Health effects of food consumption and dietary patterns during pregnancy

No. 2021/26-A2e, The Hague, June 22, 2021

Background document to:
Dietary recommendations for pregnant women
No. 2021/26, The Hague, June 22, 2021

Health Council of the Netherlands

contents

01 introduction

The committee described its working method for evaluating the literature in a separate background document.[1]
In this background document, the current state of scientific knowledge is presented on the relation between food and dietary patterns during pregnancy and maternal health, pregnancy outcomes, and offspring health. Using a decision tree (Appendix A), the committee has drawn conclusions per exposure and outcome measure if at least two RCTs or two cohort studies were summarised in a systematic review. These specific conclusions are not recommendations; recommendations for pregnant women are formulated in the advisory report.

The committee carried out a systematic literature search in PubMed and Psychinfo to retrieve systematic reviews (with or without meta-analysis) on a priori selected exposures and outcomes (Appendix B). The initial searches were performed until July 2018. They were updated in the summer of 2019 (until July 2019). When new systematic reviews were found, results were added to the evaluation of the committee. Furthermore, any publications missed by the search but known to the committee could be added. Also, a public consultation round took place in autumn 2019, asking explicitly for potentially missed publications. The committee therefore considers it reasonable to assume that the relevant publications up to autumn 2019 have been considered. An extensive description of the methodology is available in the background document '*Working method for drawing up dietary recommendations for pregnant women*'.

The focus is on health effects. Intermediary measures of health (such as maternal blood pressure or infants' head circumference) are outside the scope of this review. In addition, the committee did not include health effects for which only one RCT or cohort study was described in systematic reviews.

02
dietary patterns

In this chapter, the committee describes the evidence on the relation between dietary patterns during pregnancy and the health of mother and child. The evidence is restricted to dietary patterns that were defined in advance (*a priori*), such as a Mediterranean diet score, Healthy Eating Index, a low glycaemic index diet, and a vegan or vegetarian diet, but also Ramadan observance. Findings on *a posteriori* defined dietary patterns (i.e. defined on the basis of the study) are not considered by the committee. *A posteriori* defined dietary patterns are especially suitable for hypothesis formulation. The resulting dietary patterns depend largely on dietary habits within a cohort, resulting in study-specific dietary patterns. Analysis of these results is a first step towards the formulation of recommended dietary patterns. For the purpose of formulating dietary guidelines, such as in this advisory report, results of studies with *a priori* defined recommended dietary patterns are leading, because these are the studies in which the hypotheses are tested.

Both systematic reviews summarising intervention studies (RCTs) and cohort studies were eligible for inclusion. Systematic reviews of RCTs were available for low glycaemic index diets and dietary antigen avoidance diets. For vegetarian or vegan diets, recommended dietary patterns and Ramadan observance, the evidence came from systematic reviews of cohort studies.

Based on the available evidence, the committee could distinguish five dietary patterns: 1) vegetarian or vegan diet, 2) the low glycaemic index diet, 3) dietary antigen avoidance diet, 4) recommended dietary patterns that measure adherence to, for instance, dietary guidelines, the Dietary Approaches to Stop Hypertension (DASH) diet, and the Mediterranean diet, and 5) Ramadan observance.

2.1 Vegetarian and vegan diet

This paragraph describes the scientific evidence from systematic reviews of cohort studies on the association between a vegetarian or vegan diet during pregnancy and the risk of gestational hypertension. For other outcomes of interest, the committee did not find systematic reviews summarising at least two cohort studies. For this exposure, no systematic reviews summarising at least two RCTs were found.

The committee did find the systematic review of Tan et al. (2018) that described the evidence regarding the risks of hypospadias, impaired neurodevelopment, and intrauterine growth retardation. However, there was only one cohort study for each of these outcome measures.[2] Therefore, these results were not further evaluated by the committee.

2.1.1 Gestational hypertension

Summary: Vegetarian or vegan diet during pregnancy and risk of gestational hypertension.

Aspect	Explanation
Selected studies	One systematic review of three cohort studies[3]
Heterogeneity	Not applicable
Strength of the association	No adjusted risk estimates
Study population	Vegetarian/vegan and omnivorous women from Europe and North America

Conclusion (cohort studies):

There is too little research to draw a conclusion on the association between a vegetarian or vegan diet during pregnancy and the risk of gestational hypertension.

Explanation

There is one systematic review of a vegetarian or vegan diet during pregnancy and health outcomes of mother and child, in terms of gestational hypertension.[3] The authors emphasised that the number of studies on the effect of a vegetarian or vegan diet during pregnancy on health outcomes in mother and child are limited. The committee found no more recent cohort studies on a vegetarian or vegan diet and risk of gestational hypertension.

Piccoli et al. (2015), for instance, summarised three cohort studies narratively on gestational hypertensive disorders. One cohort had no comparison group of omnivores and only one case of pre-eclampsia.[4] The two remaining cohort studies had one overlapping outcome related to gestational hypertension (pre-eclampsia, although pre-eclampsia was not clearly defined); both cohorts were small and did not adjust their findings for potential confounders.[5,6] As there are no studies available with adjusted risk estimates or a correct comparison group, results were not further evaluated by the committee.

The committee concludes that there is too little research to draw a conclusion on the association between a vegetarian or vegan diet and the risk of gestational hypertension.

2.2 Low glycaemic index diet

This paragraph describes the scientific evidence from systematic reviews of intervention studies on the effect of a low glycaemic index diet during pregnancy on gestational age, the risk of preterm birth, a large for gestational age infant, a small for gestational age infant, and on gestational diabetes. For other outcomes of interest, the committee did not find systematic reviews summarising at least two RCTs. On this exposure, no systematic reviews summarising at least two cohort studies were found.

2.2.1 Gestational age

Summary: Low glycaemic index diet during pregnancy and gestational age.

Aspect	Explanation
Selected studies	One meta-analysis of five RCTs[7]
Heterogeneity	No
Strength of the effect	Mean difference: +0.03 weeks (95%CI -0.14 to +0.20)
Study population	Healthy pregnant women and pregnant women at high risk of or with gestational diabetes

Conclusion:

Based on RCTs, an effect of (dietary advice to follow) a low glycaemic index diet on gestational age is unlikely.

Explanation

There are three systematic reviews on the effect of a low glycaemic index diet on gestational age.[7-9] Tieu et al. updated their 2008 systematic review in 2017.[8,9] Tieu et al. (2017) summarised three RCTs. All of these were also summarised by Zhang et al. (2018) in combination with two other RCTs. The intervention in the three RCTs in both systematic reviews consisted of dietary advice to follow a low glycaemic index diet during pregnancy. In the other two studies in the systematic review of Zhang et al. (2018), either food products or dietary advice were provided to the pregnant women. Since Zhang et al. (2018) is the most recent and complete review, the committee focused on their findings (Table 1).[7] The committee did not find any more recent RCTs on glycaemic index and gestational age.

Zhang et al. (2018) found no significant effect of (dietary advice to follow) a low glycaemic index diet on gestational age. The effect estimate was close to zero, and heterogeneity was low.[7]

In conclusion, an effect of (dietary advice to follow) a low glycaemic index diet on gestational age is unlikely.

Table 1. Results from the meta-analysis of Zhang et al. (2018) on the effect of a low glycaemic index diet during pregnancy on gestational age.

Intervention	Control	Number of RCTs	n/N inter-vention	n/N control	Gestational age (weighted mean difference in weeks)	95%-CI	Hetero-geneity I^2
Low glycaemic index diet (median glycaemic index 50) from 13 until 30 weeks or the end of gestation	High glycaemic index diet (median glycaemic index 58) from 13 until 30 weeks or the end of gestation	5	n.r.	n.r.	0.03	-0.14 to +0.20	5%

CI: Confidence Interval; n/N: number of cases/total number of participants; n.r.: not reported; RCT: Randomised Controlled Trial.

2.2.2 Preterm birth

Summary: Low glycaemic index diet during pregnancy and risk of preterm birth.

Aspect	Explanation
Selected studies	One meta-analysis of four RCTs[7]
Heterogeneity	No
Strength of the effect	RR = 0.70 (95%CI 0.39-1.28)
Study population	Healthy pregnant women and pregnant women at high risk of or with gestational diabetes

Conclusion (RCTs):

There is too little research to draw a conclusion on the effect of a low versus high glycaemic index diet during pregnancy on the risk of preterm birth.

Explanation

There is one systematic review on the effect of a low glycaemic index diet on the risk of preterm birth (Table 2).[7] The committee did not find any more recent RCTs on a low glycaemic index diet and the risk of preterm birth.

Zhang et al. (2018) summarised four RCTs. The authors found an effect estimate of a low versus a high glycaemic index diet on the risk of preterm birth that was not close to one, but not statistically significant either (RR = 0.70; 95%CI 0.39-1.28). The confidence interval around the estimate was wide, limiting the interpretation of the finding. Heterogeneity was moderate. In addition, it is unclear from the systematic review how the interventions were carried out, i.e. by dietary advice or through the provision of specific foods or complete meals.[7]

Considering the number of studies, with an effect estimate that is not close to one, but with a wide confidence interval the committee concludes that there is too little research to draw a conclusion on the effect of a low versus high glycaemic index diet on risk of preterm birth.

Table 2. Results from the meta-analysis of Zhang et al. (2018) on the effect of a low glycaemic index diet during pregnancy on the risk of preterm birth.

Intervention	Control	Number of RCTs	n/N inter-vention	n/N control	RR	95%-CI	Hetero-geneity I^2
Low glycaemic index diet (median glycaemic index 50) from 13 until 30 weeks or the end of gestation	High glycaemic index diet (median glycaemic index 58) from 13 until 30 weeks or the end of gestation	4	n.r.	n.r.	0.70	0.39-1.28	30%

CI: Confidence Interval; n/N: number of cases/total number of participants; n.r.: not reported; RCT: Randomised Controlled Trial; RR: Relative Risk.

2.2.3 Large for gestational age

Summary: Low glycaemic index diet during pregnancy and risk of an infant that is large for gestational age.

Aspect	Explanation
Selected studies	Two meta-analyses of eight RCTs[7] and three RCTs[8]
Heterogeneity	Yes, in one meta-analysis
Strength of the effect	RR = 0.52 (95%CI 0.31-0.89); five open studies (RR = 0.39; 95%CI 0.12-1.31), three blinded studies (RR = 1.31; 95%CI 0.50-3.41)[7] RR = 0.60 (95%CI 0.19-1.86)[8]
Study population	Healthy pregnant women and pregnant women at high risk of or with gestational diabetes

Conclusion:

Based on RCTs, the findings of intervention studies on the effect of a low versus high glycaemic index diet during pregnancy on the risk of an infant that is large for gestational age are inconclusive.

Explanation

There are four systematic reviews on the effect of the advice to follow a low glycaemic index diet on the risk of large for gestational age infants.[7-10] Tieu et al. updated their 2008 systematic review in 2017.[8,9] Zhang et al. (2018) summarised eight RCTs. Two of these were also summarised by Tieu et al. (2017) in combination with one other RCT. The four RCTs included by Xu et al. (2018) are all included by Zhang et al. (2018). Therefore, the review of Xu et al. (2018) is not further discussed by the committee. The interventions in the RCTs in the systematic review of Tieu et al. (2017) consisted of dietary advice to follow a low glycaemic index diet during pregnancy. Zhang et al. (2018) did not explain how the dietary intervention was carried out. As the RCTs in the systematic reviews only partially overlap, the committee describes both systematic reviews below (Table 3). The committee did not find any more recent RCTs on the glycaemic index and the risk of an infant that is large for gestational age.

Zhang et al. (2018) found that a low glycaemic index diet significantly lowers the risk of a child that is large for gestational age. Heterogeneity was moderate. In subgroup analysis, the effect differed between the five RCTs with an open study design (RR = 0.39; 95%CI 0.12-1.31) and the three with a blinded design (RR = 1.31; 95%CI 0.50-3.41). In addition, the effect was stronger in women without gestational diabetes and in RCTs with a difference of seven or more glycaemic index points between the intervention and control group.[7]

Tieu et al. (2017) found no significant effect of dietary advice to follow a low glycaemic index diet on the risk of a child that is large for gestational age (RR = 0.60; 95%CI 0.19-1.86). Heterogeneity was considerable and appeared to be mostly driven by the difference between one study which found a significantly lower risk, and both other studies which found risks close to one.[8]

The combined number of RCTs is nine, but the total number of cases is unknown. Based on the number of cases included by Tieu et al. (2017) and the fact that Zhang et al. (2018) included six additional RCTs, the

committee assumes that the total number of cases exceeds 60 in the intervention and/or control group.

Based on the number of RCTs (≥ 5), the assumed number of cases (≥ 60 but < 100), the substantial heterogeneity and the fact that risk estimates had values substantially lower and substantially higher than 1.00, but with wide confidence intervals that included 1.00, the committee concludes that study findings on the effect of a low versus high glycaemic index diet on the risk of an infant that is large for gestational age are inconclusive.

Table 3. Results from the meta-analysis of Tieu et al. (2017) and Zhang et al. (2018) on the effect of a low glycaemic index diet during pregnancy on the risk of an infant that is large for gestational age.

Study type	Intervention	Control	Number of RCTs	n/N inter-vention	n/N control	RR	95%-CI	Hetero-geneity I^2
Overall meta-analysis Zhang[7]	Low glycaemic index diet (median glycaemic index 50) from 13 until 30 weeks or the end of gestation	High glycaemic index diet (median glycaemic index 58) from 13 until 30 weeks or the end of gestation	8	n.r.	n.r.	0.52	0.31-0.89	44%
Meta-analysis of open studies by Zhang[7]	Low glycaemic index diet (median glycaemic index 50) from 13 until 30 weeks or the end of gestation	High glycaemic index diet (median glycaemic index 58) from 13 until 30 weeks or the end of gestation	5	n.r.	n.r.	0.39	0.12-1.31	51%
Meta-analysis of blinded studies by Zhang[7]	Low glycaemic index diet (median glycaemic index 50) from 13 until 30 weeks or the end of gestation	High glycaemic index diet (median glycaemic index 58) from 13 until 30 weeks or the end of gestation	3	n.r.	n.r.	1.31	0.50-3.41	0%
Overall meta-analysis Tieu[8]	Dietary advice to follow a low glycaemic index diet	Dietary advice to follow a moderate/high glycaemic index diet	3	35 / 400	43 / 377	0.60	0.19-1.86	62%

CI: Confidence Interval; n/N: number of cases/total number of participants; n.r.: not reported; RCT: Randomised Controlled Trial; RR: Relative Risk.

2.2.4 Small for gestational age

Summary: Low glycaemic index diet during pregnancy and risk of an infant that is small for gestational age.

Aspect	Explanation
Selected studies	Two meta-analyses of six RCTs[7] and three RCTs[8]
Heterogeneity	No
Strength of the effect	RR = 1.33 (95%CI 0.71-2.50)[7] and RR = 0.88 (95%CI 0.53-1.45)[8]
Study population	Healthy pregnant women and pregnant women at high risk of or with gestational diabetes

Conclusion:

Based on RCTs, the findings on the effect of a low versus high glycaemic index diet during pregnancy on the risk of an infant that is small for gestational age are inconclusive.

Explanation

There are two systematic reviews on the effect (of the advice to follow) a low glycaemic index diet during pregnancy on the risk of large for gestational age infants.[7,8] Zhang et al. (2018) summarised six RCTs. Two of these were also summarised by Tieu et al. (2017) in combination with one other RCT. The interventions in the RCTs in the systematic review of Tieu et al. (2017) consisted of dietary advice to follow a low glycaemic index diet during pregnancy. As the RCTs in the systematic reviews only partially overlap, the committee describes both systematic reviews below (Table 4). The committee did not find any more recent RCTs on a low glycaemic index diet during pregnancy and the risk of an infant that is small for gestational age.

Zhang et al. (2018) neither found a significant effect of a low glycaemic index diet during pregnancy on the risk of an infant that is small for gestational age (RR = 1.33; 95%CI 0.71-2.50).[7]

Tieu et al. (2017) found no significant effect of dietary advice to follow a low glycaemic index diet during pregnancy on the risk of an infant that is small for gestational age (RR = 0.88; 95%CI 0.53-1.45). The number of cases was small.[8] Heterogeneity was low in both systematic reviews. The combined number of RCTs is seven, but the total number of cases is unknown. Based on the number of cases included by Tieu et al. (2017) and the fact that Zhang et al. (2018) included four additional RCTs, the committee assumes that the total number of cases exceeds 60 in the intervention and/or control group.

Based on the number of RCTs (≥ 5), the assumed number of cases (≥ 60 but < 100), the wide confidence intervals and the fact that the risk estimates had values substantially lower and substantially higher than 1.00, the committee concludes that study findings on the effect of a low versus high glycaemic index diet on the risk of an infant that is small for gestational age are inconclusive.

Table 4. Results from the meta-analyses of Tieu et al. (2017) and Zhang et al. (2018) on the effect of a low glycaemic index diet during pregnancy on the risk of an infant that is small for gestational age.

First author	Intervention	Control	Number of RCTs	n/N inter-vention	n/N control	RR	95%-CI	Hetero-geneity I^2
Zhang[7]	Low glycaemic index diet (median glycaemic index 50) from 13 until 30 weeks or the end of gestation	High glycaemic index diet (median glycaemic index 58) from 13 until 30 weeks or the end of gestation	6	n.r.	n.r.	1.33	0.71-2.50	0%
Tieu[8]	Dietary advice to follow a low glycaemic index diet	Dietary advice to follow a moderate/high glycaemic index diet	3	27 / 400	29 / 377	0.88	0.53-1.45	0%

CI: Confidence Interval; n/N: number of cases/total number of participants; n.r.: not reported; RCT: Randomised Controlled Trial; RR: Relative Risk.

2.2.5 Gestational diabetes

Summary: Low glycaemic index diet during pregnancy and risk of gestational diabetes.

Aspect	Explanation
Selected studies	One meta-analysis of four RCTs[8]
Heterogeneity	No
Strength of the effect	RR = 0.91 (95%CI 0.63-1.31)
Study population	Healthy pregnant women and pregnant women with gestational diabetes

Conclusion (RCTs):

There is too little research to draw a conclusion on the effect of dietary advice to follow a low versus high glycaemic index diet during pregnancy on the risk of gestational diabetes.

Explanation

There are three systematic reviews of the effect of a low glycaemic index diet during pregnancy on the risk of gestational diabetes mellitus.[8,9,11] Tieu et al. updated their systematic review from 2008 in 2017.[8,9] Fachinetti et al. (2014) summarised one RCT, which was also included in the publications of Tieu et al.[11] Therefore, the committee describes the results of Tieu et al. (2017) below (Table 5).[8] The committee did not find any more recent RCTs on a low glycaemic index diet during pregnancy and the risk of gestational diabetes.

Tieu et al. (2017) summarised four RCTs on dietary advice to follow a low glycaemic index diet during pregnancy. They found no significant effect on the risk of gestational diabetes. The number of cases was small, and heterogeneity was low.

In view of the small number of cases (< 60), the committee concludes that there is too little research to draw a conclusion on the effect of dietary advice to follow a low versus high glycaemic index diet during pregnancy on the risk of gestational diabetes.

Table 5. Results from the meta-analysis of Tieu et al. (2017) on the effect of dietary advice to follow a low glycaemic index diet during pregnancy on the risk of gestational diabetes.

Intervention	Control	Number of RCTs	n/N intervention	n/N control	RR	95%-CI	Hetero-geneity I^2
Dietary advice to follow a low glycaemic index diet	Dietary advice to follow a moderate/high glycaemic index diet	4 (3 provided cases)	47 / 468	49 / 444	0.91	0.63-1.31	0%

CI: Confidence Interval; n/N: number of cases/total number of participants; RCT: Randomised Controlled Trial; RR: Relative Risk.

2.3 Dietary antigen avoidance diet

This paragraph describes the scientific evidence from systematic reviews of intervention studies on the effect of a dietary antigen avoidance diet during pregnancy on the risk of atopic disease in the offspring. The committee did not limit the specifications to antigen avoiding diets. The committee adopted definitions that were used in the identified publications. For other outcomes of interest, the committee did not find systematic reviews summarising at least two RCTs. For this exposure, no systematic reviews summarising at least two cohort studies were found.

2.3.1 Atopic eczema and asthma-like symptoms

Summary: Dietary antigen avoidance diet during pregnancy and risk of atopic eczema and asthma-like symptoms in the offspring.

Aspect	Explanation
Selected studies	Two RCTs[12,13]
Heterogeneity	Not applicable
Strength of the effect	Atopic eczema: RR = 1.31 (95%CI 0.78-2.19)[12] and RR = 0.73 (95%CI 0.38-1.39)[13] Asthma-like symptoms: RR = 3.75 (95%CI 0.40-35.33)[12] and RR = 1.01 (95%CI 0.06-15.91)[13]
Study population	Women at high risk of atopic offspring

Conclusion (RCTs):

There is too little research to draw a conclusion on the effect of a dietary antigen avoidance diet on the risk of atopic eczema and asthma-like symptoms in the offspring.

Explanation

There are three systematic reviews of RCTs on the effect of a dietary antigen avoidance diet during pregnancy on the risk of atopic eczema or asthma in the offspring.[14-16] Each of the three systematic reviews describes the same two RCTs, which were carried out in women at high risk of atopic offspring.[12,13] As there are only two RCTs of which the risk estimates indicate opposite directions, the committee describes them separately (Table 6a and 6b). The committee did not find any more recent RCTs on a dietary antigen avoidance diet during pregnancy and the risk of atopic disease in the offspring.

Both RCTs did not find a significant effect of the avoidance or a low intake of cow's milk and eggs during pregnancy on the risk of atopic eczema or asthma-like symptoms in 18-month-old children. In one RCT, the risk of atopic eczema was not significantly increased and in the other not significantly decreased. The number of cases of asthma-like symptoms was very small.[12,13]

In view of the small number of studies (≤ 2) and cases (≤ 60), the committee concludes that there is too little research to draw a conclusion on the effect of a dietary antigen avoidance diet during pregnancy on the risk of atopic disease in the offspring in women at high risk of atopic offspring. The conclusion on too little research applies to all women, because no meta-analyses of intervention studies in women with average or low risk of atopic offspring were available.

Table 6a. Results from the RCTs of Falth-Magnusson et al. (1987) and Lilja et al. (1989) on the effect of a dietary antigen avoidance diet during pregnancy on the risk of atopic eczema in the offspring.

First author	Intervention	Control	n/N intervention	n/N control	RR	95%-CI
Falth-Magnusson [12]	Cow's milk and egg avoidance from 28 weeks of gestation onwards	Habitual diet	22 / 76	21 / 95	1.31	0.78-2.19
Lilja[13]	Low milk and low egg diet in third trimester	High milk and high egg diet in third trimester	13 / 81	18 / 82	0.73	0.38-1.39

CI: Confidence Interval; n/N: number of cases/total number of participants; RCT: Randomised Controlled Trial; RR: Relative Risk.

Table 6b. Results from the RCTs of Falth-Magnusson et al. (1987) and Lilja et al. (1989) on the effect of a dietary antigen avoidance diet during pregnancy on the risk of asthma-like symptoms in the offspring.

First author	Intervention	Control	n/N intervention	n/N control	RR	95%-CI
Falth-Magnusson [12]	Cow's milk and egg avoidance from 28 weeks of gestation onwards	Habitual diet	3 / 76	1 / 95	3.75	0.40-35.33
Lilja [13]	Low milk and low egg diet in third trimester	High milk and high egg diet in third trimester	1 / 81	1 / 82	1.01	0.06-15.91

CI: Confidence Interval; n/N: number of cases/total number of participants; RCT: Randomised Controlled Trial; RR: Relative Risk.

2.4 Recommended dietary patterns

This paragraph describes the scientific evidence from systematic reviews of cohort studies on the association between a recommended dietary pattern during pregnancy and the risk of preterm birth, large for gestational age, small for gestational age, gestational diabetes, gestational hypertension, atopic disease in the offspring, and blood pressure in the offspring. For other outcomes of interest, the committee did not find systematic reviews summarising at least two cohort studies. Furthermore, on this exposure, no systematic reviews summarising at least two RCTs were found.

2.4.1 Preterm birth

Summary: Recommended dietary patterns during pregnancy and risk of preterm birth.

