About 10-15% of dietary energy is provided by dietary proteins³³. Proteins are made of amino acids, the building blocks for body tissue. Some amino acids can be made by the body itself. Others, the essential amino acids, should be delivered through the diet. Examples of protein-rich food are fish, meat, dairy foods, eggs, nuts and legumes.

Several studies showed no association between dietary protein intake and birth weight^{32 40 41}. In a systematic review of the Cochrane Collaboration, however, protein supplementation of mothers-to-be did affect birth weight⁴². Balanced energy/protein supplementation, i.e. with supplements in which proteins provides < 25% of energy, resulted in a modest increase in mean birth weight. *High*-protein supplementation, i.e. more than 25% of total daily energy, on the other hand, was associated with a non significant reduction in mean birth weight. The review also studied energy/protein restriction in pregnant women with obesity or high weight gain, and found that the infants of these women had significantly lower birth weights.

It has been hypothesized that the association between protein intake and birth weight may depend on the stage of pregnancy. For example, Moore et al.³⁵ found that a higher dietary intake of protein in *early* pregnancy was associated with an increased birth weight. Each iso-energetic 1% increase in protein consumption was associated with a 16 grams increase in birth weight. The relation was even stronger for the percentage of energy deriving from dairy protein, compared to protein from other sources. In contrast, no association was observed in *late* pregnancy. Also Mathews et al.²⁸ did not find an association between maternal protein intake and infant birth weight in *late* pregnancy. Huh et al.⁴³ found no association between maternal protein intake in the *second* trimester and infant birth weight. In another study, however, mothers of infants with lower birth weights had lower one-day histories of dietary protein intake at 21-weeks of gestation compared to mothers of average size or large babies⁴⁴. Also a recent large Danish study showed that birth weight decreased with decreasing milk consumption in mid pregnancy. Babies of mothers who consumed no milk were on average 100 grams lighter than babies of mothers who consumed 5 glasses of milk or more. Birth weight was related to the intake of protein from milk, not the intake of fat⁴⁵. In line with these findings, Godfrey and co-workers found that low maternal intakes of dairy and meat protein during *late* pregnancy were associated with lower birth weights^{30 34}.

From the above it may be concluded that maternal protein intake is positively associated with birth weight. Contrasting results were found, however, in the Tasmanian Infant Health Study²⁹ where a high protein intake during the last trimester was associated with a *lower* birth weight. Also the results of a follow up study of women who gave birth in the period from 1948-1954 show that a high percentage of caloric intake from animal protein especially was associated with reduced birth weight³⁶. Another longitudinal study among low-income pregnant women also showed that the infants of women with high protein consumption (> 85 grams/day) in mid or late pregnancy were 71 grams lighter than infants of women who consumed 50-84.9 grams/day⁴⁶.

Next to epidemiological human studies, numerous studies with predominantly rats and pigs have studied the effect of dietary protein content on birth weight⁴⁷⁻⁵⁸. The timing and duration of maternal dietary manipulation varied between studies, but in general it can be concluded that low protein content (ranging from 1.5- to 26-fold reduction) resulted in decreased birth weight of the offspring as compared to animals exposed to control diet. Similar to some human studies, a study performed by Muaku et al.⁴⁹, demonstrated that the timing of the protein deficiency was important. They observed that a protein deficient diet during the first two trimesters had no significant effect on birth weight, whereas a protein deficient diet during the last trimester resulted in an 11% decreased birth weight. When they administered the rats a low protein diet during the complete gestational period a 22% decreased birth weight was found.

In addition to studying the effect of a low protein content, two animal studies have been described in which the protein content was increased up to 40%^{59,60}. Despite this high protein level that is not relevant for the human situation, Thone-Reineke et al.⁵⁹ found no effect on birth weight. In contrast, the study described by Daenzer et al.⁶⁰, showed a decreased birth weight. This latter finding is in line with the review of the Cochrane Collaboration, concluding that high-protein supplementation might reduce birth weight⁴².

At the RIVM, a rat study was performed to analyze the effect of perinatal exposure to a protein deficient diet on birth weight as well as body weight development during life. In this experiment exposure lasted until weaning, when the pups transit from breastfeeding to nourishment by themselves (3 weeks of age). Animals were provided *ad libitum* a low (8% w/w) or normal (16% w/w) protein diet from two weeks before mating until weaning was completed (see Appendix B for diet composition). The experimental diets contained equal amounts of energy per gram. From weaning on all offspring was fed the control diet. As shown in Figure 1, birth weight of the pups was not significantly different for rats fed a low protein diet as compared to rats fed a normal diet. However, from age 1 up to 12 weeks offspring from rats fed a low protein diet had a significant lower body weight as compared to controls ($P < 0.001$). These findings were observed both in male (Figure 1A) and female (Figure 1B) rats.

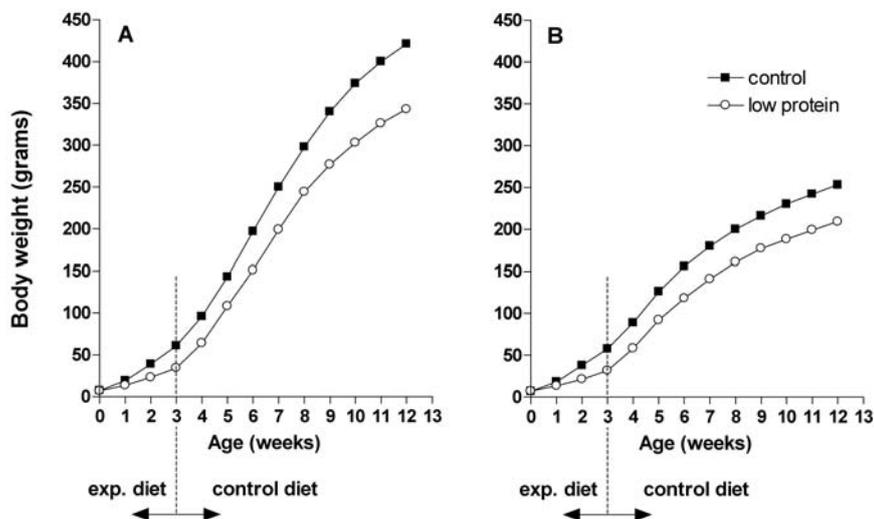


Figure 1. Increase in body weight in male (A) and female (B) offspring perinatally exposed to normal (16% w/w) or low (8% w/w) protein diets.

In summary, human and animal data show that both a low protein intake and a high protein intake during pregnancy result in reduced birth weight. Whether or not the effect of dietary protein content on birth weight depends on the stage of pregnancy needs further study, as the results on this issue are contradictory.