Aspect	Explanation
Selected studies	One meta-analysis of five relevant cohort studies and one study that was outside of the scope[17], and one additional cohort study[18]
Heterogeneity	No
Strength of the association	RR meta-analysis = 0.79 (95%CI 0.68-0.91)
Study population	Pregnant women who were generally healthy with no pre-existing health conditions reported from Australia, North America, Europe, and Asia

Conclusion:

Based on cohort studies, adherence to a healthy dietary pattern during pregnancy is associated with a 21% lower risk of preterm birth (95%CI 9% to 32%).

Level of evidence: Strong.

Explanation

There are three systematic reviews on the association between a recommended dietary pattern during pregnancy and the risk of preterm birth.[17,19,20] Only Chia et al. (2019) performed a meta-analysis, including six publications on prospective cohort studies.[17] The committee considered whether these meta-analysis results could be used, because one of the included cohorts (Saunders et al., 2014)[21] assessed dietary intake during pregnancy retrospectively after delivery. There was no heterogeneity in the direction of the risk estimates between the studies and sensitivity analyses showed that the risk estimates remained statistically significant when omitting one cohort at a time; these risk estimates ranged between 0.72 and 0.87. Therefore, the results of the main analysis are considered suitable for use and presented in Table 7a.

The second systematic review, by Raghaven et al. (2019)[20], included five publications on prospective cohort studies with an a priori defined dietary pattern, four of which were also included by Chia et al. (2019). The fifth publication, by Haugen et al. (2008)[22] from the Norwegian Mother and Child Cohort Study was not included in the meta-analysis of Chia et al. (2019) as they included another publication on the Norwegian Mother and Child Cohort Study. As Haugen et al. (2008) included a smaller sample than the other publication, the publication of Haugen et al. (2008) is not further discussed by the committee.

The third systematic review, by Biagi et al. (2019) [19], included four prospective cohort studies, two of which overlapped with either Chia et al. (2019) or Raghaven et al. (2019), or both. Both remaining publications are not described by the committee because they assessed the dietary information on the pregnancy period retrospectively, after delivery.[19]

In a search for studies published after the final search date of Chia et al. (2019) the committee found one additional cohort study: Project Viva.[18] That study is described as well (Table 7b).

Chia et al. (2019) found that a healthy dietary pattern during pregnancy was associated with a statistically significantly lower risk of preterm birth. The following healthy dietary patterns were combined: the Mediterranean Diet, the New Nordic Diet, the Healthy Eating Index for pregnant women in Singapore, the Dietary Approaches to Stop Hypertension diet, and the Australian Recommended Food Score; there were two studies on the Mediterranean Diet and one study on each of the other healthy diet scores. The definitions of the healthy dietary patterns (dietary factors included) varied substantially between the studies, but all included – amongst other factors – beneficial scores for plant foods (fruits and vegetables, some also legumes and nuts) and dairy (especially dairy types with a low(er) fat content). There was moderate heterogeneity, albeit only present in the size of the association, not in the direction.

The total number of cases was not reported in the meta-analysis, but the cumulative number of participants was high, and the additional publication included 127 cases despite being relatively small (Project Viva, 2018). Therefore, the committee assumes that the overall number of cases was at least 500.

The additional publication reported results in the same direction as the meta-analysis, although not statistically significant and with a risk estimate close to 1.00.

In view of the large number of studies, the statistical significance in the meta-analysis and the consistency in the direction of the risk estimates, the committee concludes that there is strong evidence that adherence to a healthy dietary pattern during pregnancy is associated with a 21% lower risk of preterm birth (95% CI 9% to 32%).

Table 7a. Results from the meta-analysis of Chia et al. (2019) on the association between recommended dietary patterns during pregnancy and the risk of preterm birth.

Number of cohorts	Exposure	Timing diet assessment	N participant	N cases	RR estimate (95%CI)	Heterogeneity
6[a]	Highest tertile versus lowest tertile	five cohorts during pregnancy, one cohort after delivery	114,431	n.r.	0.79 (0.68-0.91)	32%

CI: Confidence Interval; N: number; n.r.: not reported; RR: Relative Risk estimate (can also be an odds ratio or hazard ratio). [a] one study was not relevant for the committee due to its measurement procedure, this was the smallest included study (N=728).

Table 7b. Results from the additional cohort study Project Viva on the association between recommended dietary patterns during pregnancy and the risk of preterm birth.

Cohort name	Exposure	Timing diet assessment	N participant	N cases	RR estimate (95%CI)
Project Viva[18]	DASH diet; per unit diet score	Around 11 weeks of gestation	1,760	127	0.96 (0.91-1.03)

CI: Confidence Interval; N: number; n.r.: not reported; RR: Relative Risk estimate (can also be an odds ratio or hazard ratio).

2.4.2 Large for gestational age

Summary: Recommended dietary patterns during pregnancy and risk of an infant that is large for gestational age.

Aspect	Explanation
Selected studies	Four individual cohort studies[18,23-26]
Heterogeneity	Not applicable
Strength of the association	Varying from 0.71 (95%CI 0.37-1.35) for the alternate Mediterranean diet to 1.07 (95%CI 1.00-1.15) for the New Nordic Diet
Study population	Pregnant women who were generally healthy with no pre-existing health conditions from North America and Europe

Conclusion (cohort studies):

There is too little research to draw a conclusion on the association between a recommended dietary pattern during pregnancy and the risk of an infant that is large for gestational age.

Explanation

There are two systematic reviews on the association between dietary patterns during pregnancy and the risk of an infant that is large for gestational age.[17,20] Both included three prospective cohort studies that used an *a priori* index score to assess diet, and thus fit in the scope of the committee.[23-25] Chia et al. (2019) performed a meta-analysis, however they included a study on an *a posterior* defined dietary pattern as well, which is outside the committee's scope. As there was heterogeneity in the direction of the associations between the cohorts in the meta-analysis which might be explained by this exposure type, the committee judged that the summarised risk estimate from the meta-analysis could not be used. Instead, the results of the three individual cohort studies are described (Table 8).

A search for additional cohort studies that were published after the search date of Chia et al. (2019) retrieved two more publications: one additional publication on an already included cohort[18], and one additional cohort study (Table 8).[26]

The Alternate Healthy Eating Index for Pregnancy was examined as exposure in three cohorts: two American cohorts (the Infant Feeding Practice Study II, described by Poon et al. (2013)[23] and Project Viva, described both by Fulay et al. (2018)[18] and Rifas-Shiman et al. (2009)[25]); and one British cohort (Emond et al. (2018)[26]). All found a lower, but statistically non-significant risk for participants with higher scores on the index.

Poon et al. (2013) also examined the exposure 'alternate Mediterranean diet'. Again, a lower but statistically non-significant risk was found for those with high adherence versus low adherence.

Fulay et al. (2018) reported that higher adherence to the DASH diet was statistically significantly associated with a lower risk of an infant that is large for gestational age.

The New Nordic Diet was examined by Hillesund et al. (2014) in a Norwegian cohort study.[24] They found a statistically significantly higher risk for those with high adherence compared to those with low adherence.

In view of the limited number of studies (four), the mostly wide confidence intervals and mostly non-significant risk estimates ranging from protective to negative, the committee concludes that there is too little research on the association between a recommended dietary pattern during pregnancy and the risk of an infant that is large for gestational age.

Table 8. Results from the cohort studies identified from the systematic reviews of Chia et al. (2019) and Raghavan et al. (2019), an additional publication on Project Viva and one additional cohort study on the association between recommended dietary patterns during pregnancy and the risk of an infant that is large for gestational age.

Cohort name	Exposure	Timing diet assessment	N participant	N cases	RR estimate (95%CI)
Infant Feeding Practice Study II[23]	Highest versus lowest tertile	28-36 weeks of gestation. Represents last month	893	82	0.92 (0.50-1.69) Alternate Healthy Eating Index for Pregnancy 0.71 (0.37-1.35) alternate Mediterranean diet
Project Viva[18]	Per unit diet score	Around 11 weeks of gestation	1,760	234	0.94 (0.90-0.99) DASH diet
Project Viva[25]	Per 5 point score	First and second trimester	1,777	At least 228[a]	0.95 (0.89-1.02) first trimester Alternate Healthy Eating Index for Pregnancy 0.99 (0.92-1.07) second trimester Alternate Healthy Eating Index for Pregnancy
Norwegian Mother and Child Cohort Study[24]	High versus low adherence	Around 22 weeks of gestation. Represents conception to mid-pregnancy	66,597	7,427	1.07 (1.00-1.15) New Nordic Diet
New Hampshire Birth Cohort study[26]	Highest versus lowest quartile	24 to 28 weeks of gestation	862	75	0.71 (0.32-1.57) Alternate Healthy Eating index 2010

CI: Confidence Interval; N: number; RR: Relative Risk estimate (can also be an odds ratio or hazard ratio). [a] 13.7% of the sample had an infant that was large for gestational age (at first trimester N = 1,777 at second trimester N = 1,666).

2.4.3 Small for gestational age and foetal growth restriction

Summary: Recommended dietary patterns during pregnancy and risk of an infant that is small for gestational age or with foetal growth restriction.

Aspect	Explanation
Selected studies	One meta-analysis of six relevant cohort studies and one study that was outside of the scope[17], two additional publication on already included cohort studies[18,27] and one additional cohort study[26]
Heterogeneity	No
Strength of the association	RR meta-analysis = 0.87 (95%CI 0.70-1.06)[17] RR Project Viva on the DASH diet = 0.96 (95%CI 0.89-1.03)[18] RR INMA-Valencia on the Alternate Healthy Eating Index = 0.24 (95%CI 0.10-0.55)[27] RR NHBCS on the Alternate Healthy Eating Index = 0.35 (95%CI 0.11-1.08)[26]
Study population	Pregnant women who were generally healthy with no pre-existing health conditions from Australia, North America and Europe

Conclusion:

Findings from cohort studies on the association between a recommended dietary pattern and the risk of an infant that is small for gestational age or with foetal growth restriction are inconclusive.

Explanation

There are three systematic reviews reporting on the association between a recommended dietary pattern during pregnancy and the risk of an infant that is small for gestational age or that is growth restricted.[17,19,20] All reviews combined the outcomes small for gestational age and foetal growth restriction.

Biagi et al. (2019) included one publication on two cohorts, which was also included by both Chia et al. (2019) and Raghavan et al. (2019).

Chia et al. (2019) performed a meta-analysis of eight risk estimates from seven cohort studies. One cohort study was outside of the scope of the evaluation of the committee as it assessed dietary information about the pregnancy period after delivery rather than during pregnancy.[21] As this study had no substantial impact on the analysis, the committee judged that the meta-analysis was sufficiently useful for the evaluation.

The committee used the meta-analysis by Chia et al. (2019) as the primary publication (Table 9).

Raghavan et al. (2019) included five publications, four of which were also included by Chia et al. (2019). The fifth publication, by Rodriguez-Bernal et al. (2010), was on a subsample of the Infancia y Medio Ambiente (INMA) Project. A publication on the full cohort was included in the meta-analysis by Chia et al. (2019), but this publication reported on a different Healthy Eating Index.[27] The committee presents this additional publication in Table 9.

An extra search was performed to identify studies that were published after the search date of Chia et al. (2018). The committee found two relevant publications: one additional publication on Project Viva[18] and one publication on a new cohort.[26] These are also presented in Table 9.

The meta-analysis by Chia et al. (2018) found no statistically significant association, but the risk estimate was below 1.00. The included dietary

patterns were a Mediterranean Diet, the Alternate Healthy Eating Index for Pregnancy, the New Nordic Diet and the Australian Recommended Food Score. There was moderate heterogeneity, which was not explained by the authors. Visual inspection of the forest plot revealed that heterogeneity was present in both the direction and the size of the association.

The additional publication by Rodriguez-Bernal et al. (2010) on a subsample from the INMA Cohort reported that high adherence to the Alternate Healthy Eating Index for Pregnancy was associated with a statistically significantly lower risk of an infant with foetal growth restriction in weight but not in length.[27]

On Project Viva, the meta-analysis included results on the Alternate Health Eating Index for Pregnancy. The additional publication by Fulay et al. (2018) reported on the DASH diet and found a lower but statistically non-significant association between adherence to the DASH diet and the risk of an infant that is small for gestational age.[18]

Like most other studies, the newly identified British cohort found a lower but statistically non-significant association for the Alternate Healthy Eating Index.

In view of 1) the number of studies (≥ 5), 2) the fact that the risk estimate from the meta-analysis was not close to one, but not statistically significant either, with visual heterogeneity in both the direction and the size of the association, 3) the observation that two of the three additional publications found no significant association either, and 4) the only publication with a significant association, the committee concludes that study findings on the association between a recommended dietary pattern and the risk of an infant that is small for gestational age or with foetal growth restriction are inconclusive.

Table 9. Results from the meta-analysis of Chia et al. (2019), the additional publication on the INMA cohort and Project Viva and the additional cohort study on the association between recommended dietary patterns during pregnancy and the risk of an infant that is small for gestational age or with foetal growth restriction.

Study type	Number of cohorts	Timing diet assessment	N participant	N cases	RR estimate (95%CI)	Heterogeneity
Meta-analysis[17]	7[a]	Throughout pregnancy	80,726	n.r.	0.87 (0.70-1.06) highest versus lowest tertile	36%
Additional publication on Project Viva[18]	1	Around 11 weeks of gestation	1,760	97	0.96 (0.89-1.03) DASH diet; per unit diet score	n.a.
Additional publication on a subsample of the INMA cohort[27]	1	0 to 14 weeks of gestation	787	Around 78[b]	0.24 (0.10-0.55) Alternate Healthy Eating Index for Pregnancy; highest versus lowest quintile	n.a.
Additional cohort New Hampshire Birth Cohort study[26]	1	24 to 28 weeks of gestation	862	40	0.35 (0.11-1.08) Alternate Healthy Eating index 2010; highest versus lowest quartile	n.a.

CI: Confidence Interval; N: number; n.r.: not reported; n.a.: not applicable; RR: Relative Risk estimate (can also be an odds ratio or hazard ratio). [a] one of which is outside the scope of the committee due to its measurement procedure; this was the smallest included study (N=728). In the meta-analysis, the authors counted the INMA cohort as two cohorts, i.e. resulting in a total of 8 cohorts. The committee, however, counted this cohort as one. [b] 9.9% was growth restricted.

2.4.4 Gestational diabetes

Summary: Recommended dietary pattern during pregnancy and the risk of gestational diabetes.

Aspect	Explanation
Selected studies	Two systematic review of three cohort studies[28] and four cohort studies [29] and one additional publications on a new cohort[30] and two additional publication on already included cohorts[18,31]
Heterogeneity	Not reported
Strength of the association	In the four larger cohort studies, five out of seven scores on various recommended dietary patterns were associated with a significant 24% to 38% lower risk
Study population	Pregnant women without a history of diabetes mellitus or gestational diabetes mellitus from Europe, North America, and Australia

Conclusion:

Based on cohort studies, a diet according to a recommended dietary pattern during pregnancy is associated with a lower risk of gestational diabetes mellitus.

Level of evidence: Limited.

Explanation

There are four systematic narrative reviews and one meta-analysis on the association between following a recommended dietary pattern during pregnancy and the risk of gestational diabetes.[28,29,32,33] The meta-analysis of Pham et al. (2019) included four studies, two of which were outside of the scope of the committee because of study design [34] or because the dietary pattern was an *a posterior* score.[35] The remaining two studies were also described by Mijatovic-Vukas et al. (2018), which summarised six publications in total. Chen et al. (2016) summarised two prospective cohort studies, which are also described by Mijatovic-Vukas et al. (2018). The systematic review of Raghavan et al. (2019) included six publications on prospective cohort studies, four of which were also included by Mijatovic-Vucas et al. (2018); a fifth reported on a posterior dietary pattern score.[36] Hence, seven unique publications in total were retrieved from the identified systematic reviews. As the publications were found in systematic narrative reviews, the results of the cohorts are presented individually (Table 10).

The six publications included in Mijatovic-Vukas et al. (2018) cover three cohort studies: the Nurses' Health Study II, the Australian Longitudinal Study on Women's Health and a cohort of pregnant women from ten Mediterranean countries.[35,37-41] The committee also found one more recent publication on the Nurses' Health Study II.[31]

Tobias et al. (2012), Zhang et al. (2014) and Gicevic et al. (2018) each describe findings from the Nurses' Health Study II.[31,37,38] As the number of pregnancies and cases is larger in the publication of Tobias et al. (2012) and Gicevic et al. (2018), the committee focuses on these publications.

The additional publication found in Raghavan et al. (2019) was on Project Viva, an American cohort.[25] The committee found one more recent publication on that cohort, which reported on a different diet score.[18]

Additionally, one extra cohort study was identified by the committee: a publication from the Finnish Gestational Diabetes Prevention Study 2017.[30]

Nurses' Health Study

The authors showed that a high score on the Mediterranean Diet Index, the Dietary Approaches to Stop Hypertension (DASH) Index and the Alternate Healthy Eating Index before pregnancy are each associated with a significantly lower risk of gestational diabetes.[31,37] The study is, however, limited by the fact that the dietary patterns were assessed before pregnancy instead of during pregnancy.

Australian Longitudinal Study on Women's Health

From the three publications on the Australian Longitudinal Study on Women's Health Schoenaker et al. (2016) and Gresham et al. (2016) each reported results for a different index.[39,40] The third publication is outside the scope of this report, as it described posterior dietary pattern scores.[35] In this cohort study, there was a significant association between a high Mediterranean Diet Index score and a lower risk of gestational diabetes, whereas the association for the Australian Recommended Food Score was not significant.[39,40]

Cohort from ten Mediterranean countries

Karamos et al. (2014) described pregnant women from ten Mediterranean countries. The authors showed that a high score on the Mediterranean Diet Index during pregnancy was associated with a lower risk of gestational diabetes mellitus.[41] The authors described the study as a prospective cohort study. However, it is unclear whether the food intake data were collected before the oral glucose tolerance test was carried out or on the same day, which limits the interpretation of this finding.[41]

Project Viva 2018

In this American cohort, the association between the Alternate Healthy Eating Index for pregnancy (AHEI-P) and the risk of gestational diabetes mellitus was examined by Rifas-Shiman et al. (2009).[25] The association with the DASH-score was examined by Fulay et al. (2018).[18] Dietary intake assessed early in pregnancy was used by both Fulay et al. (2018) and Rifas-Shiman et al. (2009). Additionally, the latter also reported on dietary intake assessed in the second trimester. There was no significant association between the DASH diet score and the AHEI-P score and the risk of gestational diabetes.

Finnish Gestational Diabetes Prevention Study 2017

In this small cohort study (n = 137), the association between the Healthy Food Intake Index score and the risk of gestational diabetes mellitus in obese pregnant women was studied. The Healthy Food Intake Index is an indicator of adherence to the Nordic Nutrition Recommendations. A lower score on the index was not significantly associated with the risk of gestational diabetes mellitus. The number of cases was small (n = 29), which limits the interpretation of the finding.[30]

All in all, in three out of four larger cohort studies (n > 1,000), a high score on a recommended dietary pattern is significantly associated with a lower risk of gestational diabetes mellitus, whereas in the smaller study the association is not significant. The committee concludes that a high score on a recommended dietary pattern is significantly associated with a lower risk of gestational diabetes mellitus. In view of the relatively small number of large cohorts, the level of evidence is limited.

Table 10. Results from the cohort studies included in the systematic review of Mijatovic-Vukas et al. (2018) and Raghavan et al. (2019) and two additional cohort studies[18,30] on the association between recommended dietary patterns during pregnancy and the risk of gestational diabetes mellitus.

Cohort name	Timing diet assessment	N participant	N cases	RR estimate (95%CI)
Nurses' Health Study II [37]	Before pregnancy	21,376 live births	872	0.76 (0.60-0.95) Mediterranean Diet Index: highest versus lowest quartile 0.66 (0.53-0.82) Dietary Approaches to Stop Hypertension Index: highest versus lowest quartile
Nurses' Health Study II [31]	Before pregnancy	21,312 live births	916	0.63 (0.50-0.81) Alternate Healthy Eating Index: highest versus lowest quintile
Australian Longitudinal Study on Women's Health [39]	Before pregnancy	3,378 women	240	1.35 (1.02-1.60) low versus high adherence to Mediterranean diet
Australian Longitudinal Study on Women's Health[40]	Before and during pregnancy	1,907 pregnancies	83	1.70 (0.70-4.00) Australian Recommended Food Score: highest versus lowest quintile
Cohort of 10 Mediterranean countries [41]	n.r.	1,003 pregnancies	92 [a]	0.62 (0.40-0.95) High versus low score on Mediterranean Diet Index
Project Viva[25]	First and second trimester	1,777 and 1,666 women	Around 83[b]	0.97 (0.87-1.08) in the first trimester per 5 points on the Alternate Healthy Eating Index for pregnancy. 0.98 (0.87-1.09) in the second trimester
Project Viva[18]	11 weeks gestation	1,701	88	1.01 (0.93-1.09) Dietary Approaches to Stop Hypertension score (per unit)
Finnish Gestational Diabetes Prevention Study[30]	First trimester	137 obese women	29	0.91 (0.78-1.07) Healthy Food Intake Index

CI: Confidence Interval; n.r.: not reported; RR: Relative Risk estimate (can also be an odds ratio or hazard ratio).[a] Criteria of the American Diabetes Association 2010.[41] According to criteria of the International Association of the Diabetes and Pregnancy Study Groups 2012 N cases = 291; RR 0.66 (95%CI 0.55-0.86). [b] 5% developed gestational diabetes mellitus.

2.4.5 Gestational hypertension or pre-eclampsia

Summary: Recommended dietary patterns during pregnancy and risk of gestational hypertension or pre-eclampsia.

Aspect	Explanation
Selected studies	Three cohort studies from the systematic review of Raghavan et al. (2019)[29] and one additional publication on an already included cohort study[18]
Heterogeneity	Not applicable
Strength of the association	Maximal RR of 0.86 (95%CI 0.78-0.95) for high adherence versus low adherence and maximal RR of 1.41 (95%CI 1.18-1.56) for low adherence versus high adherence[a]
Study population	Women preconceptionally and during pregnancy from Europe, North America and Australia

[a] Risk estimates are based on different reference categories and are therefore in different directions. However, they all go into the direction of high adherence being favourable for health.

Conclusion:

Based on cohort studies, high adherence to a recommended dietary pattern during pregnancy is associated with a lower risk of gestational hypertension or pre-eclampsia.
Level of evidence: Limited.

Explanation

There is one systematic review summarising prospective cohort studies with a priori defined diet scores on the association between a recommended dietary pattern and the risk of hypertensive disorders during pregnancy.[29] Raghavan et al. (2019) included three cohort studies. As it was a narrative review, the committee describes the included studies individually (Table 11). Additionally, one extra publication on Project Viva was identified by the committee, which was published after the search date of Raghavan et al. (2019).[18] The results of this publication are described in Table 12 as well.

The findings in all cohort studies were consistent. Three reported that higher adherence to a recommended dietary pattern was associated with a lower risk of gestational hypertension or pre-eclampsia, although statistically significant only in one of these three studies.[18,24,25] The fourth study reported that a lower adherence to a recommended dietary pattern was associated with a statistically significant higher risk of gestational hypertension or pre-eclampsia.[39]

In view of the number of studies and the consistency of the findings across cohort studies, the committee concludes that high adherence to a recommended dietary pattern during pregnancy is associated with a lower risk of gestational hypertension or pre-eclampsia. The level of evidence was limited because the number of available cohort studies was relatively low (four) and only the two largest studies showed a statistically significant association.

Table 11. Results from the cohort studies included in the systematic review of Raghavan et al., 2019 and one additional publication on Project Viva on the association between recommended dietary patterns during pregnancy and the risk of gestational hypertension.