3.4 Maternal fat and fatty acid intake and birth weight

The main role of dietary fats is to provide metabolic energy. Foods high in fats are: oils, margarine and butter, meat, fish, and nuts. Snacks, cookies, ready cooked meals and dairy products also often contain large amounts of fats. Another role for dietary fat is to provide essential fatty acids which perform vital body functions, but cannot be generated in the human body and thus are essential in the diet³³. Fatty acids can be divided into saturated fatty acids, mono unsaturated fatty acids, polyunsaturated fatty acids, and trans fatty acids. In foetal development, fatty acids are crucial. For example, saturated fats are important constituents of membranes, while arachidonic acid (AA) and docosahexaenoic acid (DHA) are the main building blocks of brain and nervous tissue³³.

Several studies observed no associations between maternal total fat intake and birth weight^{28 29 31 32 36}. With respect to animal studies, a relatively low number of papers describing the effect of dietary fat on birth weight have been published. In the two studies that were conducted in rats, prenatal exposure to diets containing 26% or 40% fat did not significantly affect birth weight of the rat offspring compared to control diet (containing 5% fat)^{61 62}.

A large body of research has focused on diets high in long-chain n-3 fatty acids, found in many fish and fish oils. Infants of women consuming 3 or more seafood meals a week weighed by average 200 grams higher in comparison with infants of women eating no seafood at all⁶³. A Danish study among more than 8000 women also found that children of mothers who consumed fish had an higher birth weight than those of mothers who did not consume fish. Additionally, the risk of preterm delivery and low birth weight was increased in the women who consumed little or no fish⁶⁴. Two recent Dutch studies

showed a positive association between maternal EPA and/or DHA status and birth weight, especially during early pregnancy.^{65 66} In line with these findings, a review of six trials showed birth weight to be slightly higher (47 grams on average) in infants born to women consuming marine oil supplements compared with a control group⁶⁷. Also in an Icelandic study, healthy mothers who used liquid cod liver oil in early pregnancy were found to give birth to heavier infants (130 grams). In fact, they were 11 times more likely to give birth to an infant of 4500 grams or more. Concentrated cod liver oil capsules and fish consumption, however, were not related to a higher birth weight⁶⁸. Other studies also observed no association with birth weight for fish consumption, duration of maternal life time fish consumption, n-3 fatty acids or fish liver oil supplements⁶⁹⁻⁷². In contrast, negative associations were found between maternal n-3 fat intake from fish and birth weight in a US retrospective cohort. In all three trimesters of pregnancy birth weight decreased with higher intakes of EPA and DHA⁷³. Also in a large Danish cohort of 44,824 women, fatty fish consumption was associated with reduced birth weight⁷⁴.

Researchers at the RIVM have performed several additional animal studies to investigate whether the published data can be reproduced and –more importantly- whether exposure to high levels of unsaturated or saturated fatty acid during pregnancy affects bodyweight later in life. In these studies, mice or rats were perinatally exposed to high-fat or control diet containing normal fat levels and were monitored for body weight gain and other parameters later in life. Diets were provided *ad libitum*. One mouse study was carried out to analyze the effect of perinatal exposure to high levels (4.8-fold increase) of fat derived from linseed (high in n-3 PUFAs) or corn oil (high in n-6 PUFAs). Female mice were fed the experimental diets from 2 weeks before mating until weaning. Subsequently, their offspring was fed the corresponding diet until 6 weeks of age. Thereafter, all mice received the control diet containing normal levels of fat. As is shown in Figure 2A, the two high-fat containing diets did not affect birth weight, irrespective of the source of fat (linseed or corn oil). Interestingly however, pups exposed to high-fat diets had a statistically significant higher body weight ($P < 0.001$) from 3 weeks of age (time of weaning) than pups fed the (normal-fat) control diet (Figure 2B). No significant difference in body weight between the two high-fat groups could be detected until ten weeks of age. This indicates that the increase in body weight is not influenced by the specific type of fat.

The experimental study design as described here was also applied in an ongoing follow-up study with transgenic mice. Only this time, mice were monitored for a much longer period of time. Mice were exposed to high-fat diets (corn oil or linseed oil) or control diets from conception until 6 weeks of age. Again, the high-fat diets did not have an effect on birth weight, but affected body weight development later in life. At the time of weaning (3 weeks of age), pups exposed to a high-fat diet based on either corn or linseed oil had a significant higher body weight ($P < 0.01$) as compared to controls. At 28 weeks of age, the body weight of mice exposed to a high-fat diet based on corn oil no longer differed significantly from the body weight of control mice. However, despite the fact that they consumed a control diet from 6 weeks of age onwards, mice perinatally exposed to high-fat diets based on linseed oil still had significantly higher body weights at 28 weeks of age (Figure 3, $P < 0.001$). These results suggest perinatal programming of body weight.

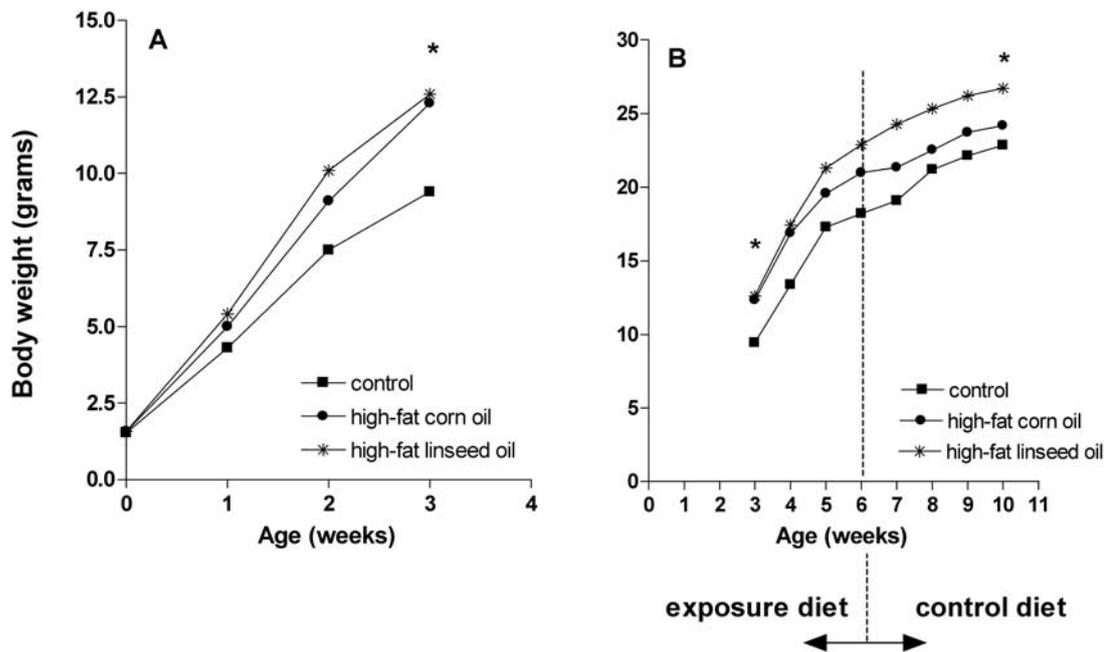


Figure 2. Body weights until 3 weeks of age (A, male and female pups combined) and 10 weeks of age (B, female pups only) of mice exposed to isocaloric normal or high-fat diets from conception until six weeks of age.

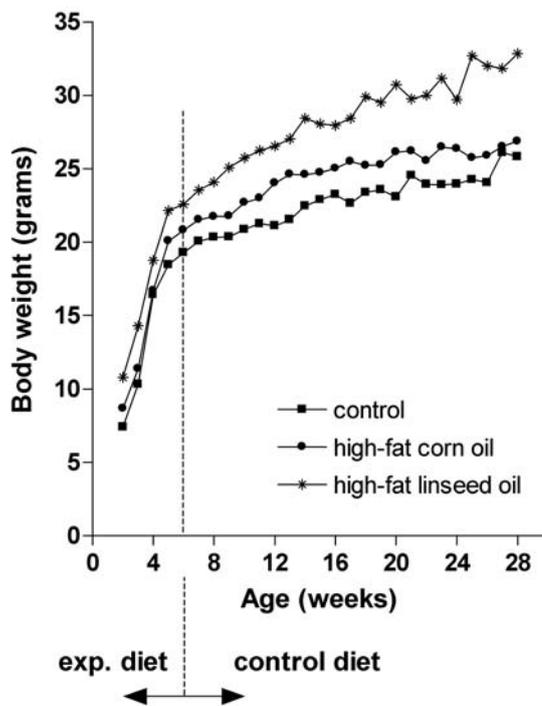


Figure 3. Body weights of female transgenic mice exposed from conception until six weeks of age to isocaloric normal or high-fat (24% w/w) diets, based on either corn oil or linseed oil.

In another experiment the effect of several high-fat diets differing in fatty acid composition on body weight has been studied. Birth weight and body weight until 12 weeks of age were monitored in rats exposed to high-fat (20% w/w) diets based on soybean and safflower oil (high in n-6 PUFAs), linseed and fish oil (high in n-3 PUFAs), and coconut oil (low in both) (see Appendix B and ref ⁷⁵ for diet composition). Animals were fed the experimental diets 2 weeks before mating until weaning was completed. From this time point onwards, all offspring was fed a high-fat control diet based on soybean oil. The pups of mothers fed the fish oil diet weighed significantly ($P < 0.05$) less compared to pups of the control group from birth until 3 weeks of age (Figure 4). However, after weaning, body weights were comparable, irrespective of the diet received perinatally.

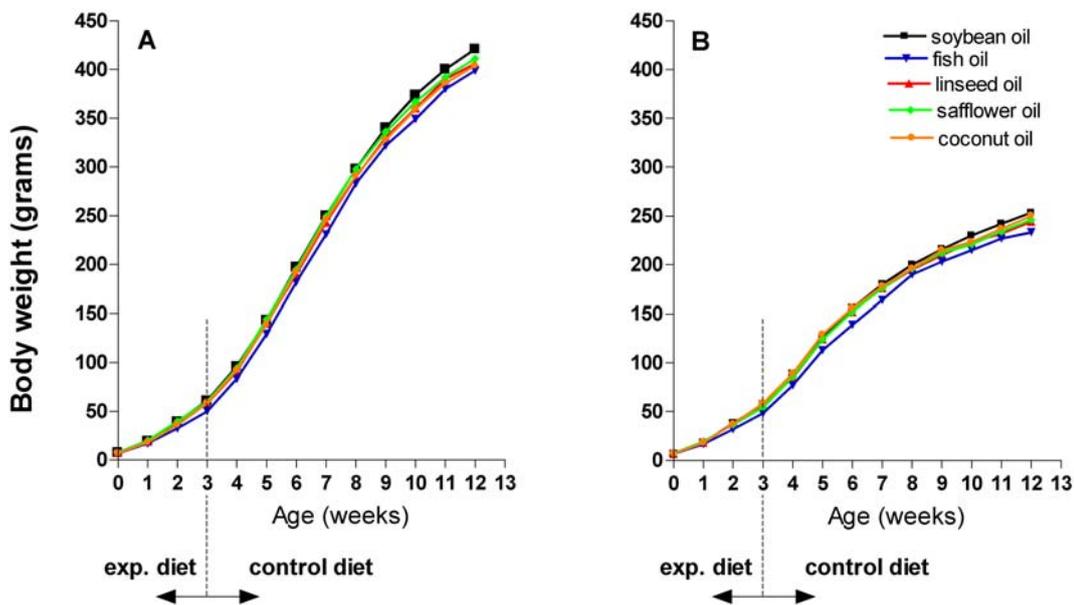


Figure 4. Body weights of male (A) and female (B) rats perinatally exposed to high-fat (20% w/w) diets based on soybean, fish, flaxseed, safflower or coconut oil.

Taken all human and experimental results described above together, we can conclude that pre-or perinatal exposure to high-fat diet does not significantly influence birth weight. However, a high fat diet might, at least in rats and mice, influence body weight gain later in life. The type of fatty acids might influence both birth weight and body weight later in life. Perinatal exposure to high-fat diets based on n-3 fatty acids resulted in heavier pups later in life as compared to exposure to n-6 fatty acids. Observational studies in humans also showed that birth weight might be higher in babies from mothers consuming diets rich in n-3 fatty acids. However, results are not conclusive, and more research is needed before definite conclusions can be drawn.

3.5 Maternal alcohol intake and birth weight

There is a clear correlation between maternal alcohol abuse during pregnancy and foetal abnormalities. Intake of more than 10 units of alcohol (80 grams) per day is linked with the foetal alcohol syndrome, which is among others characterized by reduced birth weight ⁷⁶. Modest maternal drinking, however, may also reduce birth weight. In a study among 628 French women, the consumption of three or more

alcoholic drinks per day is significantly associated with a reduction in birth weight. Birth weight was lower among the infants of women who consumed larger amounts of alcohol ⁷⁷. The Tasmanian Infant Health Survey also found an inverse association with birth weight, but it was not statistically significant ²⁹. A review of Larroque ⁷⁶ concluded that a reduced birth weight was consistent for consumption of two drinks or more daily. Below this level no clear association between alcohol consumption and birth weight can be observed. A recent systematic review of the literature also found no convincing evidence for a reduced birth weight with low to moderate alcohol consumption (< 83 grams per week) ⁷⁸. Supportive for the epidemiological studies, various animal studies also revealed an adverse impact on birth weight upon chronic maternal exposure to high amounts (i.e. 25% - 36%) of alcohol ⁷⁹⁻⁸². Gestational exposure of rats to 20% alcohol or 35% alcohol from day 14 onwards did not adversely affect birth weight ^{83 84}.