Cohort name	Timing diet assessment	N participant	N cases	RR estimate (95%CI)[a]
Australian Longitudinal Study on Women's Health[39]	Before pregnancy	3,167	273	Hypertensive disorder of pregnancy: 1.41 (1.18-1.56) Mediterranean diet; low versus high adherence
Norwegian Mother and Child Cohort Study[24]	Around 22 weeks of gestation. Representing conception to mid-pregnancy	72,072	2,908	Pre-eclampsia: 0.86 (0.78-0.95) New Nordic Diet; high versus low adherence
Project Viva[25]	Around 12 weeks of gestation. Representing time since last menstrual period	1,777	Around 60[b]	Pre-eclampsia: 0.96 (0.84-1.10) per 5 point increase in Alternate Healthy Eating Index for Pregnancy score.
Project Viva[18]	11 weeks gestation	1,701	175	Hypertensive disorder of pregnancy: 0.98 (0.93-1.04) per 5 point increase in DASH score

CI: Confidence Interval; N: number; RR: Relative Risk estimate (can also be an odds ratio or hazard ratio).
[a] Risk estimates are based on different reference categories and are therefore in different directions. However, they all go into the direction of high adherence being favourable for health. [b] 3.4% developed pre-eclampsia.

2.4.6 Atopic disease in the offspring

Wheeze and asthma-like symptoms

Summary: Recommended dietary patterns during pregnancy and risk of wheeze or asthma-like symptoms in the offspring.

Aspect	Explanation
Selected studies	Six cohort studies[42-46] Two of them are summarised in a pooled analysis[45]
Heterogeneity	Yes based on visual inspection, explained by a very small study
Strength of the association	Varies from RR = 0.22 (95%CI 0.08-0.58) in a very small study[42] to RR = 1.07 (95%CI 0.92-1.25)[44]
Study population	Europe, North America

Conclusion:

Findings from cohort studies on the association between a recommended dietary pattern during pregnancy and risk of wheeze or asthma-like symptoms in the offspring are inconclusive.

Explanation

There are seven systematic reviews of the association between a recommended dietary pattern and the risk of wheeze or asthma-like symptoms.[19,32,47-51] Together, the seven systematic reviews described results from five prospective cohort studies on predefined dietary patterns.[42-45] Three cohort studies are described individually; two were published in a pooled analysis and described as such (Table 12). Additionally, the committee found one more recent cohort study (Table 12).[46]

One small cohort study by Chatzi et al. (2008) showed a significant association between a high Mediterranean diet score and a lower risk of both persistent and atopic wheeze in offspring at 6.5 years of age.[42] The association is, however, not confirmed in the four larger cohort studies in children up to 3 years of age, showing risk estimates for various indexes for recommended dietary patterns close to one.

The committee found one more recent cohort study.[46] In the Generation R study, there was no significant association between recommended dietary patterns during pregnancy and the risk of asthma or asthma-like symptoms in children up to 10 years of age.

In view of the large number of cohorts, and the fact that results are only statistically significant in the smallest study, the committee concludes that study findings on the association between recommended dietary patterns during pregnancy and the risk of wheeze or asthma-like symptoms are inconclusive.

Table 12. Results from the cohort studies on the association between recommended dietary patterns during pregnancy and the risk of asthma-like symptoms in the offspring.

Cohort name	Exposure	Timing diet assessment	N participants (follow-up-time)	N cases	RR estimate	95%-CI
Cohort from all general practices in Menorca[42]	Mediterranean Diet Score 4-7 versus <4	During pregnancy	460 (6,5 years)	37 persistent wheeze	0.22	0.08-0.58
Cohort from all general practices in Menorca[42]	Mediterranean Diet Score 4-7 versus <4	During pregnancy	460 (6,5 years)	20 atopic wheeze	0.30	0.10-0.90
International Study of Wheezing in Infants[43]	Mediterranean Diet Score per unit	During pregnancy	1,409 (17 months)	594 any wheeze	0.96	0.90-1.10
Project Viva[44]	Mediterranean Diet Score per unit	First and second trimester	1,376 (up to 3 years)	175 Recurrent wheeze	0.98	0.89-1.08
Project Viva[44]	Mediterranean Diet Score per unit	First and second trimester	1,376 (up to 3 years)	289 Asthma-like symptoms	1.01	0.94-1.09
Project Viva[44]	Alternate Healthy Eating Index for pregnancy per 10 points	First and second trimester	1,376 (up to 3 years)	175 Recurrent wheeze	1.07	0.87-1.30
Project Viva[44]	Alternate Healthy Eating Index for pregnancy per 10 points	First and second trimester	1,376 (up to 3 years)	289 Asthma-like symptoms	1.07	0.92-1.25
Pooled analysis of Infancia y Medio Ambiente Study and RHEA Study[a] [45]	Mediterranean Diet Score high versus low	Third trimester and delivery or during pregnancy	2,516 (up to 1 year)	768 wheeze	0.97	0.77-1.24
GenerationR[46]	Healthy Diet Index per unit	14 weeks of gestation	3,610 (up to 10 years)	319 ever asthma	0.93	0.85-1.03

CI: Confidence Interval; N: number; RR: Relative Risk estimate (can also be an odds ratio or hazard ratio). [a] Heterogeneity was not statistically significant.

Atopic eczema

Summary: Recommended dietary patterns during pregnancy and risk of atopic eczema in the offspring.

Aspect	Explanation
Selected studies	Three cohort studies[44,45], two of which were pooled by Chatzi et al. (2013)
Heterogeneity	not significant in the pooled analysis
Strength of the association	Varied from RR = 0.94 (95%CI 0.82-1.08)[44] to RR = 1.22 (95%CI 0.88-1.70)[45]
Study population	Europe, North America

Conclusion (cohort studies):

There is too little research to draw a conclusion on the association between a recommended dietary pattern during pregnancy and the risk of atopic eczema in the offspring.

Explanation

There are seven systematic reviews of the association between a recommended dietary pattern during pregnancy and the risk of atopic eczema in the offspring.[19,32,47-51] Together, the seven systematic reviews describe three prospective cohort studies (from two publications).[44,45] The results of these studies are described by the committee (Table 13). The committee did not find any more recent cohort studies on a recommended dietary pattern during pregnancy and the risk of atopic eczema in the offspring.

The three cohort studies found no significant association between various recommended dietary patterns during pregnancy and the risk of atopic eczema in the offspring. Risk estimates varied from RR = 0.94 in a US cohort to RR = 1.22 in the pooled analysis of two European cohorts.[44,45] In view of the small number of studies and the risk estimates that are not statistically significant, the committee concludes that there is too little research to draw a conclusion on the association between recommended dietary patterns during pregnancy and the risk of atopic eczema.

Table 13. Results from the cohort study of Lange et al. (2010) and the pooled analysis of Chatzi et al. (2013) on the association between recommended dietary patterns during pregnancy and the risk of atopic eczema in the offspring.

Study type	Timing diet assessment	N participants (follow-up time)	N cases	RR estimate (95%CI)
Cohort study[44]	First and second trimester	1,376 (3 years)	483	1.00 (0.94-1.06) for Mediterranean Diet Score per unit 0.94 (0.82-1.08) for Alternate Healthy Eating Index for pregnancy (per 10 points)
Pooled analysis[45]	Third trimester and delivery or during pregnancy	2,516 (1 year)	426	1.22 (0.88-1.07) Mediterranean Diet Score-high versus low

CI: Confidence Interval; N: number; RR: Relative Risk estimate (can also be an odds ratio or hazard ratio).

2.4.7 Blood pressure in the offspring

Summary: Recommended dietary patterns during pregnancy and blood pressure in the offspring.

Aspect	Explanation
Selected studies	Three cohort studies included in the systematic review of Elten et al. (2018)[52], two of which are pooled by Chatzi et al. (2017)[53]
Heterogeneity	Not applicable
Strength of the association	Mean difference in systolic blood pressure range from -1.03 to 0.00 mmHG. Mean difference in diastolic blood pressure range from -0.57 to +0.02 mmHG
Study population	Healthy pregnant women in Europe and North America

Conclusion (cohort studies):

There is too little research to draw a conclusion on the association between a recommended dietary pattern during pregnancy and blood pressure in the offspring.

Explanation

The committee found one systematic review on the association between a recommended dietary pattern and blood pressure in the offspring,[52], describing a pooled analysis of two cohort studies[53] and the cohort study by Leermakers et al. (2017)[54] (Table 14).

Chatzi et al. (2017) found that higher adherence to the Mediterranean Diet was associated with a statistically significant reduction in blood pressure in the offspring (systolic as well as diastolic, at the age of 4.2-7.7 years).

Leermakers et al. (2017) did not find a significant association between the Dutch Healthy Eating Index and blood pressure in the offspring at age 6.

In view of the limited number of cohort studies and the diversity in results, the committee concludes that there is too little research to draw a conclusion on the association between a recommended dietary pattern and blood pressure in the offspring.

Table 14. Results from the cohort studies included in the systematic review of Elten et al. (2018) on the association between recommended dietary patterns during pregnancy and blood pressure in the offspring.

Cohort name	Timing diet assessment and outcome	Diet score	N participants	Mean difference mmHG (95%CI)
Pooled analysis of Project Viva and RHEA cohort [53]	1st trimester; age 4.2 and 7.7 years	Mediterranean Diet score; per 3 points increase	1,564	Systolic blood pressure: -1.03 mmHG (-1.65 to -0.42) Diastolic blood pressure: -0.57mmHG (-0.98 to -0.16)
Generation R[54]	1st trimester; age 6 years	Dutch Healthy Diet Index; per SD increase	2,548	Systolic blood pressure: 0.00mmHG (-0.04 to +0.04) Diastolic blood pressure: +0.02mmHG (-0.02 to +0.06)

CI: Confidence Interval; N: number; n.r.: not reported; RR: Relative Risk estimate (can also be an odds ratio or hazard ratio).

2.5 Ramadan

This paragraph describes the scientific evidence from systematic reviews of cohort studies on the association between Ramadan fasting during pregnancy and the risk of preterm birth and an infant that is small for gestational age. For other outcomes of interest, the committee did not find systematic reviews summarising at least two cohort studies.
For this exposure, no systematic reviews summarising at least two RCTs were found.

2.5.1 Preterm birth

Summary: Ramadan fasting during pregnancy and risk of preterm birth.

Aspect	Explanation
Selected studies	One meta-analysis of four cohort studies (five publications)[55] and one additional registry study[56]
Heterogeneity	No
Strength of the association	Meta-analysis: OR = 0.99 (95%CI 0.72 - 1.37)[55]
Study population	Europe, Asia

Conclusion:

Study findings from cohort studies on the association between Ramadan fasting during pregnancy and the risk of preterm birth (< 37 weeks) are inconclusive.

Explanation

There is one meta-analysis on the association between Ramadan fasting during pregnancy and the risk of preterm birth (< 37 weeks).[55] The authors included five publications on four cohort studies. Additionally, one more recent study was found: a registry study from Canada.[56] Publications are summarised in Table 15a and 15b.

The meta-analysis of Glazier et al. (2018) as well as the registry study did not find a significant association between Ramadan fasting during pregnancy and the risk of preterm birth (Table 15a and 15b). In the meta-analysis, three studies were classified as having a low risk of bias.[57-59] The two remaining publications from one cohort were classified as having a moderate risk of bias.[60,61] Ramadan fasting was ascertained as self-reported fasting during the month of Ramadan in four publications.[57-59,61] Daley et al. (2017), the study that accounted for the vast majority of cases in the meta-analysis, was interested in whether or not conception coincided with the month of Ramadan.[60] Although it is likely that Muslim women fasted during this period as they were probably not aware of pregnancy yet, observance of Ramadan was assumed rather than reported. This was also the case in the additional registry study of Tith et al. (2019).[56] They analysed almost 80,000 deliveries from Quebec (Canada), from 1981 to 2017, of Arabic-speaking women and determined whether Ramadan coincided with any trimester of pregnancy.
Further, the outcome of preterm birth might be prone to bias when it comes to the exposure to Ramadan observance. Ramadan is a yearly recurring event which is less likely to occur in pregnancies ending in a preterm delivery. Assuming that all pregnancies are equally distributed

throughout the year, 83% of all deliveries at exactly 40 weeks pregnancy coincide with Ramadan, versus 77% of all deliveries at 37 weeks and 67% of all deliveries at 32 weeks.[a] The association between Ramadan fasting and preterm birth is therefore biased in the direction of an inverse association: the *a priori* risk ratio in case of no association is lower than one. In the meta-analysis, four out of five publications (three out of four cohort studies) included pregnant women at a mean of 19 to 27 weeks of gestation (range 13 to 34 weeks). It is possible that some very preterm deliveries that occurred before inclusion have been missed, although most preterm deliveries occur after this period. Hence, the committee does not expect that this phenomenon induced a substantial amount of bias in the risk estimate of the meta-analysis.

In the additional registry study by Tith et al., the occurrence of Ramadan in the first and second trimester of pregnancy was assessed (Table 15b).[56] They found no association between first or second-trimester fasting and risk of all preterm birth (< 37 weeks).

[a] With a duration of Ramadan of 28 days, and an Islamic calendar year of 355 days, every 28 days of Ramadan are followed by 327 non-Ramadan days. The percentage of full-term pregnancies (exactly 40 weeks duration) coinciding with Ramadan is calculated as described below. The percentages for preterm pregnancies are calculated analogously, for pregnancy durations of exactly 37 and 32 weeks.
Pregnancies with delivery after exactly 40 weeks:
A full-term pregnancy takes 40 weeks, but 38 weeks net because the first two weeks of pregnancy are from the beginning of the last menstrual cycle until ovulation date, thus before the actual pregnancy. A full-term pregnancy thus takes 266 days. These pregnancies do not coincide with Ramadan if conception takes place in the first 61 days after Ramadan ended (327-266=61). These pregnancies coincide with Ramadan if conception takes place in the other 294 days until the next Ramadan starts (355-61). The percentage of pregnancies coinciding with Ramadan is thus (294/355) x100% = 83%.

Tith et al. also performed sub-analyses on different grades of preterm birth, and reported that the occurrence of Ramadan during 15-21 and 22-27 weeks of gestation was associated with a significant increase of the risk of preterm birth at 28-31 weeks of pregnancy:

- An increased risk of preterm birth at 28-31 weeks of pregnancy was observed when pregnancies of Arabic-speaking parents coinciding with Ramadan in week 15-27 of gestation (assuming they observed Ramadan) were compared with pregnancies of Arabic-speaking parents not coinciding with Ramadan during gestation (findings for Ramadan coinciding with 15-21 weeks of gestation are presented in Table 15b).
- An increased risk of preterm birth at 28-31 weeks of pregnancy was also observed when pregnancies of Arabic-speaking parents coinciding with Ramadan in week 15-27 of gestation (assuming they observed Ramadan) were compared with pregnancies of French or English-speaking parents coinciding with Ramadan in week 15-27 of gestation (control condition).
- There was no significant association for the comparison of pregnancies of Arabic-speaking parents not coinciding with Ramadan with French or English-speaking parents not coinciding with Ramadan.

The occurrence of Ramadan during early pregnancy (1-14 weeks) was not associated with the risk of preterm birth at 28-31 weeks of pregnancy. The risks of both preterm birth at 32-36 weeks and preterm birth at 22-27 weeks of pregnancy were not significantly associated with the occurrence

of Ramadan during any trimester of pregnancy (findings for Ramadan coinciding with 15-21 weeks of gestation are presented in Table 15b).

The risk estimate from the meta-analysis is close to one, but the number of included studies is relatively low (< 5). The additional study by Tith et al. is larger than the meta-analysis and reports no statistically significant association of Ramadan in the second trimester of pregnancy with all preterm birth, but this risk estimate is not close to one. Furthermore, the risk of preterm birth after 28-31 pregnancy weeks was significantly higher if the second trimester of pregnancy coincided with Ramadan. The committee concludes that the overall findings are inconclusive.

Table 15a. Results from the meta-analysis of Glazier et al. (2018) and the registry study of Tith et al. (2019) on the association between Ramadan fasting during pregnancy and the risk of preterm birth.

Study type	Number of cohorts	Timing of Ramadan	n/N self-reported Ramadan fasting	n/N no self-reported Ramadan fasting	RR estimate (95%CI)	Hetero-geneity I^2
Meta-analysis[55]	4	First, second, or third trimester	59 / 1,134	265 / 5,335	0.99 (0.72-1.37)	0%

CI: Confidence Interval; n/N: number of cases/total number of exposed or unexposed; RR: Relative Risk estimate (can also be an odds ratio or hazard ratio), N: number; n.a.: not applicable.

Table 15b. Results from the registry study of Tith et al. (2019) on the association between Ramadan coinciding with pregnancy and the risk of preterm birth, for pregnancies with Arabic maternal mother tongue.

Timing of Ramadan	Preterm birth	n/N trimester of pregnancy coincided with Ramadan	n/N trimester of pregnancy did not coincide with Ramadan	RR estimate (95%CI)
First trimester (wk 1-14)	All preterm birth	1.443 / n.r. (N=26,526 based on the reported 5.44 per 100)	2.676 / n.r. (N=47,957, based on the reported 5.58 per 100)	0.98 (0.92-1.04)
Second trimester (wk 15-21)	All preterm birth	927 / n.r. (N=15,901 based on the reported 5.83 per 100)	3,392 / n.r. (N=62,239 based on the reported 5.45 per 100)	1.07 (0.99-1.15)
Second trimester (wk 15-21)	Preterm 22-27 wk	42 / n.r.	181 / n.r.	0.88 (0.62-1.24)
Second trimester (wk 15-21)	Preterm 28-31 wk	101 / n.r.	283 / n.r.	1.33 (1.06-1.68)
Second trimester (wk 15-21)	Preterm 32-36 wk	784 / n.r.	2928 / n.r.	1.05 (0.98-1.14)

2.5.2 Small for gestational age

There is one systematic review on the association between maternal Ramadan fasting and the risk of an infant that is small for gestational age.[55] Glazier et al. (2018) reported that three studies had data on the risk of small for gestational age: Awwad et al. (2012), Malhorta et al. (1989), and Arab et al. (2001).[57,62,63] However, in the systematic review, no further description of the results was given. Therefore, the committee searched for these studies by itself. It turned out that Malhorta et al. (1989) and Arab et al. (2001) did not report data on small for gestational age.[62,63] Awwad et al. (2012) found no difference in the occurrence of small for gestational

age in the exposed versus the unexposed group, with 11 cases in the group of 201 pregnant women fasting during Ramadan, versus 12 cases in the group of 201 unexposed women.[57] No additional observational studies were identified by the committee. As in the end, only one observational study was available, the committee did not draw a conclusion on this outcome.

2.6 Summary of findings

The conclusions in this chapter are based on three meta-analyses [7,8,17], one systematic review[2], two individual RCTs [12,13] (which were identified via systematic reviews[14-16]) and 14 individual cohort studies.[4-6,22-25,27,37,39-45,53,54] (which were identified via systematic reviews as well[3,17,19,20,28,29,32,47-52]). Additionally, five publications were found via the searches that were performed to update the systematic reviews: three on new cohorts[26,30,56] and three on already included cohorts.[18,31,46] Most often, there was too little research to draw a conclusion on the relation between a dietary pattern during pregnancy and assessed outcomes, or study findings were inconclusive. However, the committee found strong evidence that adherence to a recommended dietary pattern during pregnancy was associated with a lower risk of preterm birth. Additionally, limited evidence was found that adherence to a recommended dietary pattern during pregnancy was associated with a lower risk of gestational diabetes mellitus and gestational hypertension/pre-eclampsia.

The committee concluded that it is unlikely that a low glycaemic index diet during pregnancy has an effect on gestational age.

The following overview presents all conclusions of the committee of this chapter on dietary patterns:

Committee's conclusion	Outcome
Strong evidence	• Preterm birth: Based on cohort studies, adherence to a healthy dietary pattern during pregnancy is associated with a 21% lower risk of preterm birth (95%CI 9% to 32%)
Limited evidence	• Gestational diabetes: Based on cohort studies, a diet according to a recommended dietary pattern during pregnancy is associated with a lower risk of gestational diabetes mellitus • Gestational hypertension or pre-eclampsia: Based on cohort studies, high adherence to a recommended dietary pattern during pregnancy is associated with a lower risk of gestational hypertension or pre-eclampsia
Unlikely	• Gestational age: Based on RCTs, an effect of (dietary advice to follow) a low glycaemic index diet on gestational age is unlikely
Contradictory	No conclusions with contradictory evidence
Too little research	• Gestational hypertension: vegetarian and vegan diet (cohort studies) • Gestational diabetes: low glycaemic index diet (RCTs) • Preterm birth: low glycaemic index diet (RCTs) • Large for gestational age: recommended dietary pattern (cohort studies) • Atopic eczema and asthma-like symptoms in the offspring: antigen avoidance diet (RCTs) • Atopic eczema in the offspring: recommended dietary pattern (cohort studies) • Blood pressure in the offspring: recommended dietary pattern (cohort studies)
Inconclusive	• Large for gestational age: low glycaemic index diet (RCTs) • Small for gestational age: low glycaemic index diet (RCTs); recommended dietary pattern (cohort studies) • Wheeze and asthma-like symptoms in the offspring: recommended dietary pattern (cohort studies) • Preterm birth: Ramadan fasting (cohort studies)

2.7 Findings cited in the advisory report

The committee based the recommendations in the advisory report primarily on the conclusions in the background documents with a strong evidence level.
In this chapter, this applies to the association (based on cohort studies) of better adherence to a recommended dietary pattern with a lower risk of preterm birth.

The committee notes here that both conclusions with a limited evidence level, which are not mentioned in the advisory report, point into the same direction as the conclusion with a strong evidence level: the associations (cohort studies) of better adherence to a recommended dietary pattern with a lower risk of (1) gestational diabetes and (2) gestational hypertension or pre-eclampsia.

In the light of the recommendation on a healthy dietary pattern, the committee mentions the inconclusive finding on the Ramadan in the advisory report, along with their expert opinion (no research available) on fasting during pregnancy.

03
meat

This chapter describes the scientific evidence from systematic reviews of cohort studies on the association between meat consumption during pregnancy and the risk of wheeze and eczema in the offspring. For other outcomes of interest, the committee did not find systematic reviews summarising at least two cohort studies. For this exposure, no systematic reviews summarising at least two RCTs were found.

3.1 Atopic disease in the offspring

3.1.1 Wheeze

Summary: Meat intake during pregnancy and the risk of wheeze in the offspring.

Aspect	Explanation
Selected studies	One systematic review of five cohort studies[48] (including a meta-analysis of three cohort studies and one pooled analysis of two cohort studies[45])
Heterogeneity	No
Strength of the association	Meta-analysis: RR = 1.16 (95%CI 0.97-1.40)[48] Pooled analysis: Total meat RR = 1.22 (95%CI 1.00-1.49) ; processed meat RR = 1.18 (95%CI 1.02-1.37)[45]
Study population	Europe, Asia

Conclusion 1:

Based on cohort studies, high versus low meat intake during pregnancy is associated with a higher risk of wheeze in the offspring.

Level of evidence: Limited.

Conclusion 2 (cohort studies):

There is too little research to draw a conclusion on the association between processed meat and the risk of wheeze in the offspring.

Explanation

There are two systematic reviews of maternal meat intake and the risk of wheeze in offspring.[16,48] Beckhaus et al. (2015) summarised five cohort studies. Netting et al. (2014) described two, one of which was also described by Beckhaus et al. (2015). As the other cohort study from the systematic review of Netting et al. (2014) did not describe the association of maternal meat intake with the risk of wheeze but instead the association of a maternal Mediterranean-diet score with risk of wheezing [43] the committee left this study out of consideration. Hence, the findings of Beckhaus et al. (2015) are used by the committee because this is the most relevant, recent and complete systematic review available (Table 16). The committee did not find any more recent cohort studies on this topic.

Beckhaus et al. (2015) did a meta-analysis of three cohort studies. A high versus low intake of meat during pregnancy was associated with a non-significantly higher risk of offspring wheeze (RR=1.16, 95% confidence interval 0.97-1.40); there was moderate heterogeneity.[48] Beckhaus et al. (2015) additionally described the results from a pooled analysis of two cohort studies by Chatzi et al. (2013), including a Spanish cohort and a Greek cohort.[45] The Spanish cohort consisted of three

subsamples from three regions, each providing their own risk estimate. Thus, Chatzi et al. (2013) pooled four risk estimates, three from the Spanish subsamples and one from the Greek cohort. As the Spanish subsamples are not independent, the committee handled them as one cohort. A high versus low total meat intake was borderline significantly associated with a higher risk of offspring wheeze; for processed meat, the association was statistically significant.[45] Heterogeneity was not significant in the pooled analysis.