3.6 Summary of macronutrients in relation to birth weight

Table 1 provides a schematic overview of the results of studies on the relation between maternal energy and macronutrient intake during pregnancy and birth weight of the child.

Table 1: Schematic overview of the relation between maternal macronutrient intake and birth weight.

	Human studies	Animal studies
Energy	0/+ ^a	+ (restriction)
Carbohydrates	0	NA
Glycemic Index	inconclusive	NA
Protein	+ (-) ^b	+ (-) ^b
Fat	0	0
n-3 fatty acids/fish	inconclusive	0
Alcohol	- ^c	-

+: positive association: higher intake is associated with higher birth weight

-: inverse association: higher intake is associated with lower birth weight

0: no association; NA: no studies available

a: no association with energy intake within the normal range, energy restriction results in lower birth weight. b: very high protein intake is also associated with lower birth weight, c: for consumption above 2 -3 glasses a day.

Both human data and data from experimental research with animals shows that a low protein intake as well as a high protein intake as compared to normal protein intake during pregnancy results in reduced birth weight of the child. Also severe energy restriction results in reduced birth weight, but no association with birth weight has been observed when energy intake is within the normal range. Although exposure to high-fat diet does not significantly influence birth weight, the type of fatty acids might. Birth weight might be higher in babies from mothers consuming diets rich in n-3 fatty acids, but results are not conclusive yet. Furthermore, more than two or three drinks of alcohol per day during pregnancy reduces birth weight, while lower intakes probably do not affect birth weight.

4 Maternal micronutrient intake and birth weight

Micronutrients are vitamins, minerals and trace elements. They do not provide energy directly, but are necessary in releasing energy from macronutrients. They are also indispensable for several cellular processes, including protein translation, enzymatic reactions and gene expression regulation³³. Several micronutrients have been shown to influence fetal growth and birth weight. A summary of relevant studies examining the association between micronutrients and birth weight is given below.

4.1 Maternal vitamin intake and birth weight

Several studies found no association between birth weight and vitamin A intake, measured either throughout pregnancy⁴⁰, in early and late pregnancy^{28 32} or in late pregnancy^{36 85}. Also vitamin A levels in maternal blood in early pregnancy or in week 18 and 30 were not associated with birth weight^{86 87}. No associations were found between birth weight and the maternal intake or blood concentrations of thiamin (vitamin B1), riboflavin (vitamin B2), niacin (vitamin B3), pyridoxine (vitamin B6), cobalamin (vitamin B12) and vitamin D^{36 40 85}.

In contrast, scientific evidence suggests that folate intake might be related to infant birth weight. Although some studies observed no association between folate intake and birth weight^{28 40 85}, many other observational studies of folate intake or folate levels during pregnancy that a good folate status improves birth weight (reviewed in⁸⁸). For example, in a study of Neggers et al. the birth weight of babies born to mothers with high folate intake (> 90th percentile) was almost 50 grams higher than the birth weight of babies from mothers with low folate intake (< 10th percentile)³². Another study also showed that mothers whose serum folate concentration were above the median (44 nmol/L) at 30 weeks gestation had significantly heavier infants (200-330 grams) as compared with those with serum folate < 44 nmol/L⁸⁹. Unlike these observational studies, randomized trials of folic acid supplementation have shown less uniform benefit on birth weight. This implies that routine supplementation may not benefit all pregnant women in this respect⁸⁸.

Maternal intake of vitamin C in early pregnancy was positively associated with birth weight in one study²⁸. Intakes above 98 mg resulted in 70 grams higher birth weights compared to intakes below 55 mg/day. However, no association with vitamin C intake in late pregnancy was found, whereas other studies also found no association with vitamin C intake measured throughout pregnancy^{32 40} and in late pregnancy^{36 85}.

Positive associations between vitamin E and birth weight were found by Scholl et al.⁹⁰ who examined maternal plasma concentrations of alpha-tocopherol at the beginning of pregnancy and at week 28 and by Lagiou et al. who examined the effect of higher intakes of vitamin E in late pregnancy⁸⁵. However, other studies found no association when relating birth weight to vitamin E intake in early or late pregnancy^{28 86 87} or to vitamin E concentration in maternal blood during late pregnancy²⁸.

In the literature, no animal studies investigating the effect of prenatal vitamin deficiency or supplementation on birth weight were found. At the RIVM, one study has been conducted, in which the effect of both dietary vitamin C and E levels on birth weight was analyzed. Female rats were exposed

to low, normal or high levels of vitamin C and E (details are indicated in Appendix C). Female rats were fed the experimental diets, provided *ad libitum*, from 2 weeks before mating until the moment of sacrifice, i.e. day of delivery. The results were opposite to those found in human studies. Pups, both male and female, born from dams fed a diet high in vitamin C and E, had a statistically significant lower birth weight compared with the control group (Table 2), pointing towards a negative effect on *in utero* growth. Low levels of vitamin C and E did not affect birth weight. The number of pups per litter was comparable between all groups.

Table 2. Average birth weight of rat pups after prenatal exposure to various levels of vitamins.

Diet	Birth weight pups (g) ¹	
	Males	Females
Normal diet	4.40 ± 0.41 (94)	4.22 ± 0.33 (90)
Low vitamin C and E	4.47 ± 0.38 (81)	4.19 ± 0.35 (68)
High vitamin C and E	4.19 ± 0.30 ^a (72)	3.91 ± 0.37 ^b (67)

Values represent means ± SD. Number of pups per group is indicated within parentheses.

^{a,b} Significantly different from controls (ANOVA): a = $P < 0.01$, b = $P < 0.001$

In a randomized double-blind placebo-controlled trial, pregnant women receiving a daily combined micronutrient supplement including folate, vitamin C, vitamin E, and zinc, had infants with 10% higher birth weights than the mothers in the placebo group. The number of birth weights under 2700 grams decreased significantly when the mother received the supplementation⁹¹. However, it is unknown which individual micronutrient is most important with respect to this effect.

4.2 Maternal mineral intake and birth weight

Several studies both in humans and animal models investigated the association of maternal mineral intake during pregnancy and birth weight. Especially the influence of iron and zinc intake has been studied frequently.

Iron Deficiency Anemia (IDA) developed before or early in pregnancy is associated with a greater than 2-fold increase in the risk for low birth weight⁹²⁻⁹⁴. The influence of iron supplementation on birth outcomes remains, however, unclear^{15 93}. Iron supplementation may improve pregnancy outcome when the mother is iron deficient, but it is also linked to maternal complications like gestational diabetes⁹². Other studies showed that high iron status, measured by high plasma ferritin or iron levels, was associated with lower birth weight^{44 86}. Dietary iron intake measured throughout pregnancy^{32 40} or in early pregnancy^{28 85} was, however, not associated with birth weight in observational studies.