In view of the number of cohort studies (five) and cases (≥ 500) on high versus low total meat consumption and the fact that both summarised risk estimates are not close to one, the committee concludes that high versus low meat intake during pregnancy is associated with a higher risk of wheeze in the offspring. Because the risk estimates were (close to) borderline significance, the committee considers the level of evidence as limited. The association of a high versus low processed meat consumption with a higher risk of wheeze was statistically significant, but based on only two cohorts, which is considered too little research.

Table 16. Results from systematic review of Beckhaus et al. (2015) on the association between meat intake during pregnancy and risk of offspring wheeze.

Study type	Exposure	Number of cohorts	N participants	N cases	RR estimate (95%CI)	Heterogeneity I^2
Meta-analysis[48]	High versus low intake	3	n.r.	n.r.	1.16 (0.97-1.40)	35%
Pooled analysis[45]	High versus low intake (3rd tertile versus 1st tertile)	2	2,516	768	1.22 (1.00-1.49) and 1.18 (1.02-1.37) specifically for processed meat	n.s.

CI: Confidence Interval; N: number; n.r.: not reported; n.s.: not significant; RR: Relative Risk estimate (can also be an odds ratio or hazard ratio).

3.1.2 Eczema

Summary: Meat intake during pregnancy and the risk of offspring eczema.

Aspect	Explanation
Selected studies	One systematic review of four cohort studies[48] (including a meta-analysis of two cohort studies and one pooled analysis of two cohort studies [45])
Heterogeneity	not significant
Strength of the association	Meta-analysis of two studies RR = 1.28 (95%CI 0.92-1.78)[48] Pooled analysis of two studies: total meat intake RR = 0.96 (95%CI 0.76-1.20), processed meat intake RR = 0.95 (95%CI 0.76-1.20)[45]
Study population	Asia; Europe

Conclusion (cohort studies):

There is too little research to draw a conclusion on the association between meat intake during pregnancy and the risk of offspring eczema.

Explanation

There are two systematic reviews of maternal meat intake and the risk of eczema in offspring.[16,48] Beckhaus et al. (2015) summarised five publications from four cohorts, whereas Netting et al. (2014) described two publications on one cohort study.[64,65] These publications were also included by Beckhaus et al. (2015). Hence, Beckhause et al. (2015) was the most complete review and was used by the committee (Table 17). The committee did not find any more recent cohort studies.

Beckhaus et al. (2015) summarised two Japanese cohort studies in a meta-analysis. As both studies were from Japan, meat intake was relatively low compared with western countries. Additionally, they described the results from a pooled analysis of two European cohorts that were originally presented in a publication of Chatzi et al. (2013).[45] They also identified an additional publication on the Osaka Maternal and Child Health Survey that was not included in their meta-analysis.[65] The committee describes the results of the additional publication on the 3-4 month follow-up separately.[65] The meta-analysis showed a higher but statistically non-significant association between high meat intake during pregnancy and the risk of eczema in the offspring. No information on heterogeneity was presented. This possible higher risk was not replicated in the pooled analysis of Chatzi et al. (2013): they found a non-significant association between meat intake or processed meat intake during pregnancy and the risk of eczema in the offspring. No significant heterogeneity was present.

In the additional publication on the Osaka Maternal and Child Health Study, there was an association between high meat intake during pregnancy and a higher risk of eczema at the age of three to four months.[65]

In view of the number of available cohort studies, the differences in the direction of the association and the fact that all combined risk estimates had a wide confidence interval that included one, the committee concludes that there is too little research to draw a conclusion on the association between intake of meat during pregnancy and the risk of eczema in the offspring.

Table 17. Results from the systematic review of Beckhaus et al. (2015) on the association between meat intake during pregnancy and risk of offspring eczema.

Study type	Exposure	Age of outcome assessment	Number of cohorts	N parti-cipants	N cases	RR estimate 95%CI	Hetero-geneity I^2
Meta-analysis[48]	High versus low intake	n.r.	2	n.r.	n.r.	1.28 (0.92-1.78)	n.r.
Pooled analysis[45]	High versus low intake (3rd tertile versus 1st tertile)	First year of life	2	2,516	426	0.96 (0.76-1.20) 0.95 (0.76-1.19) processed meat	n.s.
Cohort study: Additional publication on the Osaka Maternal and Child Health Study[65]	89.9 versus 33.4 g/d meat	3-4 months	1	771	65	2.59 (1.15-6.17)	n.a.

CI: Confidence Interval; N: number; n.r.: not reported; n.a.: not applicable; n.s.: not significant; RR: Relative Risk estimate (can also be an odds ratio or hazard ratio).

3.2 Summary of findings

The conclusions in this chapter are based on one systematic review of observational studies.[48] High meat intake during pregnancy was associated with a higher risk of wheeze in the offspring. The level of evidence was limited. Available data did not allow for differentiation in type of meat, i.e. white versus red meat. For processed meat intake during pregnancy, there was too little research to draw a conclusion. There was also too little research to draw a conclusion on the association between meat intake during pregnancy and the risk of eczema in the offspring.

The following overview presents all conclusions of the committee of this chapter on meat intake:

Committee's conclusion	Outcome
Strong evidence	No conclusions with strong evidence
Limited evidence	• Wheeze in the offspring: Based on cohort studies, high meat intake during pregnancy is associated with a higher risk of wheeze in the offspring
Unlikely	No unlikely associations or effects
Contradictory	No conclusions with contradictory evidence
Too little research	• Wheeze in the offspring: processed meat intake (cohort studies) • Eczema in the offspring (cohort studies)
Inconclusive	No inconclusive associations or effects

3.3 No findings cited in the advisory report

The committee based the recommendations in the advisory report primarily on the conclusions in the background documents with a strong evidence level.

In this chapter on meat consumption, conclusions with a strong evidence level are not available. There is one conclusion with limited evidence pointing into the direction of a benefit of a lower meat intake.
The committee considers that this evidence is not sufficient for the formulation of recommendations.

04
fish

This chapter describes the scientific evidence from systematic reviews of cohort studies on the association between fish intake during pregnancy and gestational age, and the risk of preterm birth, atopic disease in the offspring, offspring BMI, offspring overweight or obesity, and cognitive and behavioural outcomes. For other outcomes of interest, the committee did not find systematic reviews summarising at least two cohort studies. For this exposure, no systematic reviews summarising at least two RCTs were found.

4.1 Gestational age

Summary: Fish intake during pregnancy and gestational age.

Aspect	Explanation
Selected studies	One pooled analysis of 19 cohort studies[66]
Heterogeneity	No
Strength of the association	>1 to ≤3 versus ≤1 fish /week: 0.41 days (95%CI +0.25 to +0.57) >3 versus ≤1 fish /week: 0.23 days (95%CI +0.05 to +0.41)
Study population	Europe

Conclusion:

Based on cohort studies, intake of more than 1 to 3 versus 1 or fewer times fish per week during pregnancy is associated with 0.4 (0.3 to 0.6) days higher gestational age; Intake of more than 3 times versus 1 or fewer times fish per week with 0.2 (0.1 to 0.4) days higher gestational age.

Level of evidence: Strong.

Explanation

There is one analysis in which the individual data from 19 European population-based birth cohort studies was pooled (Table 18a).[66]

Leventakou et al. (2014) found no significant association between fish intake expressed in portions per week and gestational age. The authors did not test the linearity of the association. When intake was split into three categories, intake of more than 1 to 3 and more than 3 times fish per week was associated with a 0.4 and 0.2 days longer gestational age as compared with once or fewer times fish per week. A fish intake of more than 3 times per week occurred predominantly in the Mediterranean and Scandinavian cohorts. Although in subgroup analyses, the association seemed limited to fatty fish, this was not taken into consideration by the committee because there was significant heterogeneity in the latter analysis, which was not further explored by Leventakou et al. (2014).[66]

The committee found one more recent publication on a Norwegian cohort study.[67] However, the publication described the same data as had been included in the pooled analysis of Leventakou et al. (2014).[66]

The committee, therefore, did not further review the publication.

In conclusion, intake of more than one to 3 versus 1 or fewer times fish per week during pregnancy is associated with 0.4 (0.3 to 0.6) days longer gestational age and intake of more than 3 times versus 1 or fewer times

fish per week with 0.2 (0.1 to 0.4) days longer gestational age. In view of the consistency of findings, the level of evidence is strong.

Table 18a. Results from the pooled analysis from Leventakou et al. (2014) on the association between fish intake during pregnancy and gestational age.

Exposure	Number of cohorts	N participant	Beta (days)	95%-CI	Hetero-geneity I^2
Fish in times/week	19	151,880	-0.02	-0.09 to 0.05	n.s.
>1 to ≤3 versus ≤1 fish /week	13	140,337	0.41	0.25 to 0.57	n.s
>3 versus ≤1 fish /week	13	140,337	0.23	0.05 to 0.41	n.s.
Fatty fish in times/week	13	131,651	0.14	0.31 to 0.03	Significant
Lean fish in times/week	12	129,886	-0.02	-0.12 to 0.08	n.s.
Seafood other than fish in times/week	16	138,148	-0.03	-0.18 to 0.12	n.s.

CI: Confidence Interval; N: number; n.s.: not significant.

Table 18b. Additional regression analysis on the association between categories of the frequency of fish consumption with the outcome gestational age (weeks) received by the committee from L. Chatzi through personal communication.[a]

Type of fish	Frequency category	N (%)	B	95%-CI
Fatty fish	Never	11,300 (16%)	Reference group	
Fatty fish	<1 time/week	36,542 (52%)	0.07	0.03 to 0.11
Fatty fish	≥1 time/week	22,189 (32%)	0.05	0.01 to 0.09
Lean fish	Never or <1 time/week	19,239 (28%)	Reference group	
Lean fish	1-2 times/week	33,861 (50%)	0.04	0.00 to 0.07
Lean fish	≥3 times/week	15,189 (22%)	0.06	0.02 to 0.10
Other seafood	Never	28,531 (37%)	Reference group	
Other seafood	<1 time/week	39,864 (52%)	0.04	0.01 to 0.06
Other seafood	≥1 time/week	8,104 (11%)	0.01	-0.03 to 0.06

[a] The regression model was adjusted for maternal smoking during pregnancy, parity, maternal education, child sex, maternal age, maternal pre-pregnancy BMI, maternal height and cohort.

Additional regression analysis on the type of fish

The committee received an additional regression analysis through personal communication of committee member T. Vrijkotte with L. Chatzi; both were co-authors of the publication by Leventakou et al. (2014).[66] Chatzi provided results of linear regression analyses using the categorised frequency of intake of fatty fish, lean fish and other seafood as the exposure measures (Table 18b). Data was available from 11 of the European population-based birth cohort studies included by Leventakou et al. (2014); the frequency of consumption was very low in most cases, and distributions differed significantly between the cohorts.[a]

The B-estimate and 95% confidence intervals for fatty fish indicate that any consumption of fatty fish is associated with a small increase in gestational age. The B-estimate and 95% confidence intervals for lean fish indicate that at higher consumption frequencies, lean fish may also be associated with a small increase in gestational age.

Based on this additional regression analysis, the committee considers that for fatty fish, a consumption frequency of 1 time per week seems amply

[a] These were the 11 cohorts included in the additional regression analysis. Specifications per cohort between brackets are: the country and the median frequencies of intake of respectively: all fish and other seafood, fatty fish, lean fish and other seafood: GASPII (Italy; 2.2; 1.0; 0.5; 0.3); GENXXI (Portugal; 4.0; 1.0; 2.0; 0.5), HUMIS (Norway; 1.7; 0.4; 1.2; not applicable), INMA (Spain; 4.5; 0.9; 3.5; 0.9), KOALA (The Netherlands; 1.0; 0.5; 1.0; 0.0), LIFEWAYS (Ireland; 0.5; 0.0; 0.5; 0.0), LucKi (The Netherlands; 1.0; 0.5; 0.5; 0.0), MoBa (Norway; 2.0; 0.5; 1.0; 0.1), REPRO_PL (Poland; 2.0; 1.0; 0.5; 0.0), RHEA (Greece; 1.0; 0.5; 0.3; 0.0), SWS (United Kingdom; 1.9; 0.5; 1.0; 0.0). Chatzi notes that analyses of categorical outcomes such as preterm birth were not possible.

sufficient for the association with gestational age. For lean fish, a high frequency of consumption appears to be required for this association.

4.2 Preterm birth

Summary: Fish intake during pregnancy and preterm birth.

Aspect	Explanation
Selected studies	One pooled analysis of 19 cohort studies[66]
Heterogeneity	No
Strength of the association	>1 to ≤3 versus ≤1 fish /week: RR = 0.87 (95%CI 0.82-0.92) >3 versus ≤1 fish /week: RR = 0.89 (95%CI 0.84-0.96)
Study population	Europe

Conclusion:

Based on cohort studies, intake of more than 1 to 3 versus 1 or fewer times fish per week during pregnancy is associated with a 13% (8 to 18%) lower risk of preterm birth; intake of more than 3 times versus 1 or fewer times fish per week with an 11% (4 to 16%) lower risk of preterm birth. Level of evidence: Strong.

Explanation

There is one analysis in which the individual data from 19 European population-based birth cohort studies was pooled (Table 19a).[66]

Leventakou et al. (2014) found no significant association between fish intake expressed in portions per week and risk of preterm birth (< 37 weeks of gestation). There was significant heterogeneity, which was not further explored by the authors. When intake was split into three categories, intake of more than 1 to 3 times fish per week was associated with a 13% (RR = 0.87; 95%CI 0.82-0.92) lower risk of preterm birth and an intake of more than 3 times fish per week with an 11% (RR = 0.89; 95%CI 0.84-0.96) lower risk as compared with 1 or fewer times per week. A fish intake of more than 3 times per week occurred predominantly in the Mediterranean and Scandinavian cohorts. There was no clear association of fatty or lean fish or seafood other than fish with risk of preterm birth.[66]

The committee found two more recent publications.[67,68] One was on a Norwegian cohort study.[67] However, the publication described the same data as had been included in the pooled analysis of Leventakou et al. (2014).[66] The committee, therefore, did not further review the publication. The other was an American study in which fish intake was assessed during the periconceptional period (three months before and the first three months of pregnancy) (Table 19b).[68] Mohanty et al. (2016) did not find any significant association between fish intake and the risk of preterm birth (not defined). The contrast in fish intake was relatively small due to the low intake of fish in the cohort. This may have contributed to a non-significant association.[68] Therefore, the committee bases its conclusions on the pooled analysis of Leventakou et al. (2014).

In conclusion, intake of more than 1 to 3 versus 1 or fewer times fish per week during pregnancy is associated with a 13% (8 to 18%) lower risk of

preterm birth and intake of more than 3 times versus 1 or fewer times fish per week with an 11% (4 to 16%) lower risk of preterm birth. In view of the consistent findings, the level of evidence is strong.

Table 19a. Results from the pooled analysis of Leventakou et al. (2014) on the association between fish intake during pregnancy and the risk of preterm birth.

Exposure	Number of cohorts	N participants	N cases	RR estimate	95%-CI	Hetero-geneity I^2
Fish in times/week	19	151,880	n.r.[a]	1.00	0.97-1.03	Significant
>1 to ≤3 versus ≤1 times fish / week	13	140,337	n.r.	0.87	0.82-0.92	n.s.
>3 versus ≤1 times fish /week	13	140,337	n.r.	0.89	0.84-0.96	n.s.
Fatty fish in times/week	13	131,651	n.r.	1.04	0.98-1.09	Significant
Lean fish in times/week	12	129,886	n.r.	1.00	0.96-1.05	Significant
Seafood other than fish in times/week	16	138,148	n.r.	1.01	0.96-1.07	n.s.

CI: Confidence Interval; N: number; n.r.: not reported; n.s.: not significant; RR: Relative Risk estimate (can also be an odds ratio or hazard ratio). [a] The proportion of preterm birth ranged from 2.8% to 10.5% between the birth cohorts.

Table 19b. Results from the Omega prospective cohort study by Mohanty et al. (2015) on the association between fish intake during pregnancy and the risk of preterm birth.

Exposure	N participants	N cases	RR estimate	95%-CI
2.0-4.3 versus 0-2.0 g fish /month	3,279	259	0.97	0.69-1.37
4.3-7.5 versus 0-2.0 g fish /month	3,279	259	0.91	0.64-1.29
7.6-56.9 versus 0-2.0 g fish /month	3,279	259	0.88	0.61-1.27

CI: Confidence Interval; N: number; RR, Relative Risk estimate (can also be an odds ratio or hazard ratio).

4.3 Atopic disease in the offspring

4.3.1 Wheeze

Summary: Fish intake during pregnancy and offspring wheeze.

Aspect	Explanation
Selected studies	One pooled analysis of 17 cohort studies[69] and one meta-analysis of eight cohort studies[70]
Heterogeneity	No
Strength of the association	Times per week fish during pregnancy RR = 1.00 (95%CI 0.99-1.00) during infancy; RR = 1.01 (95%CI 0.97-1.05) at preschool age; RR = 1.01 (95%CI 0.98-1.03) at school age.[69] High versus low fish intake RR = 0.94 (95%CI 0.83-1.07)[70]
Study population	Europe, North America, Asia

Conclusion:

Based on cohort studies, an association between fish intake during pregnancy and risk of offspring wheeze is unlikely.

Explanation

There are three systematic reviews and one pooled analysis of the association between fish intake during pregnancy and risk of offspring wheeze.[16,48,69,70] Stratakis et al. (2016) pooled data from 17 cohort studies. Four of the 17 studies are also included by Zhang et al. (2017), who summarised eight cohort studies in total by meta-analysis. The one cohort study in the systematic review of Netting et al. (2014) and the seven cohort studies in the review of Beckhaus et al. (2015) are also summarised by Stratakis et al. (2017) and/or Zhang et al. (2017). Therefore, the committee focuses on the findings of Stratakis et al. (2017) and Zhang et al. (2017)

(Table 20a and 20b).[69,70] The committee did not find any more recent cohort studies on maternal fish intake and the risk of wheeze in the offspring.

Stratakis et al. (2017) found no significant association between fish intake (times per week) during pregnancy and risk of offspring wheeze during infancy, at preschool, and at school age. Wheeze in infancy was defined as the presence of any episode of wheezing or whistling in the chest in the first 2 years of life. Wheeze at preschool age (3-4 years) and at school age (5-8 years) was defined as the presence of wheezing or whistling in the chest in the past 12 months. Risk estimates were close to one, and there was little heterogeneity. Subgroup analyses in which fish intake was split into categories or in types of fish did not result in any significant associations.[69]

Zhang et al. (2017) found no significant association either between a high versus low intake of fish and the risk of offspring wheeze. Wheeze was defined as a parental report of symptoms, parental report of physician diagnosis, or direct diagnosis by a physician. Heterogeneity was low.[70]

In conclusion, both analyses do not find a significant association.
In addition, in the analysis with the stronger design, the pooled analysis, the estimate was close to one. The committee, therefore, concludes that an association between fish intake during pregnancy and risk of offspring wheeze is unlikely.

Table 20a. Results from the pooled analysis of Statakis et al. (2017) on the association between fish intake (in times per week) during pregnancy and offspring wheeze at different ages.

Moment of outcome assessment	Number of cohorts	N participants	N cases	RR estimate	95%-CI	Heterogeneity I^2
During infancy	17	59,986	17,518	1.00	0.99-1.01	11%
At preschool age	11	12,673	1,949	1.01	0.99-1.04	0%
At school age	13	23,317	3,050	1.01	0.98-1.03	8%

CI: Confidence Interval; N: number; RR: Relative Risk estimate (can also be an odds ratio or hazard ratio).

Table 20b. Results from the meta-analysis of Zhang et al. (2017) on the association between fish intake (high versus low) during pregnancy and offspring wheeze.

Number of cohorts	N participants	N cases	RR estimate	95%-CI	Heterogeneity I^2
8	42,096	n.r.	0.94	0.83-1.07	26%

CI: Confidence Interval; N: number; n.r.: not reported; RR: Relative Risk estimate (can also be an odds ratio or hazard ratio).

4.3.2 Asthma

Summary: Fish intake during pregnancy and offspring asthma.

Aspect	Explanation
Selected studies	One pooled analysis of 13 cohort studies[69] and one meta-analysis of three cohort studies[70]
Heterogeneity	Yes in the meta-analysis, unexplained
Strength of the association	Times per week fish RR = 1.01 (95%CI 0.97-1.05)[69] High versus low intake RR = 0.93 (95%CI 0.68-1.28)[70]
Study population	Europe, North America, Asia

Conclusion:
Based on cohort studies, an association between fish intake during pregnancy and the risk of offspring asthma is unlikely.

Explanation
There are four systematic reviews and one pooled analysis of individual birth cohort data on the association between fish intake during pregnancy and offspring asthma.[16,48,69-71]
Stratakis et al. (2017)[69] summarised individual data from 13 European and US birth cohorts. Zhang et al. (2017)[70] summarised three cohort studies by meta-analysis. Two cohort studies were included in both analyses. The three other systematic reviews, all narrative reviews, did not result in additional cohort studies: the one cohort study described by Yang et al. (2013) as well as both cohort studies described by Beckhaus et al. (2015) were also included by Stratakis et al. (2017) and/or Zhang et al. (2017). Netting et al. (2013) described one cohort study[72] which was not included by Stratakis et al. (2017) or Zhang et al. (2017), but as the fish intake of the mother was assessed at or after the assessment of the asthma symptoms, the committee did not include this study in its evaluation. Below, the committee describes the outcomes of the pooled analysis and the meta-analysis (Table 21).[69,70]

Stratakis et al. (2017) found no significant association between fish intake during pregnancy and risk of asthma at school age. Asthma was defined as satisfying at least two of the following three criteria: (1) ever-reported doctor diagnosis of asthma; (2) presence of wheezing or whistling in the chest in the past 12 months; and (3) asthma medication in the past 12 months at the ages of 3-4 years and 5-8 years, respectively. The relative risk was close to one, and heterogeneity was low. Subgroup analyses in which fish intake was split into categories or into types of fish did not result in any significant associations.[69]
Zhang et al. (2017) found no significant association either between fish intake during pregnancy and risk of asthma in three cohort studies with adjusted odds ratios. Asthma was defined as a parental report of symptoms, parental report of physician diagnosis, or direct diagnosis by a physician. The confidence interval around the estimate was rather wide (RR = 0.93; 95%CI 0.68-1.28), and heterogeneity was considerable.[70] As the meta-analysis only covers three studies, two of which were also included in the pooled analysis, the committee bases its conclusion of the findings in the pooled analysis.

The committee found a publication by Viljoen et al. (2018)[73] of an Irish cohort study from which an earlier publication was included in the pooled analysis of Stratakis et al. (2017). Viljoen et al. (2018) presented risks of asthma after 10 years of follow-up, whereas Stratakis et al. (2017) included data after 1 and 2 years of follow-up. Viljoen et al. (2018) presented data on the association with risk of asthma (at any time point) of fatty fish intake during pregnancy, but not of the total fish intake or the

lean fish intake. Viljoen et al. (2018) found no association between the intake of fatty fish during pregnancy and the risk of asthma at any time point. The risk estimate, although very low, was far from significant because of the wide confidence interval.

In view of the large number of studies summarised in the pooled analysis, the pooled risk estimate that is close to one and the limited amount of heterogeneity in that pooling study, the committee concludes that an association between fish intake during pregnancy and the risk of offspring asthma is unlikely.

Table 21. Results from the pooled analysis of Stratakis et al. (2017), the meta-analysis of Zhang et al. (2017), and an additional publication on the Lifeways Cross Generation Cohort study on the association between fish intake during pregnancy and offspring asthma.

Study type	Exposure	Number of cohorts	N participants	N cases	RR estimate	95%-CI	Heterogeneity I^2
Pooled analysis[69]	Fish (times per week)	13	23,532	2,479	1.01	0.97-1.05	27%
Meta-analysis[70]	High versus low intake of fish	3	n.r.	n.r.	0.93	0.68-1.28	66%
Cohort study: additional publication on the Lifeways Cross Generation Cohort Study[73]	Fatty fish (portions per day)	1	897	n.r.[a]	0.23	0.04-1.41	n.a.

CI: Confidence Interval ; n.a.: not applicable; n.r.: not reported; RR: Relative Risk estimate (can also be an odds ratio or hazard ratio).[a] Asthma was diagnosed in 11% of the children at 3 years of age, in 14% at 5 years of age and in 23% at 10 years of age.