The effect of maternal iron deficiency on offspring has also been studied in animals. Five rat studies – with different exposure periods to iron deficient diet and type of iron deficiency - have been described⁹⁵⁻⁹⁹. Four studies showed that an iron deficiency during the entire gestational period resulted in a reduction of birth weight. In contrast, a small mouse pilot experiment performed at the RIVM with two types of iron-deficient diets did not reveal any differences in birth weight of offspring, nor in bodyweight differences up to 4 weeks of age. Both iron-deficient diets in this pilot experiment had an 85% reduction in iron content. A study performed with monkeys showed that iron deficiency during the last two trimesters of pregnancy did not result in decreased birth weight⁹⁹.

Positive associations between maternal zinc supplementation and infant birth weight were found in a randomised double-blind placebo-controlled trial ¹⁰⁰. Infants born to women in the zinc supplement group had a significantly greater birth weight than infants in the placebo group. In women with a body mass index less than 26 kg/m², zinc supplementation was associated with an even higher infant birth weight. In line with these findings, low zinc intake (< 6 mg/day) was associated with a 2- fold increase in risk of low birth weight (< 2500 grams) in a poor urban community in Camden, USA ¹⁰¹. In contrast, Lagiou et al found that a higher intake of zinc in late pregnancy was associated with a decreased birth weight ⁸⁵. Also in a study of Metcoff et al. mothers of infants with low birth weights had higher plasma levels of zinc in week 21 of pregnancy ⁴⁴. Other studies found no association between dietary zinc intake, measured in early or late pregnancy or plasma zinc concentrations and birth weight ^{28 32 40 85 89 102}.

A zinc deficiency throughout the entire pregnancy resulted in a reduced birth weight in 2 out of 3 animal studies described ¹⁰³⁻¹⁰⁵. One of the studies performed with rhesus monkeys, found no effect. It should however be noted that in this study only a mild zinc deficiency was introduced. Finally, the timing of zinc deficiency during pregnancy was shown to influence birth weight. The longer a deficiency is maintained, the greater the effect on the offspring ¹⁰⁶⁻¹⁰⁸.

According to Metcoff et al. mothers of smaller infants had higher maternal plasma levels of copper measured in week 21 ⁴⁴. Another study, however, could not find any association between dietary copper intake and birth weight ⁸⁵.

Low maternal magnesium intake, measured in early pregnancy, was found to be highly associated with birth weight in a study among 513 women. Supplementation of these women with magnesium later in pregnancy did, however, not influence birth weight ¹⁰⁹. Another trial on magnesium supplementation also reported no effect ¹¹⁰, and magnesium intake was also not associated with birth weight in an observational study among 222 women. ⁸⁵.

No associations with birth weight were found for the dietary intake of calcium ^{32 36 85}, phosphorus ^{40 85}, sodium ^{32 85}, manganese, potassium and selenium²⁸.

4.3 Summary of maternal micronutrient intake and birth weight

Of the vitamins, only folate seems to be clearly associated with birth weight (Table 3). A higher folate intake or status of the mother during pregnancy is associated with a higher birth weight of the child. Although deficiency of the minerals iron, zinc and copper may result in reduced birth weight, no clear associations between these micronutrients and birth weight have been found when no deficiencies are present.

Table 3: Schematic overview of the relation between maternal micronutrient intake and birth weight.

	Human studies	Animal studies
Vitamins		
Vitamin A	0	NA
Thiamin (Vitamin B1)	0	NA
Riboflavin (Vitamin B2)	0	NA
Niacin (Vitamin B3)	0	NA
Pyridoxine (Vitamin B6)	0	NA
Folate	+	NA
Cobalamin (Vitamin B12)	0	NA
Vitamin C	0	- ^a
Vitamin E	inconclusive	- ^a
Vitamin D	0	NA
Minerals		
Iron	0/+ ^b	+ (iron deficiency)
Zinc	inconclusive	+ (zinc deficiency)
Copper	inconclusive	NA
Calcium	0	NA
Magnesium	0	NA
Phosphorus	0	NA
Sodium	0	NA
Potassium	0	NA
Selenium	0	NA

+: positive association: higher intake is associated with higher birth weight

-: inverse association: higher intake is associated with lower birth weight

0: no association; NA: no studies available

a: Vit C and Vit E combined, b: no association with dietary intake, clear iron deficiency results in increased risk of low birth weight.

5 Maternal intake of other food compounds and birth weight

In addition to specific macro- and micro nutrients, the intake of whole food components during pregnancy has been studied in relation to birth weight of the offspring. Besides fish, which is discussed in paragraph 3.4, maternal intake of caffeine, fruit and vegetables have been associated with birth weight. The results are discussed below.

5.1 Caffeine intake and birth weight

In a large Danish study among more than 10,000 pregnant women, maternal coffee consumption of at least four cups a day was associated with a moderate decrease in birth weight, especially among smokers ¹¹¹. A much smaller French study found a lower birth weight (187 ± 107 grams) in the group with a very high caffeine intake (> 800 mg/day), but only among non-smokers ⁷⁷. Several other studies showed that caffeine intake during pregnancy may reduce birth weight or increase the risk of intrauterine growth retardation, while others have found no association (see ¹¹²⁻¹¹⁴ for references). Animal studies focusing on prenatal exposure to caffeine and birth weight showed that caffeine can adversely affect birth weight, although this effect could only be detected after exposure to high concentrations ¹¹⁵⁻¹¹⁷. A study performed by Aeschbacher et al. ¹¹⁷ showed that maternal exposure to caffeine concentrations below 1 g/kg diet did not affect birth weight, whereas 1 g/kg diet resulted in significant smaller rat pups. Therefore, inconsistent results may relate to the amount of caffeine consumed, but more importantly discrepancies between studies may result from the fact that women with a high coffee consumption during pregnancy also more often smoke or drink alcohol. Not all observational studies were able to control for these confounders sufficiently. Therefore, a recent randomised controlled trial among 1200 pregnant women provides interesting evidence. In this study a moderate reduction in caffeine intake in the second half of pregnancy did not have an effect on birth weight in the total group, but resulted in lower birth weights in the women who smoked ¹¹². In summary, although the effect of caffeine intake on birth weight requires further clarification, it appears unlikely that caffeine intakes less than 300 mg/day (3 cups of coffee) adversely affect foetal growth.

¹¹⁸

5.2 Fruit and vegetable intake and birth weight

In a Danish study, high intake of fruit and vegetables was associated with increased birth weight in well-nourished Danish women ¹¹⁹. The association was strongest for fruit intake; birth weight increased 10.7 grams per quintile of fruit intake. The association between the consumption of green leafy vegetables and birth weight was more inconclusive. In the same study, women with a Western diet, characterized by a high consumption of red and processed meat and high-fat dairy, gave birth to somewhat (40 grams) lighter babies than women with a health conscious diet, characterized by high intake of fruits, vegetables, fish and poultry ¹²⁰.