4.3.3 Eczema

Summary: Fish intake during pregnancy and offspring eczema.

Aspect	Explanation
Selected studies	One meta-analysis of eight cohort studies[70]
Heterogeneity	Yes, in the size of the association
Strength of the association	RR = 0.84 (95%CI 0.69-1.01)
Study population	Europe, North America, Asia

Conclusion:

Findings from cohort studies on the association between fish intake during pregnancy and the risk of offspring eczema are inconclusive.

Explanation

There are three systematic reviews of the association between fish intake during pregnancy and risk of offspring eczema.[16,48,70] Zhang et al. (2017) summarised eight cohort studies in a meta-analysis. Beckhaus et al. (2015) summarised six publications on five cohort studies in a meta-analysis and additionally described the results of a pooled analysis of two cohorts (originally performed by Chatzi et al. (2013)[45]). In a narrative review, Netting et al. (2014) summarised nine publications on seven cohort studies. One of the included studies was on exposure to marine contaminants rather than fish consumption and, therefore, not of interest to the committee for this chapter.[74] One other cohort study was included by both Beckhaus et al. (2015) and Netting et al. (2014), but not by Zhang et al. (2017). This cohort study, of Oien et al. (2010), only presented

unadjusted analyses of the association between fish intake during pregnancy and risk of offspring eczema.[75] The cohort study is, therefore, not included in the committee's analysis. As Zhang et al. (2017) is the most complete and recent systematic review, the committee describes below the findings of this meta-analysis (Table 22). The committee did not find any more recent cohort studies on maternal fish intake and the risk of offspring eczema.

Zhang et al. (2017) found no statistically significant association between fish intake during pregnancy and the risk of offspring eczema, but the summarised risk estimate was not close to one either. The upper limit of the confidence interval was 1.01, and there was considerable heterogeneity in the size of the association, but not in the direction of the association. Exclusion of any single study did not materially change the combined relative risk.[70]

In view of the large number of studies, the risk estimate that is not close to one, but not statistically significant either, and the considerable heterogeneity in the size of the association, the committee concludes that study findings on the association between fish intake during pregnancy and the risk of offspring eczema are inconclusive.

Table 22 Results from the meta-analysis of Zhang et al. (2017) on the association between fish intake (high versus low) during pregnancy and offspring eczema.

Number of cohorts	N participants	N cases	RR estimate	95%-CI	Heterogeneity I^2
8	n.r.	n.r.	0.84	0.69-1.01	56%

CI: Confidence Interval; N: number; n.r.: not reported; RR: Relative Risk estimate (can also be an odds ratio or hazard ratio).

4.3.4 Allergic rhinitis

Summary: Fish intake during pregnancy and offspring allergic rhinitis.

Aspect	Explanation
Selected studies	One pooled analysis of ten cohort studies[69] and one additional cohort study[76]
Heterogeneity	No
Strength of the association	>3 versus ≤1 times/week RR = 1.01 (95%CI 0.99-1.03)[69] and 33.3 to 254.8 gram/day versus 10.9 to <33.3 gram/day RR = 0.92 (95%CI 0.67-1.28)[76]
Study population	Europe, North America

Conclusion:

Based on cohort studies, the association between fish intake during pregnancy and allergic rhinitis in the offspring at school age is unlikely.

Explanation

There are one pooled analysis and one systematic review of fish intake during pregnancy and risk of allergic rhinitis.[48,69] Stratakis et al. (2017) summarised individual data from ten European and US birth cohorts and

Beckhaus et al. (2015) described two cohort studies, one of which is also included in the pooled analysis.

The committee, therefore, describes below the findings by Stratakis et al. (2017) and the remaining cohort study of Erkkola et al. (2012) (Table 23a and 23b).[69,76] The committee did not find any more recent cohort studies on fish intake during pregnancy and risk of allergic rhinitis in the offspring.

Stratakis et al. (2017) found that fish intake during pregnancy is not statistically significantly associated with the risk of allergic rhinitis in the offspring at school age. Allergic rhinitis was defined as ever-reported diagnosis of allergic rhinitis or hay fever at the age of 5-8 years. Results were similar if fish intake was analysed either as a continuous measure or as a categorical measure. Subgroup analyses with respect to the type of fish (fatty fish, lean fish, or other seafood) did not reveal any significant associations.[69]

Erkkola et al. (2012) found no significant association either when the mid half of fish intake was compared with the lowest and highest quarter of fish intake.[76]

In view of the high number of studies and the risk estimates that were close to one, the committee concludes that the association between fish intake during pregnancy and allergic rhinitis at school age is unlikely.

Table 23a. Results from the pooled analysis of Stratakis et al. (2017) on the association between fish intake during pregnancy and offspring allergic rhinitis in the offspring at school age.

Exposure	Number of cohorts	N participants	N cases	RR estimate	95%-CI	Heterogeneity I^2
Fish (times per week)	10	35,789	1,914	1.01	0.99-1.03	0%
>1 to ≤3 versus ≤1 times/week	10	14,777	n.r.	0.99	0.84-1.16	20%
>3 versus ≤1 times/week	7	7,827	n.r.	0.99	0.77-1.26	26%

CI: Confidence Interval; N: number; n.r.: not reported; RR: Relative Risk estimate (can also be an odds ratio or hazard ratio).

Table 23b. Results from the Finnish Type I diabetes Prediction and Prevention (DIPP) Nutrition Study by Erkkola et al. (2012) on the association between fish intake during pregnancy and offspring allergic rhinitis in the offspring at school age.

Exposure	N participants	N cases	RR estimate	95%-CI
<10.9 versus 10.9 to <33.3 gram fish /day	2,441	359	0.97	0.70-1.33
33.3-254.8 versus 10.9 to <33.3 gram fish /day	2,441	359	0.92	0.67-1.28

CI: Confidence Interval; N: number; RR: Relative Risk estimate (can also be an odds ratio or hazard ratio).

4.4 Offspring body mass index

Summary: Fish intake during pregnancy and offspring body mass index (BMI).

Aspect	Explanation
Selected studies	One pooled analysis of 15 cohort studies[77]
Heterogeneity	No
Strength of the association	Per portion fish per week: 0.01 higher BMI Z-score at 2, 4 and 6 years of age (95%CI +0.001 to +0.019) >3 versus ≤1 fish /week: 0.04 to 0.05 higher BMI Z-score at 2, 4 and 6 years of age (95CI +0.001 to +0.100)
Study population	Europe, North America

Conclusion 1:

Based on cohort studies, fish intake during pregnancy (per portion/week) is associated with a 0.01 (0.00 to 0.02) units higher BMI Z-score in the offspring at age 2, 4 and 6 years.
Level of evidence: Strong.

Conclusion 2:

Based on cohort studies, intake of more than 3 times versus 1 or fewer times fish per week is associated with a 0.04 to 0.05 (0.00 to 0.10) higher BMI Z-score in the offspring at age 2, 4, and 6 years.
Level of evidence: Strong.

Explanation

There is one analysis in which the individual data of 14 European and one American birth cohort study were pooled (Table 24).[77]

Stratakis et al. (2016) found a significant association between fish intake during pregnancy (per portion/week) and a higher BMI Z-score in the offspring at 2, 4 and 6 years of age. Throughout these ages, the association remained constant at around 0.01 unit increase in BMI Z-score per portion fish per week. When fish intake was categorised, the increase in BMI Z-score (0.04 to 0.05 units) was larger for women eating more than 3 portions fish per week as compared to 1 or fewer portions of fish per week. The association was statistically significant at 2 and 4 years of age, but not at 6 years of age, although the risk estimate was similar in size. Heterogeneity was not statistically significant. There was no statistically significant association between eating fish 1 to 3 times per week versus 1 or fewer times fish per week. A fish intake of more than 3 times per week occurred predominantly in the Mediterranean and Scandinavian cohorts. Subgroup analyses into types of fish (fatty fish, lean fish, or other types of seafood) did not result in any statistically significant associations.[77]

The committee found one other recent publication on a cohort study (PIAMA) that is part of the pooled analysis of Stratakis et al. (2016).[77,78] Stratakis et al. (2016) included data on BMI Z score up to 8 years of age, whereas Van den Berg et al. (2016) presented data up to 14 years of age. The authors showed an association between maternal fish intake during pregnancy and a lower BMI Z score at the ages of 4, 7, 8.5 and 11.5 years. However, after adjustment for pre-pregnancy BMI and other

confounding factors, the association was attenuated and remained statistically significant at the age of 7 only (results were not suited for the table below).[78] The committee concludes that the findings from this additional publication are largely in line with the results of the pooled analysis. Therefore, the committee bases its final conclusions on the pooled analysis of Stratakis et al. (2016).

In conclusion, fish intake during pregnancy (per portion/week) is associated with a 0.01 (0.00 to 0.02) units higher BMI Z-score in the offspring at age 2, 4 and 6. In view of the large number of studies and the consistency of findings, the committee judges the level of evidence as strong.

In addition, intake of more than 3 times versus 1 or fewer times fish per week is associated with a 0.04 to 0.05 (0.00 to 0.10) higher BMI Z-score in the offspring at age 2, 4, and 6. In view of the large number of studies and the consistency of findings, the committee judges the evidence as strong.

Table 24 Results from the pooled analysis of Stratakis et al. (2016) on the association between fish intake during pregnancy and offspring BMI Z-score at different ages.

Exposure	Age (in years) of outcome assessment	Number of cohorts	N participant	BMI Z-score	95%-CI	Hetero-geneity I^2
Fish (times per week)	2	15	25,625	+0.009	+0.003 to +0.016	n.s.
>1 to ≤3 versus ≤1 time per week	2	8	7,281	-0.005	-0.038 to +0.028	n.s.
>3 versus ≤1 time per week	2	8	2,709	+0.050	+0.004 to +0.096	n.s.
Fish (times per week)	4	14	25,355	+0.009	+0.001 to +0.016	n.s.
>1 to ≤3 versus ≤1 time per week	4	8	7,281	-0.008	-0.051 to +0.035	n.s.
>3 versus ≤1 time per week	4	8	2,709	+0.050	+0.001 to +0.100	n.s.
Fish (times per week)	6	12	22,668	+0.010	+0.001 to +0.019	n.s.
>1 to ≤3 versus ≤1 time per week	6	7	6,879	-0.007	-0.058 to +0.044	Signifi-cant
>3 versus ≤1 time per week	6	7	1,469	+0.039	-0.033 to +0.111	n.s.

CI: Confidence Interval; N: number; n.s.: not significant.

4.5 Offspring overweight/obesity

Summary: Fish intake during pregnancy and rapid growth and overweight/obesity in the offspring.

Aspect	Explanation
Selected studies	One pooled analysis of 15 cohort studies[77]
Heterogeneity	No
Strength of the association	>3 versus ≤1 fish /week: RR 2 years = 1.22 (95%CI 1.05-1.44); RR 4 years = 1.14 (95%CI 0.99-1.32) and RR 6 years = 1.22 (95%CI 1.01-1.47)
Study population	Europe, North America

Conclusion:

Based on cohort studies, more than 3 times versus 1 or fewer times fish per week during pregnancy is associated with a higher risk of rapid growth in the offspring at 2 years and of overweight/obesity in the offspring at 4 and 6 years.
Level of evidence: Strong.

Explanation

There is one analysis in which the individual data of 15 European and one American birth cohort study were pooled (Table 25).[77] The committee did not find any more recent cohort studies on maternal fish intake and the risk of childhood overweight/obesity.

Stratakis et al. (2016) found no significant association between fish intake during pregnancy (per portion/week) and risk of rapid growth in the offspring at 2 years of age and risk of overweight or obesity in the offspring at 4 and 6 years of age. Rapid growth was defined as a weight gain z score of more than 0.67 based on WHO growth standards. Overweight or obesity was defied as a BMI at the 85th percentile or more for age and sex based on the WHO growth standards. When fish intake was categorised, the risk of overweight/obesity in the offspring at the ages of 2, 4, and 6 years was larger for women eating more than 3 portions fish per week during pregnancy as compared with 1 or fewer portions of fish per week. The association was significant at 2 and 6 years of age, but not significant at 4 years of age. A fish intake of more than 3 times per week occurred predominantly in the Mediterranean and Scandinavian cohorts. Heterogeneity was not significant. There was no significant association between eating fish 1 to 3 times per week versus 1 or fewer times per week and risk of rapid growth or overweight or obesity in the offspring. Subgroup analyses into types of fish (fatty fish, lean fish, or other types of seafood), did not result in any significant associations.[77]

In conclusion, intake of more than 3 times versus 1 or less times fish per week during pregnancy is associated a higher risk of rapid growth in the offspring at 2 years and offspring overweight/obesity at 4 and 6 years. In view of the fact that the association was not significant at 4 years and the risk estimates varied between ages, the committee did not quantify the association. In view of the otherwise consistent findings, it judges the level of evidence as strong.

Table 25. Result from the pooled analysis of Stratakis et al. (2016) on the association between fish intake during pregnancy and offspring rapid growth and overweight/obesity.

Exposure	Outcome and age (in years) of assessment	Number of cohorts	N parti-cipants	RR estimate	95%-CI	Hetero-geneity I^2
Fish (times per week)	Rapid growth; 2	15	26,184	1.02	0.99-1.04	n.s.
>1 to ≤3 versus ≤1 time per week	Rapid growth; 2	8	7,362	0.96	0.87-1.05	n.s.
>3 versus ≤1 time per week	Rapid growth; 2	8	2,739	1.22	1.05-1.44	n.s.
Fish (times per week)	Overweight / obesity; 4	14	25,355	1.02	0.99-1.04	n.s.
>1 to ≤3 versus ≤1 time per week	Overweight/ obesity; 4	8	7,281	0.95	0.85-1.06	n.s.
>3 versus ≤1 time per week	Overweight/ obesity; 4	8	2,709	1.14	0.99-1.32	n.s.
Fish (times per week)	Overweight/ obesity; 6	12	22,668	1.02	0.99-1.05	n.s.
>1 to ≤3 versus ≤1 time per week	Overweight/ obesity; 6	7	6,879	0.93	0.81-1.06	n.s.
>3 versus ≤1 time per week	Overweight/ obesity; 6	7	1,469	1.22	1.01-1.47	n.s.

CI: Confidence Interval; n.s.: not significant; RR: Relative Risk estimate (can also be an odds ratio or hazard ratio).

4.6 Cognitive and behavioural outcomes in the offspring

The committee did not find a systematic review focusing specifically on fish intake and cognitive and behavioural outcomes. However, there is one systematic review by Borge et al. (2017) [79] that summarised 18 cohort studies on the association between a healthy dietary pattern during pregnancy and cognitive function (13 studies) and behavioural outcomes (eight studies, 13 outcomes) in children up to the age of 8. In 11 of the 18 studies, fish intake was used as an indicator of a healthy diet. In the other studies, the omega-3/omega-6 fatty acids ratio, fruit, total fat or a posteriori defined dietary patterns were used. The analysis was limited, among other reasons, by the incomplete adjustment for potential confounding factors such as maternal energy intake in most studies. Moreover, the authors did not carry out subgroup analyses of the fish intake studies only. The committee, therefore, does not describe the results of the systematic review.

4.7 Summary of findings

The conclusions in this chapter are based on four systematic reviews of observational studies[66,69,70,77] and one individual cohort study.[76] The committee found strong evidence that fish intake (> 1 to 3 portions per week vs 1 or fewer) during pregnancy is associated with a higher gestational age and a lower risk of preterm birth. The same was found for > 3 portions per week vs 1 or fewer, although the sizes of the associations are smaller. Furthermore the consumption of > 3 portions of fish per week vs 1 or fewer during pregnancy is associated with a higher BMI Z-score in the offspring and with a higher risk of rapid growth at age 2 and overweight/ obesity at ages 4 and 6. The evidence for these findings was strong as well.

Additionally, the committee concluded that it is unlikely that fish intake during pregnancy is associated with offspring wheeze, asthma and allergic rhinitis. Evidence was inconclusive for the association between fish intake during pregnancy and the risk of offspring eczema.

The following overview presents all conclusions of the committee of this chapter on fish intake:

Committee's conclusion	Outcome
Strong evidence	• Gestational age: Based on cohort studies, intake of more than 1 to 3 versus 1 or fewer times fish per week during pregnancy is associated with 0.4 (0.3 to 0.6) days higher gestational age; intake of more than 3 times versus 1 or fewer times fish per week with 0.2 (0.1 to 0.4) days higher gestational age • Preterm birth: Based on cohort studies, intake of more than 1 to 3 versus 1 or fewer times fish per week during pregnancy is associated with a 13% (8 to 18%) lower risk of preterm birth; intake of more than 3 times versus 1 or fewer times fish per week with 11% (4 to 16%) lower risk of preterm birth • BMI Z-score: Based on cohort studies, fish intake during pregnancy (per portion/ week) is associated with a 0.01 (0.00 to 0.02) units higher BMI Z-score in the offspring at age 2, 4 and 6 years • BMI Z-score: Based on cohort studies, intake of more than 3 times versus 1 or fewer times fish per week is associated with a 0.04 to 0.05 (0.00 to 0.10) higher BMI Z-score in the offspring at age 2, 4 and 6 years • Rapid growth: Based on cohort studies, more than 3 times versus 1 or fewer times fish per week during pregnancy is associated with a higher risk of rapid growth in the offspring at 2 years and of overweight/obesity in the offspring at 4 and 6 years
Limited evidence	No conclusions with limited evidence
Unlikely	• Wheeze in the offspring: Based on cohort studies, an association between fish intake during pregnancy and risk of offspring wheeze is unlikely • Asthma in the offspring: Based on cohort studies, an association between fish intake during pregnancy and the risk of offspring asthma is unlikely • Allergic rhinitis in the offspring at school age: Based on cohort studies, the association between fish intake during pregnancy and allergic rhinitis in the offspring at school age is unlikely
Contradictory	No conclusions with contradictory evidence
Too little research	No associations or effect with too little research
Inconclusive	• Eczema in the offspring (cohort studies)

4.8 Findings cited in the advisory report

The committee based the recommendations in the advisory report primarily on the conclusions in the background documents with a strong evidence level.

In this chapter, this applies to the association of the consumption of fish two or three times per week with a lower risk of preterm birth (conclusion based on cohort studies). This is in line with the conclusion that the use of fish fatty acid supplements lowers the risk of preterm birth (conclusion based on RCTs) in the background document on nutrient supplements.[80] Based on this additional regression analysis in paragraph 4.1, the committee considers that for fatty fish, a consumption frequency of one time per week seems amply sufficient for the association with gestational age. For lean fish, a high frequency of consumption appears to be required for this association.

There are two conclusions with strong evidence in this chapter which are not used in the advisory report based on cohort studies: a high frequency of fish consumption is associated with 1) a higher BMI and 2) a higher risk of rapid growth. There are two reasons why these conclusions are not mentioned in the advisory report.
Firstly, the conclusions based on cohort studies on the outcomes of BMI and rapid growth were related to a very high frequency of fish intake (at least 4 times per week) and were not observed for the frequency of fish

consumption recommended by the committee in the advisory report (2 times per week). Therefore, these findings are not relevant in relation to the recommendation made by the committee.

Secondly, the association with BMI is not in line with the conclusion in the background document on nutrient supplements, based on RCTs, that an effect of the use of fish fatty acid supplements on overweight or obesity in the offspring is unlikely.[80] Please note that this type of conclusion ('an effect is unlikely') requires strong evidence as well.[1] The committee considers that the finding from RCTs outweighs those from cohort studies, because RCTs provide evidence on causality, whereas cohort studies do not; findings of cohort studies may be subject to confounding.

05 eggs

This chapter describes the scientific evidence from systematic reviews of cohort studies on the association between egg intake during pregnancy and the risk of atopic disease (more specific eczema) in the offspring. For other outcomes of interest, the committee did not find systematic reviews summarising at least two cohort studies. For this exposure, no systematic reviews summarising at least two RCTs were found.

5.1 Atopic disease in the offspring

5.1.1 Eczema

Summary: Egg intake during pregnancy and the risk of offspring eczema.

Aspect	Explanation
Selected studies	Two cohort studies[65,81]
Heterogeneity	Not applicable
Strength of the association	RRs were 0.73 (95%CI 0.33-1.61)[65] and 0.81 (95%CI 0.62-1.06)[81]
Study population	Europe, Asia

Conclusion (cohort studies):

There is too little research to draw a conclusion on the association between egg intake during pregnancy and the risk of offspring eczema.

Explanation

There is one systematic review of maternal egg intake and the risk of eczema in offspring.[16] Netting et al. (2014) describe two cohort studies narratively (Table 27); therefore, the results of the individual studies are presented (Table 26).[65,81] The committee did not find any more recent cohort studies.

In the Japanese cohort study, there was no significant association between the maternal intake of eggs and risk of eczema in 3 to 4 month-old infants.[65] In the larger German cohort , there was no significant association with risk of eczema in 2 year old infants either.[81]

In view of the small number of studies, the committee concludes that there is too little research to draw a conclusion on the association between egg intake during pregnancy and the risk of offspring eczema.

Table 26. Results from the two cohort studies included in Netting et al. (2014) on the association between egg intake during pregnancy and risk of offspring eczema.

Cohort study	Exposure	Age of outcome assessment	N parti-cipants	N cases	RR estimate	95%-CI
Osaka Maternal and Child Health Study[65]	61.3 versus 9.7 g/d	3-4 months	771	55	0.73	0.33-1.61
Influences of Lifestyle-related Factors on the Immune System and Development of Allergies in Childhood Study[81]	High versus low intake	2 years	2,508	445	0.81	0.62-1.06

CI: Confidence Interval; N: number; RR: Relative Risk estimate (can also be an odds ratio or hazard ratio).

5.2 Summary of findings

The following overview presents all conclusions of the committee of this chapter on egg intake based on one systematic review of observational studies.[16]

Committee's conclusion	Outcome
Strong evidence	No conclusions with strong evidence
Limited evidence	No conclusions with limited evidence
Unlikely	No unlikely associations or effects
Contradictory	No conclusions with contradictory evidence
Too little research	• Eczema in the offspring (cohort studies)
Inconclusive	No inconclusive associations or effects

5.3 No findings cited in the advisory report

The committee based the recommendations in the advisory report primarily on the conclusions in the background documents with a strong evidence level.

In this chapter on egg consumption, conclusions with a strong evidence level are not available.

06 dairy

This chapter describes the scientific evidence from systematic reviews of cohort studies on the association between dairy intake during pregnancy and the risk of an infant that is small for gestational age and atopic disease in the offspring (wheeze, asthma, and eczema). For other outcomes of interest, the committee did not find systematic reviews summarising at least two cohort studies. For this exposure, no systematic reviews summarising at least two RCTs were found.

6.1 Small for gestational age

Summary: Dairy intake during pregnancy and the risk of an infant that is small for gestational age.

Aspect	Explanation
Selected studies	One systematic review of two cohort studies[82]
Heterogeneity	Not applicable
Strength of the association	RR = 0.84 (95%CI 0.49-1.43)[83]; RR = 0.89 (95%CI 0.83-0.96)[84]
Study population	Healthy pregnant women with normal weight or normal BMI in Europe

Conclusion (cohort studies):

There is too little research to draw a conclusion on the association between dairy intake during pregnancy and the risk of an infant that is small for gestational age.

Explanation

There is one systematic review on the association between dairy intake and the risk of an infant that is small for gestational age.[82] It included two prospective cohort studies on this outcome.[83,84] As no meta-analysis is available, the committee describes the results of the individual cohort studies (Table 27).

Heppe et al. (2011) explored the association between maternal daily milk consumption during pregnancy and the risk of an infant that is small for gestational age in the Dutch Generation R study. They found that > 3 glasses of milk per day versus 0-1 glass a day was associated with a lower but statistically non-significant risk of an infant that is small for gestational age. In a Spanish cohort, a significantly lower risk of an infant that is small for gestational age was found in mothers who consumed higher amounts of dairy products (i.e. milk, yoghurt, cheese, custard, and ice-cream).

In view of the limited number of available studies, the committee concludes that there is too little research to draw a conclusion on the association between dairy intake during pregnancy and the risk of an infant that is small for gestational age.

Table 27. Results from the cohort studies included in the systematic review of Achon et al. (2019) on the association between dairy intake during pregnancy and risk of an infant that is small for gestational age.