6 Discussion

This literature review showed that maternal diet during pregnancy, at least in industrialised populations, only seems to have a small effect on birth weight. Nevertheless, some clear associations have been observed. A schematic overview of the results has been given in chapters 3 and 4, and all results are also summarised below in Table 4.

In summary, human data and data from experimental research with animals show that both a low and a high protein intake as compared to normal protein intake during pregnancy result in reduced birth weight of the child. Also severe energy restriction results in reduced birth weight of the offspring. Furthermore, more than moderate alcohol consumption, i.e. two to three drinks or more per day, reduces birth weight. There is, however, no convincing evidence that low to moderate alcohol consumption unfavourably affects birth weight. Similar observations have been found for caffeine consumption. A high intake during pregnancy might result in lower birth weights of the offspring, whereas it appears unlikely that caffeine intakes less than 300 mg/day (3 cups of coffee) adversely affect foetal growth. Although exposure to high-fat diet does not significantly influence birth weight, the type of fatty acids might. Birth weight might be higher in babies from mothers consuming diets rich in n-3 fatty acids, but results are not conclusive yet. Of the vitamins, only folate seems to be clearly associated with birth weight. A higher folate intake or status during pregnancy is associated with a higher birth weight. Although deficiency of iron, zinc and copper may result in reduced birth weight, no clear associations between these micronutrients and birth weight have been found when no deficiencies are present.

Table 4: Schematic overview of the relation between diet and birth weight.

	Human studies	Animal studies
Energy	0/+ ^a	+ (restriction)
Macronutrients		
Carbohydrates	0	NA
Glycemic Index	inconclusive	NA
Protein	+ (-) ^b	+ (-) ^b
Fat	0	0
n-3 fatty acids/fish	inconclusive	0
Alcohol	- ^c	-
Vitamins		
Vitamin A	0	NA
Thiamin (Vitamin B1)	0	NA
Riboflavin (Vitamin B2)	0	NA
Niacin (Vitamin B3)	0	NA
Pyridoxine (Vitamin B6)	0	NA
Folate	+	NA
Cobalamin (Vitamin B12)	0	NA
Vitamin C	0	- ^d
Vitamin E	inconclusive	- ^d
Vitamin D	0	NA

Table 4: Schematic overview of the relation between diet and birth weight (continued).

	Human studies	Animal studies
Minerals		
Iron	0/+ ^e	+ (iron deficiency)
Zinc	inconclusive	+ (zinc deficiency)
Copper	inconclusive	NA
Calcium	0	NA
Magnesium	0	NA
Phosphorus	0	NA
Sodium	0	NA
Potassium	0	NA
Selenium	0	NA

+: positive association: higher intake is associated with higher birth weight

-: inverse association: higher intake is associated with lower birth weight

0: no association; NA: no studies available

a: no association with energy intake within the normal range, energy restriction results in lower birth weight. b: very high protein intake is also associated with lower birth weight, c: for consumption above 2 glasses a day, d: Vit C and Vit E combined, e: no association with dietary intake, clear iron deficiency results in increased risk of low birth weight.

The results of this unique combined literature review and analysis of experimental RIVM research showed that the effects of maternal diet on birth weight in industrialised countries are small if present at all. The mother's pre-pregnancy nutritional status, weight, body composition as well as maternal weight gain during pregnancy might be more important for determining birth weight than the composition of the diet, at least in industrialised countries^{15 121}. The maternal nutritional status defines the availability of nutrients for supplying the foetus¹⁵. The pre-pregnancy period seems to be the best time to prepare for the nutritional demands of pregnancy¹²¹. The pre-pregnancy nutritional state directly influences the oocyte and the development of the embryo^{15 122}. Moreover, there is evidence that the foetal growth trajectory in later gestation is also determined in the periconceptual period¹²³. The availability of nutrients to supply to the foetus is not only related to the maternal nutritional status, but is also affected by the mother's pre-pregnancy weight and body composition^{15 121}. Low maternal pre-gravid weight is considered a marker for minimal tissue nutrient reserves and pre-gravid weight is strongly related to birth weight¹²². Women with a low pre-pregnancy BMI are at an increased risk for a number of adverse pregnancy outcomes, including preterm birth and intrauterine growth retardation (IUGR)¹²⁴. Accordingly, high maternal pre-gravid weight increases the risk of delivering offspring with high birth weight¹⁵. Furthermore, low weight gain during pregnancy has been associated with lower birth weight¹²⁵, whereas higher gestational weight gains are related to higher birth weights and better growth and development during the first postnatal year¹²⁶.

Clear effects of maternal undernutrition on birth weight have been shown, suggesting that only with maternal undernutrition the foetal supply may not meet foetal demand, necessitating a slowing of the foetal growth trajectory¹²³. In developed countries, however, dietary macronutrient or micronutrient deficiencies are rarely thought to be responsible for clinically significant impaired foetal growth¹²⁷. For most women in industrialised countries the supply of nutrients to their foetus is probably not really limited, although it may be suboptimal. We cannot rule out the possibility that a combination of only minor effects of individual food components may give rise to significant effects on birth weight. Furthermore, we limited our literature review to the effects of maternal nutrition during pregnancy on birth weight. Some nutrients, although not deficient, may have an effect that becomes more prominent

in later life. Differences in birth weight of the child between women with a high and low intake of a certain nutrient lie around 50-200 grams, while on average the birth weight of the babies is within the normal range. A difference of 200 grams may have little impact on the individual level, but may have an impact on the development of obesity and related diseases later in life at the population level.

In several human observational studies and animal experiments the period of gestation during the nutritional intervention was critical for the effect of nutrient intake on birth weight. Foetal demand for nutrients occurs primarily during the last half of gestation when > 90% of the foetal growth occurs¹²¹. This suggests that this is a period when nutrient supply may be most important for certain outcomes. However, as described in chapter 3, some studies showed an association between the intake of a certain nutrient, for example protein, and birth weight in early pregnancy, but not in late pregnancy. This suggests that also the nutrient supply in early pregnancy, or even preconceptional nutrition might influence birth weight. It has been suggested that the foetal growth trajectory in later gestation is determined in the periconceptional period. This may explain why numerous studies in maternal nutrient supplementation fail to show a clinically significant effect on birth weight¹²³, as supplementation starts later in pregnancy. Recent animal experiments demonstrate that nutrition prior to and around conception indeed can alter foetal physiology¹⁵. However, there is limited evidence-based information on preconceptional nutrition and pregnancy outcome in women¹⁵. The exact critical time window during development is therefore yet not known and should be determined in the future.

Furthermore, early *postnatal* exposure may be important. The results from some of the RIVM animal studies indeed support this hypothesis. While no differences in birth weight were found for a low protein diet as compared to control diets, the growth rate of the pups was lower, even after the pups in the experimental group were switched back to the control diet after 3 weeks of life. A similar, but opposite association was found for a high fat diet. These observations suggest that nutritional environment early in life may indeed influence growth later in life, so-called programming. Although quite some studies investigated the association between maternal diet during pregnancy and birth weight in humans, very few studies investigated the association between maternal diet and the development of overweight later in life. Therefore more research into this specific relation is needed. Animal studies are an important research approach addressing this question. Namely, in animals the exposure time period during pregnancy as well as *postnatal* exposure can be precisely managed. In addition, food supplies are rather easily controlled. Also, combinations of increased or lowered micro- or macronutrient levels can be mimicked in an experimental setting. One has to keep in mind however that results obtained in animal studies do not always represent similar effects in humans, as can also be seen in the current report. It is difficult to study this association in human observational studies, since it is likely that women who are aware of their diet during pregnancy are those women that are health conscious anyway. They probably provide their (young) children with a healthier diet and lifestyle, which makes it hard to entangle physiological effects or perinatal programming from lifestyle effects. Nevertheless, associations between maternal diet and health have been observed in the field of asthma. Results from the PIAMA study showed that daily consumption of nut products during pregnancy increased the risk of asthma symptoms in their children at two years of age, even when adjusted for the diet of the child itself¹²⁸. A study to evaluate the association between maternal diet and the development of overweight within the PIAMA cohort is currently ongoing.

Physiologic programming in early life has been documented in a variety of organisms. It reflects the action of a factor during a sensitive period or window of development to exert organizational effects that persist throughout life. Programming agents might include growth factors, hormones, and nutrients. In the case of early life conditions of malnutrition, stress, or other deprivation, these factors may produce physiological adaptations that permanently alter adult metabolism and responses in a

direction optimizing survival under these same conditions. However such persisting adaptations might be detrimental when the later environment is unexpectedly less challenging¹²⁹. For example, exposure to either low or high levels of intrauterine nutrition can result in an increase in adiposity and circulating leptin concentrations in later life. Leptin may act as a signal of energy supply and have a ‘lipostatic’ role before birth⁸. Research has also shown that there is a direct relationship between birth weight and BMI attained in later life by lasting changes in proportions of fat and lean body mass, central nervous system appetite control and pancreatic structure and function¹².

The mechanisms underlying developmental programming are not fully elucidated at the moment. Firstly, there are indications that placental growth is influenced by nutritional supply and that it adapts to the maternal environment, changing both its structure and function¹³⁰. Secondly, programming may be accomplished by epigenetic factors which permanently change gene function and related proteins without changing the DNA itself. Epigenetic changes during embryonic development and early in life, may determine gene expression and development later in life. Moreover, they might be transmitted to the next generation^{131 132}. This subject is more extensively discussed in RIVM-report 350020005¹³³, and will be the subject of follow-up animal studies performed at the RIVM in the context of the EU 7th Framework program.

The interactive programme ‘Hallo World’ (Hallo Wereld in Dutch) has been developed to stimulate the health of mothers to be and the child. At present the dietary advice that is given to pregnant women deviates in some aspects from the general dietary guidelines. These specific guidelines are given because of increased nutritional demands during pregnancy (such as folate, vitamin D and calcium) and because of risks associated with certain nutrients or foods. For example, overconsumption of vitamin A should be avoided, just as raw foods that may be contaminated with *Listeria* or *Toxoplasma gondii* (source: www.voedingscentrum.nl). There is evidence that fetal undernutrition as well as excessive energy supply (offspring of obese or diabetic women) has adverse consequences for birth weight and the risk for overweight later in life, so both should be avoided¹³⁴. Besides this, there is, however, no convincing evidence to date that the dietary guidelines for pregnant women should be specified in the light of the prevention of unfavorable birth weights.

7 Conclusions

- Protein intake, high alcohol and caffeine consumption, folate intake, and possibly n-3 fatty acid intake during pregnancy influence birth weight of the offspring.
- The impact of diet during pregnancy on birth weight may depend on the period of gestation. As the exact critical time window during development is yet not known further research on this topic both in humans and animal experiments is needed.
- Overall, maternal diet during pregnancy, at least in industrialised populations, seems to have only a small effect on birth weight. However, it is unknown whether combinations of food components will affect birth weight.
- Foetal undernutrition and overnutrition should be avoided, but there is no evidence to date that the dietary guidelines for pregnant women should be specified in order to prevent unfavorable birth weights.
- More research is needed into the association between maternal dietary composition during pregnancy and (over)weight and chronic diseases later in life.

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APPENDIX A: Overview of animal studies cited in this report

Macronutrients

Species	diet	modulation	control	Restriction#	Birthweight *	Ref.
Rat	food restriction	30%	100%	all	♀ ↓	18
Rat		30%	100%	all	↓	19
Rat		30%	100%	all	↓ -34%	20
Guinea pig		60%	100%	all	↓ -40%	21
Sheep	food restriction	50%	100%	days 0-30	-	27
Sheep		50%	100%	days 28 to 78	↓	22
Rat		50%	100%	d11-term	↓ -15%	23
Rat		50%	100%	2nd half	↓	24
Guinea pig		60%	100%	d0-d25	↓ -12%	21
Guinea pig		60%	100%	d25-term	↓ -50%	21
Rats		70%	100%	d0-d18	↓	25
Monkey		75%	100%	d66-term	-	26
Monkey		75%	100%	d99-term	-	26
Pig	low protein	0.5%	13%	all	↓	47
Pig		0.7%	13%	all	↓	48
Rat		5%	20%	all	↓ -22%	49
Rat		5%	12%	all	↓	50
Rat		5%	12%	all	↓	51
Rat		8%	20%	all	↓ -17%	52
Mouse		8%	20%	all	↓	53
Rat		8%	12%	all	↓	50
Rat		8%	12%	all	↓	51
Rat		8.5%	19%	all	↓	54
Rat		9%	19%	all	↓	55
Rat		9%	18%	all	↓	56
Rat		9%	18%	all	-	75
Rat		10%	20%	all	♀ ↓, ♂ -	57
Rat		10%	20%	all	↓	58
Pig	low protein	0.5%	13%	d1-d44	↓	47
Pig		0.5%	13%	d81-term	↓	47
Pig		0.7%	13%	d1-d63	↓	48
Rat		5%	20%	last week only	↓, -11%	49
Rat	high protein	40%	20%	all	-	59
Rat		40%	20%	all	↓ -10%	60
Rat	high fat	40%	5%	all	-	61
Rat		26%	5%	all	-	62
Mouse		24% linseed oil	5%	all	-	†
Mouse		24% corn oil	5%	all	-	†
Rat		20% fish oil	20% soybean	all	-	75
Rat		20% linseed oil	20% soybean	all	-	75
Rat		20% safflower oil	20% soybean	all	-	75
Rat		20% coconut oil	20% soybean	all	-	75