Cohort name	Exposure	N participants	N cases	RR estimate	95%-CI
Generation R[83]	> 3 glasses of milk per day versus 0 to 1 glass of milk per day	3,405	169	0.84	0.49-1.43
Cohort from Granada[84]	Dairy intake; per 100g/day increment	973	127	0.89	0.83-0.96

CI: Confidence Interval; N: number; RR: Relative Risk estimate (can also be an odds ratio or hazard ratio).

6.2 Atopic disease in the offspring

6.2.1 Wheeze

Summary: Dairy intake during pregnancy and the risk of offspring wheeze.

Aspect	Explanation
Selected studies	One systematic review of six cohort studies[48] (including a meta-analysis of four cohort studies and one pooled analysis of two cohort studies)[45]
Heterogeneity	Yes, in the meta-analysis
Strength of the association	Meta-analysis of four studies: RR = 0.88 (95%CI 0.69-1.13)[48] Pooled analysis of two studies: RR = 0.83 (95%CI 0.72-0.96)[45]
Study population	Europe, Asia

Conclusion:

Based on cohort studies, high versus low dairy intake during pregnancy is associated with a lower risk of wheeze in the offspring.

Level of evidence: Limited.

Explanation

There are three systematic reviews of maternal dairy intake and the risk of wheezing in offspring.[16,48,85]

Beckhaus et al. (2015)[48] summarised six publications of seven cohort studies. Of the three cohort studies that were summarised by Netting et al. (2014)[16], one was not included by Beckhaus et al. (2015). However, in this cohort study, data on maternal intake were collected at the same time as data on offspring wheezing. Therefore, the committee did not further review this cohort study.[43] The one cohort study in the systematic review of Saadeh et al. (2013) was included in both other systematic reviews. The committee, therefore, focused on the findings of Beckhaus et al. (2015) (Table 28).[48] The committee did not find any more recent cohort studies.

Beckhaus et al. (2015) conducted a meta-analysis on four of the seven cohort studies and found a statistically non-significant association between a higher dairy intake during pregnancy and a lower risk of offspring wheeze. There was considerable heterogeneity. However, it is unclear whether the heterogeneity occurred in the size or rather the direction of the association, as the risk estimates in the individual cohort studies were not presented in the systematic review.

Beckhaus et al. (2015) also present the result of the pooled analysis of two cohort studies published by Chatzi et al. (2013)[45]: a high versus low dairy consumption during pregnancy was associated with a statistically

significant lower risk of wheeze in the offspring. No statistically significant heterogeneity was present in this analysis.
The remaining cohort study found by Beckhaus et al. (2015) was not incorporated in either the meta-analysis or the pooled analysis, and was outside the scope of the committee as it used 'fat from dairy products' as an exposure rather than 'dairy consumption overall'.[86]

In view of the large number of studies (≥ 5), the fact that the risk estimates were not close to one and statistically significant in the pooled analysis but not in the meta-analysis, the committee concludes that there is limited evidence that a high versus low dairy intake during pregnancy is associated with a lower risk of offspring wheeze.

Table 28. Results from the systematic review of Beckhaus et al. (2015) on the association between dairy intake during pregnancy and risk of offspring wheeze.

Study type	Exposure	Number of cohorts	N participants	N cases	RR estimate	95%-CI	Hetero-geneity I^2
Meta-analysis[48]	High versus low intake of dairy	4	n.r.	n.r.	0.88	0.69-1.13	62%
Pooled analysis[45]	High versus low intake of dairy (3rd tertile versus 1st tertile)	2	2,516	768	0.83	0.72-0.96	n.s.

CI: Confidence Interval; N: number; n.r.: not reported; n.s.: not significant; RR: Relative Risk estimate (can also be an odds ratio or hazard ratio).

6.2.2 Asthma

Summary: Dairy intake during pregnancy and the risk of offspring asthma-like symptoms and asthma.

Aspect	Explanation
Selected studies	Four cohort studies[87-91]
Heterogeneity	Not applicable
Strength of the association	RR varies from 0.35 (0.16-0.80)[89] to 1.03 (0.86-1.22)[90]
Study population	Europe, North America

Conclusion (cohort studies):
There is too little research to draw a conclusion on the association between dairy intake during pregnancy and the risk of offspring asthma-like symptoms and asthma.

Explanation
There are two systematic reviews of maternal dairy intake and the risk of asthma-like symptoms and asthma in offspring.[16,48] Beckhaus et al. (2015) and Netting et al. (2014) together describe six publications on five cohort studies in children aged 2 years or over.[76,86-89,91] Willers et al. (2007) do measure maternal dairy consumption, but used it to assess the exposure to fat from dairy products rather than dairy intake in itself. Therefore this study is left out of the evaluation of the committee.[86] Hence, a total of four cohort studies was used by the committee. As no meta-analysis is available, the results of the individual cohort studies were reviewed by the committee (Table 29).

Project Viva

The publication of Camargo et al. (2007) was included in the systematic review of Netting et al. (2014).[89] Additionally, the committee found one more recent publication on the project Viva, with a longer follow-up time.[90] In this American cohort, the intake of 1 to 2 cups of milk per day during pregnancy was associated with a lower risk of asthma-like symptoms (≥ 2 wheezing attacks among children with a personal history of eczema or a parental history of asthma) in the offspring at the age of 3 years as compared to no milk consumption during pregnancy. There were no significant associations for a smaller (less than 1 cup per day) of larger (more than 2 cups per day) milk intake during pregnancy, nor was there an association between milk intake during pregnancy and the risk of asthma in the offspring at the age of 7.9 years old.[89,90]

Finnish Type I Diabetes Prediction and Prevention Study

Both Erkkola et al. (2012) (from the systematic review of Beckhaus et al. (2015)) and Lumia et al. (2011) (from the systematic review of Netting et al.(2014)) described findings of the Finnish Type I Diabetes Prediction and Prevention Study. As Lumia et al. (2011) described a larger number of participants and focused on total dairy intake rather than the intake of various dairy products (as Erkkola et al. (2012) did), the committee describes the findings of Lumia et al. (2011) in their evaluation.[76,87] The authors did not find a statistically significant association between dairy intake during pregnancy and the risk of asthma-like symptoms in the offspring at the age of 5 years, although the risk estimate was below one.

Prevention and Incidence of Asthma and Mite Allergy Study 2008

No statistically significant association between dairy intake during pregnancy and the risk of asthma-like symptoms or asthma at age 3 through 8 years was found in this cohort either.[88] However, the risk estimate was below one.

Kyushi Okinawa Maternal and Child Health Study

In this cohort, a lower but statistically non-significant association between total dairy intake during pregnancy and risk of physician-diagnosed asthma in the offspring at the age of 23 to 29 months was found. Different sources of dairy showed no statistically significant associations either, except for cheese: mothers with a median cheese consumption of 11.6 grams per day had a 56% (95%CI 3% to 82%) lower risk of a child with physician-diagnosed asthma compared with mothers who had a low cheese consumption (median 0.1 gram per day).[91] The overall number of cases was low in this study, limiting the interpretation of findings.

In view of the relatively small number of studies and the fact that in most studies, risk estimates were below one but did not reach statistical significance, the committee concludes that there is too little research

to draw a conclusion on the association between dairy intake during pregnancy and the risk of offspring asthma-like symptoms and asthma.

Table 29. Results from the cohort studies on the association between dairy intake during pregnancy and risk of offspring asthma-like symptoms and asthma.

Cohort study	Age of outcome assessment	N participants	N cases	RR estimate (95%CI)
US Viva project 2007[89]	3 years	1,194	186	0.57 (0.27-1.24) for <1 cup/day versus no milk 0.35 (0.16-0.80) for 1-1.9 cups/day versus no milk 0.45 (0.20-1.02) for ≥2 cups/day versus no milk
US Viva project 2014[90]	7.9 years	1,277	n.r.	0.89 (0.74-1.07) high versus low milk in first trimester 1.03 (0.86-1.22) high versus low milk in second trimester
Prevention and Incidence of Asthma and Mite Allergy Study 2008[88]	3 to 8 years	2,788	854 at 3 years and 437 at 8 years	0.92 (0.74-1.15) for daily versus regular or rare dairy intake[a]
Finnish Type I Diabetes Prediction and Prevention Study 2011[87]	5 years	2,679	158	0.85[c] (0.56-1.28) for 547-1099 versus < 546 gram/day dairy[b] 0.73 (0.43-1.21) for >1099 versus 547-1099 gram/day dairy
Kyushi Okinawa Maternal and Child Health Study[91]	23 to 29 months	1,354	56	0.82 (0.35-1.86) for total dairy intake in the 4th quartile (median 255.3 gram/day) versus 1st quartile (median 31.9 gram/day) of intake

CI: Confidence Interval; N: number; n.r.: not reported; RR: Relative Risk estimate (can also be an odds ratio or hazard ratio). [a] intake in the second and/or third trimester, [b] intake in the third trimester, [c] the relative risk was calculated by taking the inverse of the reported relative risk, to obtain a risk estimate comparing a moderate with a low intake of dairy.

6.2.3 Eczema

Summary: Dairy intake during pregnancy and the risk of offspring eczema.

Aspect	Explanation
Selected studies	One systematic review of six cohort studies[48] (including a meta-analysis of four studies and one pooled analysis of two cohort studies)[45] and one more recent cohort study[90]
Heterogeneity	Not reported in meta-analysis, not significant in pooled analysis
Strength of the association	Meta-analysis of four cohort studies: RR = 0.95 (95%CI 0.81-1.11)[48] Pooled analysis of two cohort studies: RR = 0.95 (95%CI 0.76-1.18)[45]
Study population	Europe, North America, Asia

Conclusion:

Findings from cohort studies on the association between dairy intake during pregnancy and the risk of offspring eczema are inconclusive.

Explanation

There are two systematic reviews of maternal dairy intake and the risk of eczema in offspring.[16,48] Beckhaus et al. (2015) is the most recent and complete of the two and provided a meta-analysis of a subset of studies. Therefore, this publication is described by the committee (Table 30).

They found six publications on seven cohort studies. The cohort study of Willers et al. (2007) used total fat from dairy products as exposure rather than dairy intake itself and was therefore not included in the evaluation of the committee.[86] As Netting et al. (2014) do provide an additional publication (Saito et al., 2010) with a different measurement moment

of the Osaka Maternal and Child Health Study, the committee describes the results of Saito et al. 2010 separately.[65]

In a meta-analysis of four out of six cohorts, Beckhaus et al. (2015) found no statistically significant association between maternal dairy intake and risk of offspring eczema. They do not provide information on heterogeneity.[48] The pooled analysis of the remaining two cohorts (originally performed by Chatzi et al. (2013) showed a similar image.[45] No statistically significant heterogeneity was present.

Saito et al. (2010) found no statistically significant association between dairy intake during pregnancy and risk of eczema in 3 to 4-month-old Japanese infants.[65] However, outcomes at 16 to 24 months and 23 to 29 months of the same cohort study have been included in the meta-analysis of Beckhaus et al. (2015). Hence, this publication does not provide an independent estimate. In addition, the confidence interval was rather wide, limiting the interpretation of the findings.

The committee found one more recent cohort study.[90] Bunyavanich et al. (2014) summarised findings from the Project Viva pre-birth cohort. There were no statistically significant associations between dairy intake in the first or second trimester of pregnancy and risk of eczema (more specifically, atopic dermatitis) in the offspring at the age of 7.9 years.

In view of the fact that there are seven cohort studies from six research groups with > 500 cases, reporting non-significant results with wide confidence intervals and with a large range in the ages at which eczema was assessed, the committee concludes that research findings on the association between dairy intake during pregnancy and the risk of offspring eczema are inconclusive.

Table 30. Results from the systematic review of Beckhaus et al. (2015), the additional publication on the Osaka Maternal and Child Health Study and the additional cohort studies (Project Viva) on the association between dairy intake during pregnancy and risk of offspring eczema.

Study type	Age of outcome assessment	Number of cohorts	N parti-cipants	N cases	RR estimate (95%CI)	Hetero-geneity I^2
Meta-analysis[48]	n.r.	4[a]	n.r.	n.r.	0.95 (0.81-1.11) High versus low intake of dairy	n.r.
Pooled analysis[45]	In the first year of life	2	2,516	426	0.95 (0.76-1.18) Highest tertile versus lowest tertile of intake	n.s.
Cohort study: additional publication on the Osaka Maternal and Child Health [b,65]	3-4 months	1	763	65	1.84 (0.82-4.27) 288.3 versus 52.7 gram/day dairy	n.a.
Cohort study: additional cohort Project Viva 2014[90]	7.9 years	1	1,277	n.r.	0.95 (0.72-1.26) High versus low milk in first trimester 0.97 (0.73-1.29) High versus low milk in second trimester	n.a.

CI: Confidence Interval; N: number; n.a.: not applicable; n.r.: not reported; n.s.: not significant; RR: Relative Risk estimate (can also be an odds ratio or hazard ratio). [a] Two publications were from the same research group but not on the same cohort. [b] In the two systematic reviews, another publication on the same cohort covering infants at age 16 to 24 months was included.[16,48,92]

6.3 Summary of findings

The conclusions in this chapter are based on three systematic reviews of observational studies [16,48,82] and one additional publication.[90] There was limited evidence for an association between high versus low dairy intake during pregnancy and a lower risk of wheeze in the offspring. In the reviews used by the committee, no distinction was made between different dairy products. Therefore, no conclusions could be drawn on specific dairy products like milk, yoghurt, cheese, etc.

The following overview presents all conclusions of the committee of this chapter on dairy intake:

Committee's conclusion	Outcome
Strong evidence	No conclusions with strong evidence
Limited evidence	• Wheeze in the offspring: Based on cohort studies, high versus low dairy intake during pregnancy is associated with a lower risk of wheeze in the offspring
Unlikely	No unlikely associations or effects
Contradictory	No conclusions with contradictory evidence
Too little research	• Small for gestational age (cohort studies) • Asthma in the offspring (cohort studies)
Inconclusive	• Eczema in the offspring (cohort studies)

6.4 No findings cited in the advisory report

The committee based the recommendations in the advisory report primarily on the conclusions in the background documents with a strong evidence level.

In this chapter on dairy consumption, conclusions with a strong evidence level are not available. There is one conclusion with limited evidence pointing into the direction of a benefit of a higher dairy intake. The committee considers that this evidence is not sufficient for the formulation of recommendations and, therefore, the finding is not mentioned in the advisory report.

Please note that the committee did formulate a recommendation on calcium-rich foods in the advisory report, based on findings in the background document on nutrient supplements, i.e. strong evidence from RCTs that calcium supplements lower the risks of preterm birth, gestational hypertension and pre-eclampsia.[80]

A higher dairy intake will generally result in a higher calcium intake.

The association of a higher dairy intake with a lower risk of wheeze in the offspring is not put forward in the advisory report as an argument for the recommendation to eat sufficient foods rich in calcium, as the committee considers that this association is based on limited evidence, but the committee notes that the finding does comply with the recommendation on calcium-rich foods in the advisory report.

07 fruit and vegetables

This chapter describes the scientific evidence from systematic reviews of cohort studies on the association between fruit and vegetable intake during pregnancy and the risk of an infant that is small for gestational age, and the risk of atopic disease in the offspring (wheeze, asthma, and eczema). For other outcomes of interest, the committee did not find systematic reviews summarising at least two cohort studies. For this exposure, no systematic reviews summarising at least two RCTs were found.

7.1 Small for gestational age

Conclusion (cohort studies):

there is too little research to draw a conclusion on the association between fruit and/or vegetable intake during pregnancy and the risk of a small for gestational age infant.

Explanation

The committee found one systematic review of two cohort studies on the association between fruit and/or vegetable intake during pregnancy and the risk of a small for gestational age infant.[93] One of the included cohort studies measured pre-pregnancy fruit and vegetable intake and is therefore outside of the committee's scope.[94] A search for additional cohort studies published after the search of the systematic review retrieved one paper.[95] However, in this paper, a combined measure of small for gestational age, preterm birth and low Apgar score was used as an outcome. No information was available on the individual association between fruit or vegetable intake and the risk of a small for gestational age infant. Therefore, the committee did not use this paper in its evaluation.

In summary, only one cohort study is available on this topic.[96] It found that lower intake of vegetables during pregnancy was associated with a higher risk of an small for gestational age infant. No such association was found for fruit intake. As only one cohort study is available, the committee concludes that there is too little research to draw a conclusion on the association between fruit or vegetable intake and the risk of a small for gestational age infant.

7.2 Atopic disease in the offspring

7.2.1 Wheeze

Summary: Fruit and vegetable intake during pregnancy and risk of wheeze in the offspring.

Aspect	Explanation
Selected studies	Fruit: one meta-analysis of four cohort studies.[97] Vegetables: one systematic review of seven cohort studies,[48] including a meta-analysis of four studies and a pooled analysis of two studies[45]
Heterogeneity	Yes in the meta-analysis, not explained
Strength of the association	Fruit: RR = 0.94 (95%CI 0.73-1.27)[97] Vegetables[a]: meta-analysis RR = 0.90 (95%CI 0.69-1.18)[48]; pooled analysis RR = 0.94 (95%CI 0.79-1.12)[45]
Study population	Europe, Asia

[a] One study did not report risk estimate for vegetable intake, however, authors did report there is no significant association.

Conclusion (cohort studies):
There is too little research to draw a conclusion on the association between fruit and intake during pregnancy and the risk of wheeze in the offspring.

Conclusion:
Findings from cohort studies on the association between vegetable intake during pregnancy and the risk of wheeze in the offspring are inconclusive.

Explanation
The committee identified three systematic reviews on the association between fruit or vegetable intake during pregnancy and the risk of wheeze in the offspring: Nurmatov et al. (2010), Beckhaus et al. (2015), and Seyedrezazadeh et al. (2014).[47,48,97] Nurmatov et al. (2010) included two cohort studies, both of which are included by Seyedrezazadeh et al. (2014) and Beckhaus et al. (2015) as well.

For fruit intake during pregnancy, Seyedrezazadeh et al. (2014) included four cohort studies. Beckhaus et al. (2015) included six. However, one publication (combining the results of two cohorts) used fruit and nut intake as exposure.[45] Hence, no results on fruit intake alone were available, and the publication was therefore excluded by the committee.
When excluding this pooled study of two cohorts, Seyedrezazadeh et al. (2014) and Beckhaus et al. (2015) included the same four cohort studies. As Seyedrezazadeh et al. (2014) presented a combined risk estimate from a meta-analysis of the four studies and Beckhaus et al. (2015) did not, the results of Seyedrezazadeh et al. (2014) are described below (Table 31a). For vegetable intake during pregnancy Seyedrezazadeh et al. (2014) included four studies and Beckhaus et al. (2015) included seven (from six publications). Seyedrezazadeh et al. (2014) had a complete overlap with Beckhaus et al. (2015). As Beckhaus et al. (2015) is the most complete systematic review, their results are discussed by the committee (Table 31b).

Fruit
Seyedrezazadeh et al. (2014) did not find a significant association between maternal fruit intake during pregnancy and the risk of offspring wheeze at the age of 1 to 8 years in a meta-analysis of four cohort studies from Europe (the Netherlands, United Kingdom, and Finland) and Japan. It does not become clear whether or not the summarised studies incorporated fruit juice consumption in the definition of fruit intake. There was substantial heterogeneity, but since no overview of the individual risk estimates was presented the committee could not judge whether the heterogeneity was only present in the size of the association or also in the direction. As no subgroup analyses were performed, the committee cannot explain this heterogeneity.
In addition to the total fruit intake, Seyedrezazadeh et al. (2014) presented a separate risk estimate for apple intake based on two cohort studies. Again no significant association was found (RR = 0.84; 95%CI 0.48-1.46; I^2 71.8%).[97]

Since there was substantial heterogeneity which could not be interpreted and a non-significant risk estimates that were not close to one with rather wide confidence intervals, the committee concludes that there is too little research to draw a conclusion on the association between fruit intake during pregnancy and the risk of wheeze in the offspring.

Vegetables

Based on a meta-analysis of four cohort studies, the pooled analysis of Chatzi et al. (2013) and the cohort study of Willer st al (2007), Beckhaus et al. (2015) found no significant association between vegetable intake during pregnancy and the risk of childhood wheezing at the age of 1 to 8 years.[48] There was substantial heterogeneity in the meta-analysis of four studies, but an overview of the individual risk estimates was not presented, nor were subgroup analyses performed, to clarify the heterogeneity. No heterogeneity was present in the pooled analysis of two cohorts.[45]

In view of the number of studies, the fact that the risk estimate was not close to one but was not statistically significant and there was substantial heterogeneity which could not be interpreted, the committee concludes that the study findings on the association between vegetable intake during pregnancy and the risk of wheezing in the offspring are inconclusive.

Table 31a. Results of the meta-analysis of Seyedrezazadeh et al. (2014) on the association of fruit intake during pregnancy on the risk of offspring wheeze.

Exposure	Number of cohorts	Follow-up time	N participant	N cases	RR estimate	95%-CI	Heterogeneity I^2
Total fruit intake; highest versus lower intake	4	1 to 8 years	Around 7,289	n.r[a]	0.94	0.73-1.27	70%
Apple intake; highest versus lowest intake	2	16 months to 5 years	Around 2,016	n.r[a]	0.84	0.48-1.46	72%

CI: Confidence Interval; N: number; RR: Relative Risk estimate (can also be an odds ratio or hazard ratio); n.r.: not reported. [a] number of cases varies over time in one study.[88]

Table 31b. Results of the systematic reviews of Beckhaus et al. (2015) on the association of vegetable intake during pregnancy on the risk of offspring wheeze.

Study type	Exposure	Number of cohorts	Follow-up time (years)	N participant	N cases	RR estimate	95%-CI	Heterogeneity I^2
Meta-analysis[48]	Highest versus lower intake	4	1 to 8	Around 6,504	n.r[a]	0.90	0.69-1.18	62%
Pooled analysis[45]	High versus low intake (3rd tertile versus 1st tertile)	2	1	2,516	768	0.94	0.79-1.12	n.s.
Cohort study[86]	Servings per day	1	5	1,253	253[b]	n.s.	n.r.	n.r.

CI: Confidence Interval; N: number; RR: Relative Risk estimate (can also be an odds ratio or hazard ratio); n.r.: not reported; n.s.: not significant. [a] number of cases varies over time in one study.[88] [b] ever wheezed.

7.2.2 Asthma

Summary: Fruit and vegetable intake during pregnancy and risk of asthma or asthma-like symptoms.

Aspect	Explanation
Selected studies	Fruit: one systematic review of three cohort studies[97] and one additional cohort study[98] Vegetables: one systematic review of four cohort studies[48] and two additional cohort studies[73,98]
Heterogeneity	Not applicable
Strength of the association	Fruit[a]: RR = 0.97 (95%CI 0.60-1.58)[76]; RR = 0.91 (95%CI 0.77-1.09)[88]; RR = 0.82 (95%CI 0.62-1.10)[98] Vegetables[a]: RR = 1.02 (95%CI 0.58-1.81)[75]; RR = 0.75 (95%CI 0.46-1.22)[76]; RR = 0.98 (95%CI 0.84-1.14)[88]; RR = 0.96 (95%CI 0.88-1.05)[73]; RR = 0.88 (95%CI 0.71-1.08)[98]
Study population	Europe

[a] one study did not report a risk estimate, but did report that results on fruit and vegetable intake were non-significant

Conclusion (cohort studies):

There is too little research to draw a conclusion on the association between fruit intake during pregnancy and the risk of asthma in the offspring.

Conclusion:

Findings from cohort studies on the association between vegetable intake during pregnancy and the risk of asthma in the offspring are inconclusive.

Explanation

There are three systematic reviews available on the association between fruit and vegetable intake during pregnancy and the risk of asthma in the offspring.[47,48,97] Seyedrezazadeh et al. (2014) and Beckhaus et al. (2015) report separate results for fruit and vegetable intake. In contrast, Nurmatov et al. (2010) describe combined results for fruits and vegetables. Nurmatov et al. (2010) included three cohort studies, two of them are included by Seyedrezazadeh et al. (2014) as well. The other cohort study reported on combined results of fruits and vegetables and therefore could not contribute to separate conclusions. As Beckhaus et al. (2015) included two cohort studies on fruit intake which are also included by Seyedrezazadeh et al. (2014); the results of Beckhaus et al. (2015) on fruit intake are left out of the evaluation. Seyedrezazadeh et al. (2014) included between two and four cohort studies on fruit intake in a meta-analysis. Since it is not specifically reported on which studies the combined risk estimates are based, the committee does not describe the combined estimates of this systematic review. Instead the committee describes the results of the individual studies that are included by Seyedrezazadeh et al. (2014) (Table 32a).

Beckhaus et al. (2015) included four cohort studies on vegetable intake. Seyedrezazadeh et al. (2014), included between two and four cohort studies on vegetable intake. Both reviews overlap by at least two studies. Since it is not reported on which studies the combined risk estimates of the review by Seyedrezazadeh et al. (2014) are based, and since Beckhaus et al. (2015) did not perform a meta-analysis, the committee describes the results of the individual cohort studies that were included by the authors of the review (Table 32b).

Fruit

The results of the three individual cohort studies that were included in the review of Seyedrezazadeh et al. (2014) are presented below (Table 32a).[86,76,88] Supplemented with one cohort study that was identified in the additional search.[98] The estimates of the meta-analysis from the review are not adopted in the overview of the committee since it does not become clear on which studies their estimates were based. The number of studies described in the text did not correspond with the number of studies in the tables.[97]

None of the four studies found evidence of a statistically significant association between total fruit intake during pregnancy and the risk of asthma or asthma-like symptoms in the offspring at the age of 1 to 8 years.[86,76,88,98] Although not explicitly stated, it is highly likely that the study of Erkkola et al. (2012) included fruit juice in their definition of total fruit intake. However, when analyses are split by juice and type of fruit, no different associations were found.

In view of the number of studies and all risk estimates not being close to one but not reaching statistical significance, the committee concludes that there is too little research to draw a conclusion on the association between fruit intake during pregnancy and the risk of asthma in the offspring.

Vegetables

Seysedrezazadeh et al. (2014) included two cohort studies that were also included by Beckhaus et al. (2015). In total, Beckhaus et al. (2015) included four cohort studies, but did not perform a meta-analysis. Therefore, the results of the individual studies are described by the committee (Table 33b). All cohort studies reported a non-significant association for the risk of asthma-like symptoms in the offspring at age 1 to 8.[75, 76,86,88]

In an update of the literature until July 2018, two new studies were identified.[73,98] Neither found a significant association between vegetable intake during pregnancy and the risk of physician-diagnosed asthma between the age of 3 to 10.

Overall, risk estimates range from 0.75 to 1.02. Four out of five risk estimates were below one, suggesting a reduced risk of asthma or asthma-like symptoms in the offspring when the mother consumes a higher amount of vegetables compared with lower amounts during pregnancy. However, none of the risk estimates reached statistical significance, and confidence intervals were rather wide. Therefore, the committee concludes that their study findings on the association between vegetable intake during pregnancy and the risk of asthma in the offspring are inconclusive.

Table 32a. Results from cohort studies summarised by Seyedrezazadeh et al. (2014) and one additional cohort study on the association of fruit intake during pregnancy on the risk of asthma or asthma-like symptoms in the offspring.

Cohort name	Exposure	Follow-up time (years)	N participants	N cases	RR estimate	95%-CI
Cohort from Aberdeen Maternity Hospital [86]	Servings per day	5	1,253	156[a]	n.s.	n.r.
Prevention and Incidence of Asthma and Mite Allergy (PIAMA) cohort[88]	Daily intake versus regular plus rare intake	1 to 8[b]	2,832[c]	Varying over time from 419 to 854	0.91	0.77-1.09
Type I Diabetes Prediction and Prevention (DIPP) Nutrition Study[76]	Highest quartile (793.9 to 3,908 grams/day) versus mid half (326.2 to 793.9 grams/day)[d]	5	2,441[c]	143	0.97	0.60-1.58
Avon Longitudinal Study of Parents and Children (ALSPAC)[98]	Highest quartile of intake versus lowest quartile	7.5	8,915	n.r.	0.82	0.62-1.10

CI: Confidence Interval; N: number; RR: Relative Risk estimate (can also be an odds ratio or hazard ratio); n.r.: not reported; n.s. not significant. [a] ever had asthma. [b] asthma symptoms first ascertained at 3 years. [c] participants with complete data. [d] Highly likely that this study included fruit and berry juice in total fruit intake [e] varying over time from 10.9% at 3 years to 23.1% at 10 years. Number of participants differs over time as well.

Table 32b. Results from cohort studies summarised by Beckhaus et al. (2015) and two additional cohort studies on the association between vegetable intake during pregnancy and the risk of asthma or asthma-like symptoms in the offspring.

Cohort name	Exposure	Follow-up time (years)	N participants	N cases	RR estimate	95%-CI
Cohort from Aberdeen Maternity Hospital [86]	Servings per day	5	1,253	156[a]	n.s.	n.r.
Prevention and Incidence of Asthma and Mite Allergy (PIAMA) cohort[88]	Daily versus regular or rare intake	1 to 8[b]	2,832[c]	Varying over time from 419 to 854	0.98	0.84-1.14
Prevention of Allergy among Children in Trondheim study [75]	Almost daily versus 1 time or less per week	2	3,086	183	1.02	0.58-1.81
Type I Diabetes Prediction and Prevention (DIPP) Nutrition Study[76]	Highest quartile (321.1-2,532.2 grams/day) versus mid half (149.1-315.1 grams/day)	5	2,441[c]	143	0.75	0.46-1.22
Lifeways[73]	Servings per day	3 to 10	897	Estimate at 60 to 100[d]	0.96	0.88-1.05
Avon Longitudinal Study of Parents and Children (ALSPAC)[98]	Highest quartile of intake versus lowest quartile	7.5	8,915	n.r.	0.88	0.71-1.08

CI: Confidence Interval; N: number; RR: Relative Risk estimate (can also be an odds ratio or hazard ratio); n.r.: not reported; n.s. not significant. [a] ever had asthma. [b] asthma symptoms first ascertained at 3 years. [c] participants with complete data. [d] varying over time from 10.9% at 3 years to 23.1% at 10 years. Number of participants differs over time as well.

7.2.3 Eczema

Summary: Fruit and vegetable intake during pregnancy and risk of eczema.

Aspect	Explanation
Selected studies	Fruit: one systematic review of three cohort studies[48] Vegetables: one systematic review of six cohort studies[48] including a meta-analysis of two studies and a pooled analysis of two studies[45]
Heterogeneity	Not reported for fruit; for vegetables not in meta-analysis and not in pooled analysis. However, the 95% confidence intervals of the meta-analysis and pooled analysis results did not overlap
Strength of the association	Fruit[a]: RR = 0.78 (95%CI 0.45-1.35)[99]; RRs ranged between 0.85 (n.s.) for exotic fruit to 1.03 for citrus fruits and bananas (n.s.)[81] Vegetable[a]: meta-analysis RR = 0.71 (95%CI 0.53-0.96) (two cohorts) pooled analysis RR of two cohort studies = 1.21 (95%CI 0.97-1.51)[45,48] and RRs ranged between 0.83 (n.s.) for raw tomatoes to 1.26 for spinach (n.s.)[81]
Study population	Europe, Asia

[a] one study did not report risk estimates, but did report that results on fruit and vegetable intake were non-significant

Conclusion (cohort studies):

There is too little research on the association between fruit intake during pregnancy and the risk of eczema in the offspring.

Conclusion:

Findings from cohort studies on the association between vegetable intake during pregnancy and the risk of eczema in the offspring are contradictory.

Explanation

The committee found one systematic review on the association between fruit or vegetable intake of the mother during pregnancy and the risk of eczema in the offspring.[48] The results of Beckhaus et al. (2015) are described below (Table 33a and 33b).

Fruit

Beckhaus et al. (2015) included four papers on five cohort studies in their systematic review on fruit intake during pregnancy and the risk of eczema in the offspring (Table 34a). However, one publication (combining the results of two cohorts) used fruit and nut intake as exposure.[45] Hence, no results of fruit intake alone were available, and the publication was therefore excluded by the committee. Thus, the three remaining cohort studies were used by the committee. Beckhaus et al. (2015) did not perform a meta-analysis on all the risk estimates of the included studies. Therefore, the results of the individual papers are described by the committee. All papers presented rather similar, non-significant associations between maternal fruit intake and the risk of eczema in the offspring at age 1 to 5 years.[81,86,99]

Since the number of studies is limited and the risk estimates are not close to one but not statistically significant, the committee concludes that there is too little research to draw a conclusion on the association between fruit intake during pregnancy and the risk of eczema in the offspring.

Vegetables

Beckhaus et al. (2015) included five papers on six cohort studies in their systematic review (Table 34b). They combined the odds ratios of a

Japanese and a Norwegian cohort study in a meta-analysis.[75,99] This analysis showed a significantly lower risk of eczema in offspring of mothers with a high vegetable intake during pregnancy compared with a lower vegetable intake. However, the pooled analysis of Chatzi et al. (2013) that was included in the review showed a non-significant higher risk of eczema when combining a Spanish and Greek cohort.[45] The confidence intervals of the two analyses do not overlap, indicating that they truly differ from each other. Two other studies, which were neither included in the meta-analysis nor in the pooled analysis, showed non-significant results.[81,86]

Since the risk estimates are not close to one and the heterogeneity between the two combined risk estimates and their confidence intervals appeared substantial on visual inspection, the committee concludes that study findings on the association between vegetable intake and the risk of eczema in the offspring are contradictory.

Table 33a. Results from the cohort studies included in the systematic review of Beckhaus et al. (2015) on the association between fruit intake during pregnancy and the risk of eczema in the offspring.

Cohort name	Exposure	Follow-up time (years)	N participant	N cases	RR estimate	95%-CI
Osaka Maternal and Child Health Study (OMCHS)[99]	Highest versus lowest quartile	16 to 24 months	763	142	0.78	0.45-1.35
Cohort from Aberdeen Maternity Hospital [86]	Servings per day	5	1,253	406	n.s.	n.r.
Influences of Lifestyle-related Factors on the Immune System and the Development of Allergies in Childhood Study[81]	Highest versus lower intake (either 3rd tertile versus 1st + 2nd tertile OR 3rd + 2nd tertile versus 1st tertile)	First 2 years of life	2,641	446	1.03 citrus fruit 0.92 apples 0.85 exotic fruit 1.03 bananas 1.02 strawberries	0.78-1.35 0.72-1.21 0.66-1.11 0.77-1.38 0.77-1.35

CI: Confidence Interval; N: number; RR: Relative Risk estimate (can also be an odds ratio or hazard ratio); n.r.: not reported; n.s.: not significant.

Table 33b. Results from the systematic review of Beckhaus et al. (2015) on the association between vegetable intake during pregnancy and the risk of eczema in the offspring.

Study type	Exposure	Number of cohorts	Follow-up time (years)	N parti-cipant	N cases	RR (95% CI)	Hetero-geneity I^2
Meta-analysis [48]	Highest versus lower intake	2	16 to 24 months	Around 3,849	608	0.71 (0.53-0.96)	0%
Pooled analysis[45]	Highest versus lowest tertile	2	1	2,516	426	1.21 (0.97-1.51)	n.s.
Cohort study[86]	Servings per day	1	5	1,253	406	n.s.	n.a.
Cohort study[81]	Highest versus lower intake (either 3rd tertile versus 1st + 2nd tertile OR 3rd + 2nd tertile versus 1st tertile)	1	First 2 years of life	2,641	446	1.12 (0.85-1.46) carrots 1.26 (0.99-1.61) spinach 1.24 (0.96-1.59) cabbage 0.94 (0.67-1.31) celery 0.83 (0.63-1.10) tomatoes 0.97 (0.75-1.27) sweet pepper 0.92 (0.69-1.22) salad	n.a.

CI: Confidence Interval; N: number; RR: Relative Risk estimate (can also be an odds ratio or hazard ratio); n.a.: not applicable; n.r.: not reported; n.s.: not significant.

7.3 Summary of findings

The conclusions in this chapter are based on three systematic reviews of observational studies [48,93,97] and two additional cohort studies.[73,98] Study findings on the association between vegetable intake during pregnancy and the risk of eczema in the offspring were contradictory.

The following overview presents all conclusions of the committee of this chapter on fruit and vegetable intake:

Committee's conclusion	Outcome
Strong evidence	No conclusions with strong evidence
Limited evidence	No conclusions with limited evidence
Unlikely	No unlikely associations or effects
Contradictory	• Eczema in the offspring: vegetables (cohort studies)
Too little research	• Small for gestational age: fruit (cohort studies); vegetables (cohort studies) • Wheeze in the offspring: fruit (cohort studies) • Asthma in the offspring: fruit (cohort studies) • Eczema in the offspring: fruit (cohort studies)
Inconclusive	• Wheeze in the offspring: vegetables (cohort studies) • Asthma in the offspring: vegetables (cohort studies)

7.4 No findings cited in the advisory report

The committee based the recommendations in the advisory report primarily on the conclusions in the background documents with a strong evidence level.

In this chapter on fruit and vegetable consumption, conclusions with a strong evidence level are not available.

08
sodium

This chapter describes the scientific evidence from systematic reviews of intervention studies on the effect of sodium during pregnancy on the risk of pre-eclampsia. For other outcomes of interest, the committee did not find systematic reviews summarising at least two RCTs. For this exposure, no systematic reviews summarising at least two cohort studies were found.

8.1 Pre-eclampsia

Summary: Sodium reduction during pregnancy and risk of pre-eclampsia.

Aspect	Explanation
Selected studies	Two RCTs[100,101]
Heterogeneity	Not applicable
Strength of the effect	RR = 2.40 (95%CI 0.22-26.12)[100] and RR = 0.96 (95%CI 0.37-2.51)[101]
Study population	Healthy pregnant women and pregnant women with blood pressure >85 mmHg

Conclusion (cohort studies):

There is too little research to draw a conclusion on the effect of sodium reduction during pregnancy on the risk of pre-eclampsia.

Explanation

The committee found one systematic review of sodium reduction during pregnancy and the risk of pre-eclampsia.[102] The systematic review summarised two Dutch RCTs.[100,101] The committee describes the results of the two RCTs individually as they show results in opposite directions (Table 34). The committee did not find any more recent RCT.

Van Buul et al. (1997) found no significant effect of the advice to restrict salt intake to 1.1 grams of table salt per day compared with no restriction in salt intake on the risk of pre-eclampsia in healthy pregnant women. Mean urinary sodium excretion during 24 hours was around 70 mmol per day (equivalent of an intake of 4.3 grams of table salt[a]) in the low-sodium group and around 135 mmol per day (8.3 grams of table salt) in the control group. However, the study was limited due to the small number of cases.[100] Knuist et al. (1998) studied pregnant women with a diastolic blood pressure over 85 mmHg or a weight gain of over 1 kg per week during three consecutive weeks. They found no significant effect of the advice to restrict salt intake to 2.9 grams of table salt per day compared to no restriction in salt intake on the risk of pre-eclampsia either. Mean urinary sodium excretion was 84 mmol per day (5.2 grams of table salt) in the low sodium group to and 124 mmol per day (7.6 grams of table salt) in the control group. Again, the number of cases was relatively small (8 in each group).[101]

In view of the small number of RCTs and the small number of cases in the RCTs, the committee concludes that there is too little research to draw a conclusion on the effect of sodium reduction during pregnancy on the risk of pre-eclampsia.

[a] Calculation: ((70*(100/95))*23)*(58,5/23) = 4,310 mg NaCl = 4.3 g NaCl.
Explanation: the sodium excretion during 24 hours is 95% of the sodium intake, therefore the excretion should be multiplied by 100 / 95 to calculate the total sodium intake.103 To convert mole to grams: multiply by 23 (the molar mass of sodium)
To convert grams of sodium to grams of table salt (NaCl): multiply by 58.5 / 23 (as the molar mass of NaCl is 58.5).

Table 34. Results from the RCTs included in Duley et al. (2005) on the effect of sodium reduction on the risk of pre-eclampsia.

First author	Intervention versus control	Start sodium reduction	n/N intervention	n/N control	RR	95%-CI
Van Buul[100]	Advice to eat about 20 mmol sodium (1.1 gram table salt) per day versus no salt restriction	12 weeks of gestation	2 /110	1 /132	2.40	0.22-26.12
Knuist[101]	Advice to eat less than 50 mmol sodium (2.9 gram table salt) per day versus no salt restriction	20 weeks of gestation	8 /184	8 /177	0.96	0.37-2.51

RCT: Randomised Controlled Trial; CI: Confidence Interval; n/N: number of cases/total number of participants; RR: Relative Risk.

8.2 Summary of findings

A major part of the total sodium intake in the included studies will most likely be from table salt. However, there are other sources of sodium as well such as baking soda (sodium bicarbonate) which is used as a rising product in dough, sodium lactate which is used in meat products, and sodium glutamate (also known as MSG or Ve-Tsin) a flavour enhancer that is used in Oriental cuisine and savoury foods.

The following overview presents all conclusions of the committee of this chapter on sodium intake based on one systematic review of intervention studies.[102]

Committee's conclusion	Outcome
Strong evidence	No conclusions with strong evidence
Limited evidence	No conclusions with limited evidence
Unlikely	No unlikely associations or effects
Contradictory	No conclusions with contradictory evidence
Too little research	• Pre-eclampsia (cohort studies)
Inconclusive	No inconclusive associations or effects

8.3 No findings cited in the advisory report

The committee based the recommendations in the advisory report primarily on the conclusions in the background documents with a strong evidence level.

In this chapter on sodium intake, conclusions with a strong evidence level are not available.

09 coffee

The number of systematic reviews on the relation between coffee consumption during pregnancy and the health of mother and child is limited, as compared with the number of systematic reviews on caffeine consumption. The latter are described in the background document '*Harmful effects of substances and microorganisms in the diet during pregnancy*'.

There is one systematic review of intervention studies on the effects of coffee restriction on pregnancy outcomes. However, as it summarised only one RCT per outcome measure, the results are not further described.[104] This chapter, therefore, describes the scientific evidence from systematic reviews of cohort studies on the association between coffee consumption during pregnancy and the risk of neural tube defects and pregnancy loss. For other outcomes of interest, the committee did not find systematic reviews summarising at least two cohort studies.

9.1 Pregnancy loss

Summary: Coffee consumption during pregnancy and risk of pregnancy loss.

Aspect	Explanation
Selected studies	One meta-analysis of three cohort studies[105] and two more recent cohort studies[106,107] (one of these included high versus no coffee consumption[107])
Heterogeneity	No
Strength of the association	high versus no coffee consumption RR = 1.21 (95%CI 1.09-1.35) [105]
Study population	Europe, North America

Conclusion:

Based on cohort studies, high coffee consumption during pregnancy is associated with a higher risk of pregnancy loss compared with no coffee consumption.

Level of evidence: limited.

Explanation

There are two umbrella reviews (Poole et al. (2017))[108] and Grosso et al. (2017)[109]) and one systematic review (Li et al. (2015)[105]) on the association between coffee consumption and risk of pregnancy loss. Pregnancy loss includes miscarriages, spontaneous abortions and foetal deaths. Both umbrella reviews based their conclusions with respect to coffee and the risk of pregnancy loss on the findings of the systematic review of Li et al. (2015); therefore, only the results of the systematic review by Li et al. are described.

The main meta-analyses by Li et al. (2015) combine the results of cohort studies and case-control studies, but Li et al. also present results per study type (cohort studies and case-control studies). Table 35a presents the meta-analyses by Li et al. of the results of cohort studies[a], excluding the study by Andersen 2012.[b] In the categorical analysis, Li et al. reported that heavy versus no coffee intake was associated with a significantly higher risk of pregnancy loss, whereas light versus no coffee intake as well as moderate versus no coffee intake were not associated with the risk of pregnancy loss. The exposures included in each coffee intake category varied substantially and partially overlapped:

- light intake, presented as coffee intakes lower than 2 cups/day, included findings on 0.5-1 cup/day (Fenster 1997), 1-2 cups/day (Armstrong 1992) and >0 cups/day (Savitz 2008);
- moderate intake, presented as intakes of 2-3 cups/day, included findings on 1-3 cups/day (Wisborg 2003), 2 cups/day (Fenster 1997) and 3-4 cups/day (Armstrong 1992);
- heavy intake, presented as ≥4 cups/day, included findings on ≥3 cups/day (Fenster 1997), ≥4 cups/day (Wisborg 2003), 5-9 cups/day and ≥10 cups/day (both Armstrong 1992).

Because of the variation in exposure within the coffee intake categories in the meta-analysis used by Li et al., the committee considers that this meta-analysis is not suitable for quantification of the level of coffee intake associated with the risk estimates.
In addition, the heavy versus no coffee intake meta-analysis included two risk estimates from the same cohort (Armstrong 1992). As these risk estimates are not independent, the contribution of this cohort study to the overall estimate was not proportional to the size of the study.
Furthermore, Li et al. do not account for different cup sizes and brewing strengths between countries in which the cohort studies were carried out (i.e. US, Canada and Denmark).[105]

The committee found two more recent Danish cohort studies (Hahn et al. (2015)[106] and Morales Suarez-Varela et al. (2018)[107]). These additional studies are presented in Table 35b. Please note that another more recent study (Gaskins et al. (2018))[110], describing findings of the Nurses' Health Study II) is not taken into consideration because coffee consumption was assessed before conception and not during pregnancy.
Hahn et al. (2015) described findings from the Snart-Gravid cohort, in which there was no clear association between consumption of coffee,

[a] The cohort studies were: Armstrong 1992 (Canada), Fenster 1997 (USA), Savitz 2008 (USA) and Wisborg 2003 (Denmark). Information in Table 35a which was not presented by Li et al. in their Table 1 was deduced from the supplementary material; the assignment of findings to the categories of coffee intake (light, moderate and heavy) was deduced from figure 2B in the publication of Li et al.

[b] The study by Andersen 2012 describes findings from the Danish National Birth Cohort. Li et al. note that these data were an outlier; therefore, Li et al. present meta-analyses including and excluding this reference.
The reference provided by Li et al. for Andersen 2012 is a publication on the exposure alcohol intake which does not provide findings on the association of coffee intake with pregnancy loss. The committee found a more recent publication from the Danish National Birth Cohort which did describe the association of coffee intake with pregnancy loss: Morales Suarez-Varela et al. (2018). Therefore, Li's meta-analysis excluding the results of Anderson 2012 is presented in Table 35a, and the findings from the Danish National Birth Cohort by Morales Suarez-Varela et al. (2018) are described as one of the additional, more recent findings in Table 35b.

assessed in the first trimester of pregnancy, and the risk of spontaneous abortion. The contrast in coffee intake was limited, and the number of cases in the group of women drinking more than 2 servings of coffee per day was low, hampering the interpretation of the finding.
Morales Suarez-Varela et al. (2018) described findings from the Danish National Birth Cohort. Coffee consumption was assessed during the first pregnancy interview. Their meta-analyses on the association between coffee consumption and pregnancy loss showed an interaction with cigarette smoking. Drinking more than 3 cups of coffee per day was associated with a higher risk of pregnancy loss in women smoking >10 cigarettes/day (RR=1.85; 95%CI 1.33-2.56) and in women smoking ≤10 cigarettes/day (RR=1.33; 95%CI 1.01-1.75). In non-smokers, the risk estimate was higher than one as well, but without reaching statistical significance (RR=1.17; 95%CI 0.91-1.51).
Thus, there were two additional recent cohort studies, both from Denmark. The largest of the two, the Danish National Birth Cohort, reported significant associations for high coffee consumption and indicated that the risk is determined by an interaction between coffee and cigarette use.[107]
The smaller one did not report findings for high coffee consumption.

All discussed cohort studies adjusted their analysis for maternal age. However, the adjustment for confounders did not consistently include all potentially relevant confounders. For instance, only one of the cohort studies included in the meta-analysis by Li et al. adjusted for maternal smoking, which hampers the interpretation of findings, because of the interaction between coffee consumption and smoking which was reported by Morales Suarez-Varela et al. (2018). Furthermore, only one cohort study adjusted for decaffeinated coffee.

In conclusion, high coffee consumption is associated with a higher risk of pregnancy loss. In view of the number of studies on high coffee consumption (four), the variety of the exposures included, and the lack of adjustment for some relevant covariates in most studies, the committee judges the level of evidence as limited.