Species	diet	modulation	control	Restriction#	Birthweight *	Ref.
Rat	alcohol	5% up to 20%	0%	all	-	83
Rat		up to 30%	0%	all	↓	79
Rat		36%	0%	all	↓	80
Mouse	alcohol	25%	0%	d7-17	↓	81
Rat		35%	0%	d14-term	-	84
Rat		15g/kg/day	0mg/kg/day	d6-d20	↓	82

Micronutrients

Species	diet	modulation	control	Restriction#	Birthweight *	Ref
Rat	low vitamin C + E	0 g/kg vitC 18 mg/kg vitE	0,2 g/kg vitC 100 mg/kg vitE	all	-	†
Rat	high vitamin C + E	40 g/kg vitC 2000 mg/kg vitE	0,2 g/kg vitC 100 mg/kg vitE	all	↓	†
Rat	low iron	3 mg/kg diet iron subcarbonate	153 mg/kg diet	all	↓	95
Rat		3 mg/kg diet iron subcarbonate	150 mg/kg diet	all	↓	96
Rat		7.5 mg/kg FeSO4	50 mg/kg	all	↓	97
Rat		7,5 mg/kg FeSO4	50mg/kg	all	↓	98
Mouse		7.5 mg/kg FeSO4	50 mg/kg	all	-	†
Mouse		7,5 mg/kg FeSO4	50mg/kg	all	-	†
Monkey	low iron	10 µg/g diet	100 ug/g diet	d28 a 30 - term	-	99
Monkey	Low zinc	2 µg/g	50 or 100 ug/g	all	-	103
Monkey		4 ppm	100 ppm	all	↓	104
Mouse		15 g/kg diet	25 g/kg diet	all	↓	105
rat	low zinc	< 1 mg/kg diet	25 mg/kg water	after 2 weeks	↓	106
Mouse		5 ppm	100ppm	d7-term	↓	107
Guinea pig		3 mg/ L water	15 mg/L water	d30- term	-	108
Rat	low fiber	0.5%	5%	all	-	75
Mouse	caffeine	500 mg/liter drinking water	0mg/liter	all	-	115
Monkey		35 mg/kg/day	0 mg/kg/day	all	↓	116
Rat		0.25 g/kg diet	0 g/kg diet	all	-	117
Rat		0.5 g/kg diet	0 g/kg diet	all	-	117
Rat		1.0 g/kg diet	0 g/kg diet	all	↓	117
Rat	caffeine	84 mg/kg/day	0 mg/kg/day	d6-d20	↓	84

Studies were selected as described in chapter 2, Methods.

Ref: Reference.

- = unaltered; ↓ = lower birth weight as compared to controls;

↑ = higher birth weight as compared to controls.

gestational days mouse = 19, rat = 21, guinea pig = 68, pig = 112-115, sheep = 144-151, monkey = 164.

† RIVM study

APPENDIX B: Example of composition of experimental diets used in perinatal exposure study of rats with different sources of fat

1.1 Composition of the experimental diets

g/100 g diet	Control Diet	Flaxseed oil diet	Fish oil diet	Safflower oil diet	Coconut oil diet	Low fiber diet
<i>ingredients:</i>						
sour casein	18	18	18	18	18	18
L-cystein	0,3	0,3	0,3	0,3	0,3	0,3
wheat starch	51,45	51,45	51,45	51,45	51,45	55,76
cellulose	5	5	5	5	5	0,5
choline						
bitartrate	0,25	0,25	0,25	0,25	0,25	0,25
Ain93G minerals	3,09	3,09	3,09	3,09	3,09	4,05
KH2PO4	-	-	-	-	-	-
Ain 93						
vitamins	1,1	1,1	1,1	1,1	1,1	1,14
soybean oil	20	-	-	-	-	20
coconut oil	-	-	-	-	19	-
safflower oil	-	-	-	20	1	-
flaxseed oil	-	20	-	-	-	-
menhaden oil	-	-	20	-	-	-

1.2 Macronutrient composition (analysed by TNO-Nutrition, Zeist)

diet	protein (g/100 g)	fat (g/100 g)	carbohydrates (g/100 g)	energy (kcal/100 g)
control diet	15,8	18,4	42,5	399
flaxseed oil diet	15	18,5	43,4	400
fish oil diet	15,5	18,1	44,5	403
safflower oil diet	14,9	18,1	43,5	397
coconut oil diet	15,4	18,4	43,3	400
low fiber diet	15,5	18,4	45,8	411
low protein diet	8,3	18,5	48,7	395

APPENDIX C: Glossary

Ad Libitum:

providing (an animal) free access to feed or water thereby allowing the animal to self-regulate intake according to its biological needs.

Barker hypothesis:

also known as thrifty phenotype hypothesis – named after David Barker: exposure to either excess or poor nutrition *in utero* can lead to an adaptation of foetal metabolism and can program susceptibility of the foetus to development of obesity, cardiovascular disease, hypertension, diabetes and cancer later in life.

Dutch Famine Birth Cohort Study:

ongoing study investigating the effects of exposure to the 1944-1945 famine in utero on health in adulthood. Over 900 babies born between 1st November 1943 and 28th February 1947 in het Wilhelmina Gasthuis in Amsterdam participated in the study at a age 50. Over 850 people participated at age 59.

Glycaemic index:

an indicator ranking carbohydrate foods according to their effects on their postprandial blood glucose response and hence their effect on blood insulin levels. Carbohydrates that break down rapidly during digestion releasing glucose rapidly into the bloodstream have a high glycaemic index; carbohydrates that break down slowly, releasing glucose gradually into the bloodstream, have a low glycaemic index.

Iso-caloric:

containing equal amounts of energy, while the macronutrient composition of the diet may differ.

Perinatal exposure:

exposure to e.g. experimental diets during pregnancy, and during early life of the pups.

Postnatal exposure:

exposure to e.g. experimental diets after birth.

Prenatal exposure:

exposure to e.g. experimental diets during pregnancy.

Programming:

reflects the action of a factor during a sensitive period or window of development to exert organizational effects that persist throughout life. Programming agents might include growth factors, hormones, and nutrients. These factors may produce adaptations that permanently alter adult metabolism and responses in a direction optimizing survival under continued conditions of malnutrition, stress, or other deprivation, but such responses might be detrimental when the later environment is unexpectedly less challenging.

Thrifty phenotype hypothesis:

see Barker hypothesis.

Weaning:

moment when offspring are separated from their mother and are permanently deprived of breast milk. For mice, weaning usually occurs at 3 weeks of age.

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