Caffeinated versus decaffeinated coffee

Exposure assessment in part of the cohorts did not explicitly assess caffeinated coffee or decaffeinated coffee. A single cohort study included in the meta-analysis of Li et al. (2015) reported on the association between decaffeinated coffee intake versus no coffee intake and found an elevated risk of pregnancy loss as well: ≥ 3 cups per day versus 0 cups per day RR = 2.40 (95%CI 1.30-4.70).[111] Because there is only one single cohort study available and no additional cohort studies were found, the committee could not draw a conclusion on this exposure.

Table 35a. Results from the meta-analysis of Li et al. (2015) on the association between coffee consumption during pregnancy and risk of pregnancy loss.

Coffee exposure	Number of cohort (number of comparison)	N / n coffee groups	N / n reference groups[a]	RR estimate	95%-CI	Hetero-geneity I^2
Light coffee intake	3 (3)	16,196 / 3,320	20,043 / 3,508	1.01	0.91-1.13	18%
Moderate coffee intake	3 (3)	10,753 / 1,103	25,533 / 3,360	1.02	0.91-1.11	0%
Heavy coffee intake	3 (4)	6,725 / 722	25,533 / 3,360	1.21	1.09-1.35	9%

CI: Confidence Interval; N / n, number of participants / number of cases; n.r.: not reported; RR: Relative Risk estimate (can also be an odds ratio or hazard ratio). [a] The reference groups are the groups with no coffee intake, the differences in this column reflect different cohorts included in the meta-analysis.

Table 35b. Results from the additional cohort studies as reported by Hahn et al. (2015)[106] and Morales Suarez-Varela et al. (2018)[107] on the association between coffee consumption during pregnancy and risk of pregnancy loss.

Cohort name	N participants	N cases	RR estimate (95%CI)
Snart-Gravid cohort [106]	5,132	732	1.38 (0.88-2.17) >0 up to 1 serving/day versus 0 0.66 (0.28-1.52) 2 servings/day versus 0
Danish National Birth Cohort [107]	90,086 [a]	1,178 [a]	non-smoking women: 1.04 (0.88-1.23) for ≤3 versus 0 cups of coffee/day 1.17 (0.91-1.51) for >3 versus 0 cups of coffee/day women smoking <10 cigarettes/day: 0.96 (0.74-1.25) for ≤3 versus 0 cups of coffee/day 1.33 (1.01-1.75) for >3 versus 0 cups of coffee/day women smoking ≥10 cigarettes/day: 0.99 (0.59-1.66) for ≤3 versus 0 cups of coffee/day 1.85 (1.33-2.56) for >3 versus 0 cups of coffee/day

CI: Confidence Interval; N: number; RR: Relative Risk estimate (can also be an odds ratio or hazard ratio).
[a] The group of non-smoking women covered 2,634,226 pregnancy weeks and 826 cases of pregnancy loss; the group of women smoking <10 cigarettes/day covered 694,773 pregnancy weeks and 251 cases of pregnancy loss; the group of women smoking ≥ 10 cigarettes/day covered 218,220 pregnancy weeks and 101 cases of pregnancy loss.

9.2 Neural tube defects

Conclusion (cohort studies):

There is too little research to draw a conclusion on the association between coffee consumption during pregnancy and the risk of neural tube defects in the offspring.

Explanation

There are two systematic reviews on the association between coffee consumption during pregnancy and the risk of neural tube defects.[112,113] Browne et al. (2006) and Li et al. (2016) described one retrospective cohort study by McDonald et al. (1992) in combination with respectively one and six case-control studies. McDonald et al. (1992) collected information on coffee consumption and risk of neural tube defects both during current pregnancies and during previous pregnancies. For previous pregnancies, the information on coffee consumption and risk of neural tube defects was collected at the same time. Therefore, the committee did not include the cohort study in its analysis.[114]
The committee did not find any more recent cohort studies on maternal coffee consumption and the risk of neural tube defects.

As no cohort studies are left to base a conclusion on, and case-control studies are only used as ancillary evidence by the committee, the committee concludes that there is too little research to draw a conclusion on the

association between coffee consumption during pregnancy and the risk of neural tube defects.

9.3 Summary of findings

The conclusions in this chapter are based on two systematic reviews of observational studies[105,112] and three individual cohort studies.[106,107] The committee found that high coffee consumption during pregnancy was associated with a higher risk of pregnancy loss compared with no coffee consumption. The level of evidence was limited.

The following overview presents all conclusion of the committee of this chapter on coffee intake:

Committee's conclusion	Outcome
Strong evidence	No conclusions with strong evidence
Limited evidence	• Based on cohort studies, high coffee consumption during pregnancy is associated with a higher risk of pregnancy loss compared with no coffee consumption
Unlikely	No unlikely associations or effects
Contradictory	No conclusions with contradictory evidence
Too little research	• Neural tube defects (cohort studies)
Inconclusive	No inconclusive associations or effects

9.4 Findings cited in the advisory report

The committee based the recommendations in the advisory report primarily on the conclusions in the background documents with a strong evidence level.

In this chapter on coffee consumption, conclusions with a strong evidence level are not available. There is one conclusion with limited evidence pointing into the direction of an association between a higher coffee consumption with a higher risk of pregnancy loss. Despite the limited evidence level of this finding, the committee does mention this conclusion in the advisory report because of the consistency with the conclusion on the association between caffeine intake and pregnancy loss. The latter finding is described in the background document on harmful substances and micro-organisms.[115] The conclusion on caffeine is also based on cohort studies. The number of cohort studies is larger for caffeine compared with coffee.

Please note that Li et al. (2015) presented two meta-analyses in their publication: one on coffee consumption and one on caffeine intake.[105] Three out of the five cohort studies included in their meta-analysis on coffee intake were not included in their meta-analysis on caffeine intake. Eight out of the ten cohort studies included in their meta-analysis on caffeine intake were not included in the meta-analysis on coffee intake. Thus, only two cohort studies were included in both meta-analyses (Fenster et al. (1997) and Savitz et al. (2008)) and both were relatively small compared with the other cohorts included. This is why the committee considers the evidence on coffee consumption supportive to the evidence on caffeine intake.

There was only one cohort study on the association between the consumption of decaffeinated coffee and the risk of pregnancy loss, reporting a high risk estimate and statistical significance (paragraph 9.1). Although one cohort study is too little evidence for a conclusion on decaffeinated coffee, the committee does mention this finding in the advisory report in the light of the recommendation to limit caffeine intake during pregnancy.

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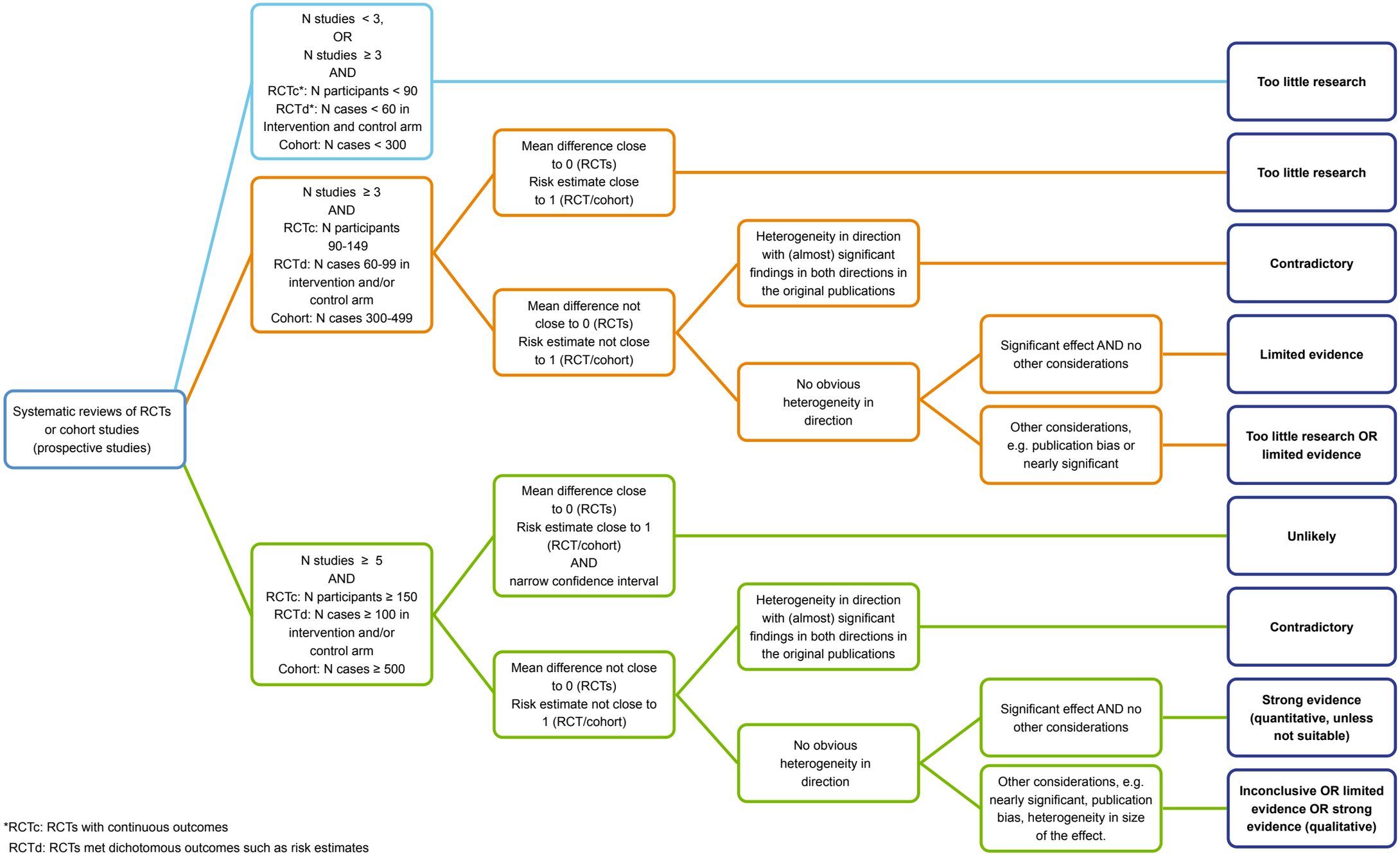
annexes

A decision tree



*RCTc: RCTs with continuous outcomes
RCTd: RCTs met dichotomous outcomes such as risk estimates

B literature search terms

The committee carried out a search in PubMed and Psychinfo to identify systematic reviews on the health effects of maternal food intake in the mother and the offspring.
In addition, for each of the outcome measures for which systematic reviews of RCTs and/or cohort studies were available, additional searches were carried out to identify individual cohort studies or RCTs that were published after the systematic review(s). The initial search for systematic reviews was performed until July 2018, the search for systematic reviews and meta-analyses has been updated in Pubmed until July 2019.

Search in PubMed and Psychinfo until July 2018

Topic		Search terms	Hits
1. Exposure			
A. Pregnancy		Pregnancy[Mesh Terms] OR pregnancy[tiab] OR pregnant[tiab] OR carrying[tiab] OR expecting[tiab] OR expectant[tiab] Or gestating[tiab] OR gestational[tiab] OR gravid[tiab] OR parous[tiab] OR parturient[tiab] OR enceinte[tiab]	1,066,491
B. Diet/nutrition/foods (general terms)		"Diet, Food, and Nutrition"[Mesh] OR diet[tiab] OR ((dietary[tiab] OR nutritional) AND pattern[tiab]) OR nutrition[tiab] OR "nutritional sciences"[MeSH Terms] OR "nutritional status"[MeSH Terms] OR "nutritional status"[tiab] OR food[MeSH Terms] OR ((intake[tiab] OR consumption[tiab] OR eating[tiab]) AND (food[tiab] OR foods[tiab] or "food product"[tiab] OR "food products"[tiab] OR "beverages"[tiab] OR "beverage"[tiab] or drink[tiab] OR drinks[tiab]))	1,218,648
C. Specific diets		vegetarians[MeSH Terms] OR vegetarians[tiab] OR vegetarian[tiab] OR "diet, vegetarian"[MeSH Terms] OR "vegetarian diet"[tiab]	258,011
	OR	"diet, vegan"[MeSH Terms] OR "vegan diet"[tiab] OR vegans[MeSH Terms] OR vegans[tiab] OR vegan[tiab]	
	OR	(low[tiab] AND (carbohydrates[MeSH Terms] OR carbohydrates[tiab] OR carbohydrate[tiab])) OR "diet, carbohydrate-restricted"[MeSH Terms] OR "carbohydrate-restricted diet"[tiab] OR "low carbohydrate diet"[tiab]	
	OR	"diet, paleolithic"[MeSH Terms] OR "paleolithic diet"[tiab] OR "paleo diet"[tiab]	
	OR	"diet, fat-restricted"[MeSH Terms] OR "fat-restricted diet"[tiab] OR "low fat diet"[tiab]	
	OR	(elimination[tiab] AND (diet[MeSH Terms] OR diet[tiab]))	
	OR	(("weights and measures"[MeSH Terms] OR "weights and measures"[tiab] OR weight[tiab] OR "body weight"[MeSH Terms] OR "body weight"[tiab]) AND ("prevention and control"[Subheading] OR "prevention and control"[tiab]))	
	OR	(low[tiab] AND (calorie[tiab] OR calories[tiab]))	
	OR	(crash[tiab] AND (diet[MeSH Terms] OR diet[tiab] oR diets[tiab]))	
	OR	(detox[tiab] AND (diet[MeSH Terms] OR diet[tiab] OR diets[tiab]))	
	OR	(junk food[tiab] AND (diet[MeSH Terms] OR diet[tiab] OR diets[tiab]))	
	OR	Diet, Gluten-Free[Mesh Terms] OR ((gluten-free[tiab] OR "gluten free"[tiab]) AND (diet[MeSH Terms] OR diet[tiab] OR diets[tiab]))	
	OR	((dairy-free[tiab] OR "dairy free"[tiab]) AND (diet[MeSH Terms] OR diet[tiab] OR diets[tiab]))	
	OR	"dietary approaches to stop hypertension"[Mesh Terms] OR DASH[tiab]	
	OR	"Diet, Mediterranean"[Mesh Terms] OR (mediterranean [tiab] AND (diet[MeSH Terms] OR diet[tiab] OR diets[tiab]))	
	OR	(Nordic [tiab] AND (diet[MeSH Terms] OR diet[tiab] OR diets[tiab]))	
D. Intake/consumption of specific foods/nutrients		(intake[tiab] OR consumption[tiab] OR eating[tiab])	
	AND	("dietary fiber"[Mesh Terms] OR (dietary[tiab] AND (fibre[tiab] OR fibres[tiab] OR fiber[tiab] OR fibers[tiab]))	
	OR	oil[tiab] OR oils[tiab]	
	OR	fruit[MeSH Terms] OR fruit[tiab] OR fruits[tiab]	
	OR	vegetables[MeSH Terms] OR vegetables[tiab]	
	OR	"edible grain"[MeSH Terms] OR "edible grain"[tiab] OR cereals[tiab] OR (grain[tiab] AND products[tiab]) OR wholegrain[tiab]	
	OR	fabaceae[MeSH Terms] OR fabaceae[tiab] OR legume[tiab] OR legumes[tiab] OR soy[tiab] OR soya[tiab]	
	OR	nuts[MeSH Terms] OR nuts[tiab] OR seeds[MeSH Terms] OR seeds[tiab]	
	OR	"dairy products"[MeSH Terms] OR dairy[tiab]	
	OR	eggs[MeSH Terms] OR eggs[tiab]	
	OR	meat[MeSH Terms] OR meat[tiab] OR fishes[MeSH Terms] OR fishes[tiab] OR fish[tiab]	
	OR	"solanum tuberosum"[MeSH Terms] OR "solanum tuberosum"[tiab] OR potato[tiab] OR potatoes[tiab]	

Topic		Search terms	Hits
D. Intake/consumption of specific foods/nutrients	OR	"sodium chloride"[MeSH Terms] OR "sodium chloride"[tiab] OR salt[tiab] OR "potassium, dietary"[MeSH Terms] OR "dietary potassium"[tiab] OR potassium[tiab] OR potassium[MeSH Terms]	143,848
	OR	tea[MeSH Terms] OR tea[tiab] OR coffee[MeSH Terms] OR coffee[tiab] OR decaffeinated[tiab] OR water[MeSH Terms] OR water[tiab] OR "drinking water"[MeSH Terms] OR "drinking water"[tiab]	
	OR	((sugars[MeSH Terms] OR sugars[tiab] OR sugar[tiab] OR sweetened[tiab] OR sweetener[tiab]) AND (beverages[MeSH Terms] OR beverages[tiab]))	
	OR	(((non[tiab] OR non-[tiab]) AND (alcoholics[MeSH Terms] OR alcoholics[tiab] OR alcoholic[tiab])) AND (beer[MeSH Terms] OR beer[tiab])) OR beer[MeSH Terms] OR beer[tiab] OR wine[MeSH Terms] OR "wine"[tiab])	
E. Weight change		weight gain[MeSH Terms] OR "weight gain"[tiab] OR "body weight changes"[MeSH Terms] OR "body weight changes"[tiab] OR "weight change"[tiab]	105,926
	OR	(pre-pregnancy[tiab] AND ("body mass index"[MeSH Terms] OR "body mass index"[tiab] OR BMI[tiab] OR weight[tiab]))	
Exposure overall		**A and (B or C or D or E)**	**96,239**
2. Outcomes			
A. Perinatal outcome measures		congenital abnormalities[Mesh Terms] ((birth[tiab] OR birthed[tiab] OR congenital[tiab] OR genetic[tiab]) AND (defect[tiab] OR abnormalities[tiab] OR abnormality[tiab] OR malformation[tiab]))	1,839,000
	OR	abortion spontaneous[Mesh Terms] OR abort*[tiab] OR miscarriage[tiab]	
	OR	premature birth[Mesh Terms] OR premature birth*[tiab] OR premature*[tiab]	
	OR	Mortality[Mesh Terms] OR mortality[Subheading] OR mortality[tiab] OR death[tiab]	
	OR	Gestational age[Mesh Terms] or gestational duration[tiab] OR "pregnancy duration"[tiab] OR "duration of pregnancy"[tiab]	
	OR	pregnancy outcome[Mesh Terms] OR "pregnancy outcome*"[tiab]	
B. Pregnancy complications		((Parturition[Mesh Terms] OR parturition*[tiab] OR childbirth*[tiab] OR delivery[tiab] OR confinement[tiab] OR labor[tiab] OR labour[tiab] OR birth[tiab] OR obstetric*[tiab] OR pregnancy[tiab]) AND (complication*[tiab] OR problem*[tiab]))	164,376
	OR	Diabetes gravidarum[tiab] OR gestational diabetes[tiab]	
	OR	pre-eclampsia[MeSH Terms] OR pre-eclampsia[tiab] OR "pre eclampsia"[tiab] OR "pregnancy hypertension"[tiab] OR "hellp syndrome"[Mesh Terms] OR "hellp syndrome"[tiab] OR ((pregnancy[tiab] OR pregnancy[Mesh]) AND (hypertensive disorder[tiab] OR hypertensive disease[tiab] OR hypertensive complication[tiab]))	
C. Long-term effects in offspring		asthma[MeSH Terms] OR asthma[tiab]	936,588
	OR	hypersensitivity[MeSH Terms] OR hypersensitivity[tiab] OR allergy[tiab] OR "allergy and immunology"[MeSH Terms] OR "allergy and immunology"[tiab]	
	OR	(cognition[MeSH Terms] OR cognition[tiab] AND impairment[tiab]) OR intelligence[MeSH Terms] OR intelligence[tiab]	
	OR	"diabetes mellitus, type 2"[MeSH Terms] OR "type 2 diabetes mellitus"[tiab] OR "diabetes type 2"[tiab]	
	OR	"neurocognitive disorders"[MeSH Terms] OR "neurocognitive disorders"[tiab] OR hyperkinesis[MeSH Terms] OR hyperkinesis[tiab] OR hyperactivity[tiab] OR "attention deficit disorder with hyperactivity"[MeSH Terms] OR "attention deficit disorder with hyperactivity"[tiab] OR adhd[tiab] OR "attention deficit and disruptive behavior disorders"[MeSH Terms] OR "attention deficit and disruptive behavior disorders"[tiab] OR "oppositional defiant disorder"[tiab] OR "conduct disorder"[MeSH Terms] OR "conduct disorder"[tiab]	
Outcomes overall		**A or B or C**	**2,832,214**
3. Intermediate outcome measures			
A. Perinatal outcome measures		"fetal growth retardation"[MeSH Terms] OR "fetal growth retardation"[tiab] OR "fetal growth restriction"[tiab]	131,718
	OR	"intrauterine growth restriction"[tiab] OR "intrauterine growth retardation"[tiab] OR IUGR[tiab]	
	OR	"gestational age"[MeSH Terms] OR "gestational age"[tiab] OR SGA[tiab] OR LGA[tiab] OR "foetal macrosomia"[tiab] OR "fetal macrosomia"[MeSH Terms] OR "fetal macrosomia"[tiab]	

Topic		Search terms	Hits
B. Long-term effects in the offspring		"cardiovascular system"[MeSH Terms] OR "cardiovascular system"[tiab] OR cardiovascular[tiab] OR "blood pressure"[MeSH Terms] OR "blood pressure"[tiab] OR "arterial pressure"[MeSH Terms] OR "arterial pressure"[tiab]	2,613,516
	OR	((glucose[MeSH Terms] OR glucose[tiab]) AND (regulation[tiab] OR control[tiab] OR metabolism[tiab])) OR "glucose intolerance"[MeSH Terms] OR "glucose intolerance"[tiab] OR "impaired glucose tolerance"[tiab]	
	OR	hypertriglyceridemia[MeSH Terms] OR hypertriglyceridemia[tiab] OR "high triglycerides"[tiab]	
	OR	overweight[MeSH Terms] OR overweight[tiab] OR BMI[tiab] OR obesity[MeSH Terms] OR obesity[tiab]	
	OR	"fat body"[MeSH Terms] OR "fat body"[tiab] OR "body fat"[tiab] OR "adipose tissue"[MeSH Terms] OR "adipose tissue"[tiab] OR ((body[tiab] AND fat[tiab]) AND percentage[tiab])	
	OR	hypertension[MeSH Terms] OR hypertension[tiab]	
	OR	dyslipidemias[MeSH Terms] OR dyslipidemias[tiab] OR dyslipidaemia[tiab]	
	OR	"metabolic syndrome"[MeSH Terms] OR "metabolic syndrome"[tiab]	
	OR	((emotions[MeSH Terms] OR emotions[tiab] OR emotional[tiab]) AND ("growth and development"[Subheading] OR "growth and development"[tiab] OR development[tiab] OR problem[tiab] OR problems[tiab] OR issues[tiab]))	
	OR	aggression[MeSH Terms] OR aggression[tiab] OR "aggressive behavior"[tiab] OR "aggressive behaviour"[tiab]	
Intermediate outcome measures overall		**A or B**	**2,720,001**
4. Publication types			
A. Reviews/meta-analyses		review[pt] OR meta-analysis[pt] OR "systematic review"[tiab] OR "systematic literature review"[tiab] OR meta-analysis[tiab]	2,469,.961
B. Other study types		clinical study[pt] OR clinical trial[pt] OR Pragmatic Clinical Trial[pt] OR comparative study[pt] OR controlled clinical trial[pt] OR Randomized Controlled Trial[pt] OR Multicenter Study[pt] OR Observational Study[pt] OR "prospective study"[tiab] OR "nested case-control"[tiab] OR case-cohort[tiab] NOT (case reports[pt] OR editorial[pt] OR letter[pt] OR news[pt] OR comment[pt] OR congresses[pt] OR "cross-sectional study"[tiab])	2,544,106
5. Animal studies (NOT)			
		(Animals[Mesh] NOT (Humans[Mesh] AND Animals[Mesh]))	4,456,827
Reviews		**1 and (2 or 3) and 4A not 5**	**7,231**
+ time limit Published in past 10 years: per 01-01-2008 + English language only			3,459
Reviews		**1 and 2 and 4B (all study types except reviews for main outcomes) not 5**	**5,241**
+ time limit Published per 01-01-2000 + English language only			3,553

The Health Council of the Netherlands, established in 1902, is an independent scientific advisory body. Its remit is “to advise the government and Parliament on the current level of knowledge with respect to public health issues and health (services) research...” (Section 22, Health Act).
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